Privacy Office
Legal Services
Centennial 1-031
1276 South Park Street
Halifax NS B3H 2Y9
Telephone: (902)473-2626
Fax: (902)473-7850

29 May 2020

Sent via email

Re: No Responsive Records – OUR FILE# NSHA-2020-25

On 22 May 2020, Nova Scotia Health Authority (NSHA) received your request under the Freedom of Information and Protection of Privacy (FOIPOP) Act for a copy of the following:

Documents, correspondence, briefing notes and/or emails having to do with the consideration and/or establishment of an immunity certificate system in the province of Nova Scotia since March 13 2020.

We have conducted a thorough search of our records, but we have not been able to locate any records responsive to your request. We contacted the Department of Health & Wellness and they do not have any responsive records either. We were informed that while there has been a national position statement on this, this has not been actively discussed for Nova Scotia at all and the Department has not seen or reviewed recent drafts on this. We are, therefore, closing your application with NSHA.

You have the right to seek a review of this decision within 60 days with the Review Officer. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review . Notwithstanding, within 30 days you have the right to appeal directly to the Supreme Court if there is no third party notified pursuant to section 22 of the Act.

Should you have any questions or comments, please do not hesitate to contact me at the address or telephone number provided above.

Sincerely,

Fola Adeleke

Freedom of Information Officer

c/c: to file

Privacy Office
Legal Services
Centennial 1-031
1276 South Park Street
Halifax NS B3H 2Y9
Telephone: (902)473-2626
Fax: (902)473-7850

June 23, 2020

Sent via e-mail

Re: Full Disclosure – OUR FILE# NSHA-2020-29

On 9th June 2020, Nova Scotia Health Authority (NSHA) received your request transferred from the Department of Health and Wellness under the Freedom of Information and Protection of Privacy (FOIPOP) Act for a copy of the following:

Records showing the total cost and total numbers of masks, gloves and visors purchased and delivered for the date range March 11, 2020 to present (June 2, 2020) in relation to COVID 19

Please find attached a copy of the records located in response to your request. These records are being provided to you in their entirety. We are now closing your application with our Office.

Should you have any questions or comments, please do not hesitate to contact me at the address or telephone number provided above.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review

Sincerely,

Fola Adeleke

For: The Privacy Office
Nova Scotia Health Authority

c/c: to file

Glove, Mask, Shield Orders between March 11th and June 2nd

Note that we interpreted "Visor" in the original request to mean Shield as that is how we refer to this product in our data.
Table 1 breaks down the orders by NSHA operational versus Covid19 purchases in case this is helpful to have
We have included quantities and values received between the dates in the event the request is interpreted to be just what has been received, versus ordered

Table 1: NSHA Operations and Covid19 Glove, Mask and Shield orders between March 11, 2020 and June 2, 2020

Type	PPE	Unit of Measure	Quantity Ordered between March 11th to June 2nd	Net Order Value Ordered between March 11th to June 2nd	Quantity delivered by June 2nd	Net Order Value delivered by June 2nd
Covid 19 Purchase	Glove	Pair	0	$0.00	0	$0.00
Covid 19 Purchase	Mask	Each	12,975,900	$11,260,384.00	6,176,400	$5,862,574.00
Covid 19 Purchase	Shield	Each	2,470,000	$9,298,950.00	776,240	$2,824,614.40
		Grand Total	15,445,900	$20,559,334.00	6,952,640	$8,687,188.40

Privacy Office
Legal Services
Centennial 1-031
1276 South Park Street
Halifax NS B3H 2Y9
Telephone: (902)473-2869
Fax: (902)473-7850

23 July 2020

Re: Full Disclosure – OUR FILE# NSHA-2020-32

On June 17 2020, Nova Scotia Health Authority (NSHA) received your request under the Freedom of Information and Protection of Privacy (FOIPOP) Act for a copy of the following:

Please provide documentation on the number of cancelled or postponed surgeries, health procedures and consultations due to COVID-19. Please be sure to provide any other documentation related to the impact on health care waiting lists due to COVID-19 (and postponed/cancelled health procedures, surgeries, consultations, etc).

Please find attached a copy of the records located in response to your request. These records are being provided to you in their entirety.

Please also note that information system across NSHA differ by clinical area, as such, the availability of electronic information to respond to this FOIPOP request is limited. Cancellation data is provided for all surgical and diagnostic imaging related procedures. Cancellations are not readily available for other clinical areas at this time. The attached provides data for all of NSHA for the time period of Mar 16 – May 25, 2020 and was captured on June 22, 2020.

We are now closing your application with our Office.

Should you have any questions or comments, please do not hesitate to contact me at the address or telephone number provided above.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review

Sincerely,

Fola Adeleke

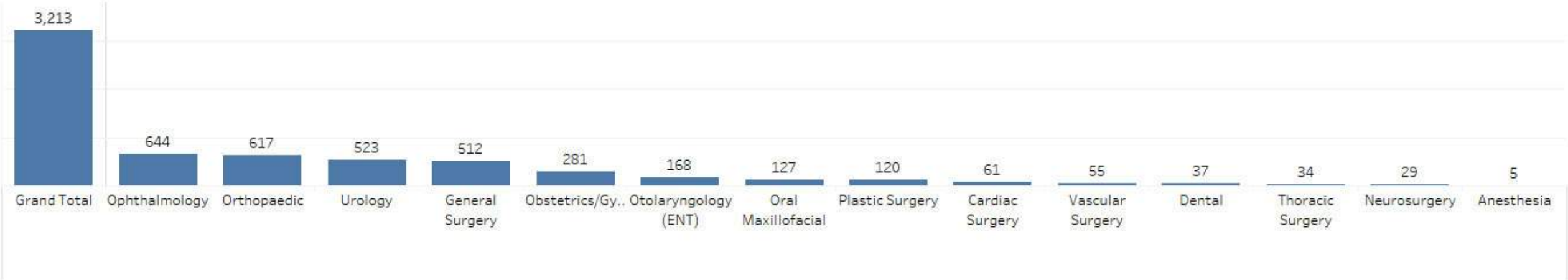
For: The Privacy Office
Nova Scotia Health Authority

c/c: to file

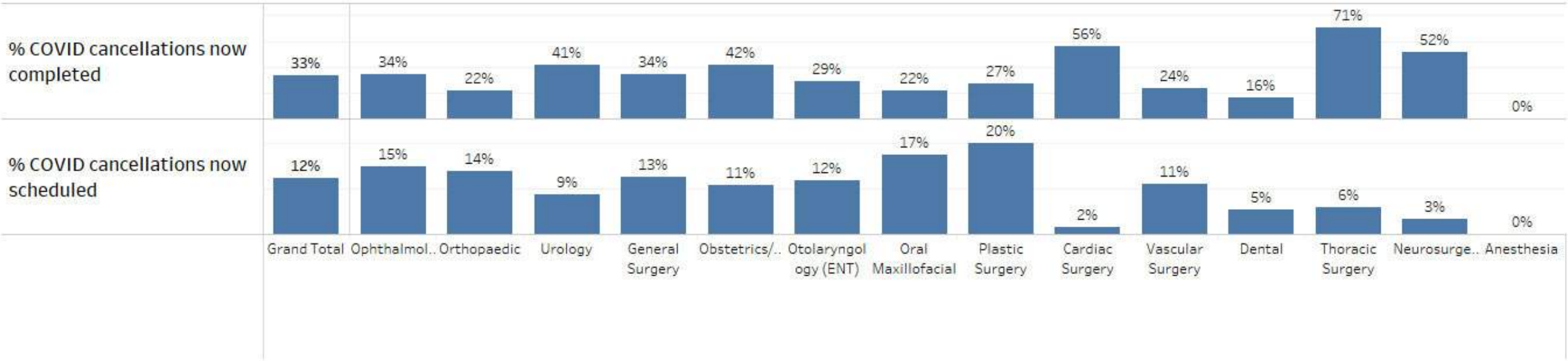
Surgical Cancellations during COVID Slowdown

(Mar 16-May 25, 2020) *(excludes Endoscopy)*

Cancellations by Specialty

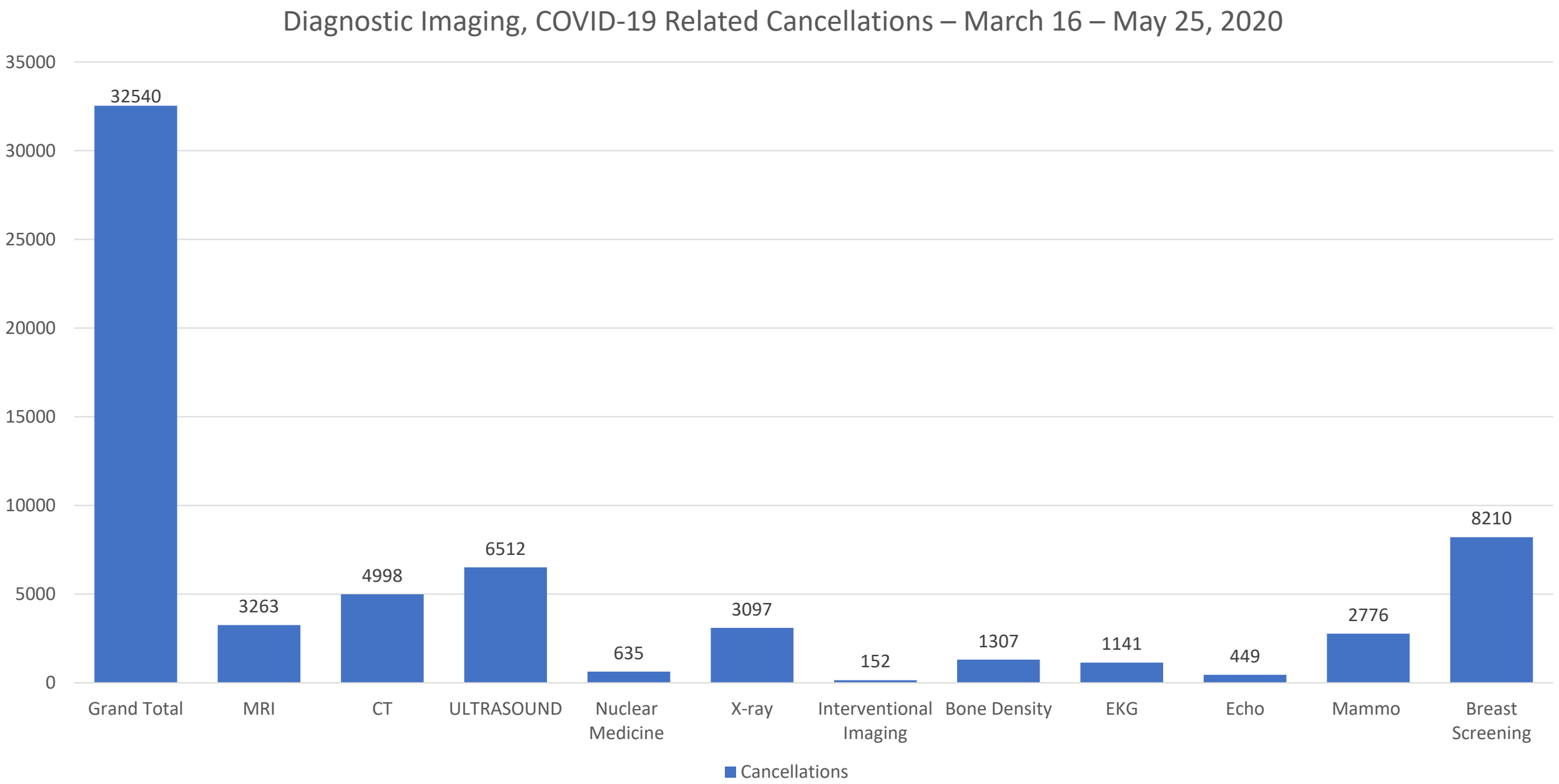


Current Status of Cancellations



Data source(s): PARNS

Prepared by: NSHA Performance and Analytics


Diagnostic Imaging, COVID-19 Related Cancellations – March 16 – May 25, 2020
35000
30000
25000
20000
15000
10000
5000
0
32540
3263
4998
6512
635
3097
152
1307
1141
449
2776
8210
Grand Total
MRI
CT
ULTRASOUND
Nuclear Medicine
X-ray
Interventional Imaging
Bone Density
EKG
Echo
Mammo
Breast Screening
Cancellations

Privacy Office
Legal Services
Centennial 1-031
1276 South Park Street
Halifax NS B3H 2Y9
Telephone: (902)473-2869
Fax: (902)473-7850

10 October 2020

Sent via e-mail

Re: Full Disclosure – OUR FILE# NSHA-2020-45

On August 8 2020, Nova Scotia Health received your request under the Freedom of Information and Protection of Privacy (FOIPOP) Act for a copy of the following:

Record of surgical backlog as of March 18, 2020 and July 27, 2020. If possible, break down this backlog into elective and non-elective surgeries

Record of diagnostic backlog as of March 18, 2020 and July 27, 2020. If possible, break down this backlog into types of diagnostic procedures (CAT, MRI, etc)

Please find attached a copy of the records located in response to your request. These records are being provided to you in their entirety. We are now closing your application with our Office.

For your first request, there is no formalized description of the 6 categories in the attached as they are designations that are subjectively assigned by doctors. There is also no specific distinction between elective or non-elective surgeries.

P3 requests in the attached are those requests that are deemed semi urgent and should be completed within 30 days, based on the Canadian Association of Radiologists (CAR) guidelines. P4 requests in the attached are those requests that are deemed elective and should be completed within 60 days, based on CAR guidelines.

Please also note that the numbers shown are not a backlog. Each month, some of these surgeries would have been completed and others added.

Should you have any questions or comments, please do not hesitate to contact me at the address or telephone number provided above.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review

Sincerely,
Fola Adeleke
For: The Privacy Office

Surgery Waitlist

The numbers of surgeries at each priority level on the waitlist at the end of each month. The number in the priority level (i.e. the "21" in "IIb-21") indicates the number of days the surgery should be completed within at that level.

	Priority Level					
Month	**IIa-7**	**IIb-21**	**III-42**	**IV-91**	**V-182**	**VI-365**
March	273	1534	4760	19217	17467	10532
April	136	766	2441	9748	8854	5360
May	134	759	2489	9805	9022	5428
June	134	770	2257	9644	9112	5444
July	137	774	2358	9368	8893	5249

Diagnostic Imaging Waitlist

Cancelled Diagnostic Imaging Exams

A list of pending exams is not available for the earlier date requested. What we have are the numbers of exams cancelled on a weekly basis beginning with the week of March 22nd.

	MRI	**CT**	**US**	**Breast Screening**	**Mammo**
Week of March 22	**362**	**678**	**590**	**591**	**174**
Week of March 29	**428**	**985**	**1002**	**838**	**335**
Week of April 5	**453**	**812**	**840**	**722**	**326**
Week of April 12	**318**	**656**	**687**	**548**	**336**
Week of April 19	**296**	**412**	**567**	**552**	**316**
Week of April 26	**322**	**409**	**632**	**638**	**196**
Week of May 3	**296**	**280**	**542**	**694**	**221**
Total	**2475**	**4232**	**4860**	**4583**	**1904**

DI Pending Exams

As of July 29, 2020

Row Labels	Sum of Pending P3	Sum of Pending P4
CT	6100	5175
MRI	3639	8565
Ultrasound	4347	11690
Grand Total	14086	25430

Privacy Office
Legal Services
Centennial 1-031
1276 South Park Street
Halifax NS B3H 2Y9
Telephone: (902)473-2869
Fax: (902)473-7850

31st August 2020

Sent via e-mail

Re: Full Disclosure – OUR FILE# NSHA-2020-46

On 12 August 2020, Nova Scotia Health received your request under the Freedom of Information and Protection of Privacy (FOIPOP) Act for a copy of the following:

Excel spreadsheet of PPE supply available to NSHA by day, for the months of March, April and May 2020. Requested PPE items are surgical masks, N95 masks, gowns, face shields and gloves.

Please find attached a copy of the records located in response to your request. These records are being provided to you in their entirety. We are now closing your application with our Office.

Should you have any questions or comments, please do not hesitate to contact me at the address or telephone number provided above.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review

Sincerely,

Fola Adeleke

For: The Privacy Office
Nova Scotia Health Authority

c/c: to file

PPE Available to NSHA By Day					
Date	**Surgical Masks (EACH)**	**N95 Masks (EACH)**	**Gowns (EACH)**	**Face Shields (EACH)**	**Gloves (PAIR)**
1-Mar-20	Weekend, no data				
2-Mar-20	233976	44580	195740	328800	6911371
3-Mar-20	230576	44260	197050	328110	6796445
4-Mar-20	221521	43280	195110	327288	6683740
5-Mar-20	236420	43430	195340	327148	6598702
6-Mar-20	250145	43190	193690	326428	6922598
7-Mar-20	Weekend, no data				
8-Mar-20	Weekend, no data				
9-Mar-20	266368	44120	191450	324308	6855924
10-Mar-20	262472	44600	191000	324257	6755490
11-Mar-20	264552	45560	267301	318384	6710919
12-Mar-20	278145	24740	267199	314554	6706098
13-Mar-20	322282	23170	274455	315024	6822036
14-Mar-20	Weekend, no data				
15-Mar-20	Weekend, no data				
16-Mar-20	306382	22490	266465	314444	7256131
17-Mar-20	315828	23848	248357	312618	7043707
18-Mar-20	341659	25448	283207	313448	6946223
19-Mar-20	340648	23938	292944	310513	6903889
20-Mar-20	332438	24078	288517	308031	6683040
21-Mar-20	Weekend, no data				
22-Mar-20	Weekend, no data				
23-Mar-20	328643	22948	276675	273077	6652787
24-Mar-20	330688	21838	262108	270265	6890650
25-Mar-20	332288	19908	258742	265743	6850951
26-Mar-20	317978	37057	267885	259074	6828778
27-Mar-20	301777	36567	323779	257999	6808248
28-Mar-20	Weekend, no data				
29-Mar-20	Weekend, no data				
30-Mar-20	321896	35931	324191	254998	6811670
31-Mar-20	287051	34121	347965	244852	6661847
1-Apr-20	276176	32461	342712	237043	6629680
2-Apr-20	253476	32911	335392	235619	6624761
3-Apr-20	237876	30990	327406	238759	7596441
4-Apr-20	Weekend, no data				
5-Apr-20	Weekend, no data				
6-Apr-20	199726	30310	350456	229543	7555697
7-Apr-20	237222	29539	330689	232259	7474250
8-Apr-20	198996	28599	323192	228343	7296092
9-Apr-20	190121	28739	331359	224293	7283370
10-Apr-20	Holday, no data				
11-Apr-20	Weekend, no data				
12-Apr-20	Weekend, no data				
13-Apr-20	Holday, no data				
14-Apr-20	142996	30488	303007	210590	7060032
15-Apr-20	166663	31688	302889	206705	6941220
16-Apr-20	165038	29058	296575	204289	6845065

17-Apr-20	174613	32038	362067	196505	6859534
18-Apr-20	Weekend, no data				
19-Apr-20	Weekend, no data				
20-Apr-20	759184	34688	332562	180098	6913314
21-Apr-20	2483358	40198	336286	202382	6817638
22-Apr-20	2701608	45058	334766	199222	9244466
23-Apr-20	2698283	184393	352607	247667	9172612
24-Apr-20	3185948	191808	385222	246037	9493517
25-Apr-20	Weekend, no data				
26-Apr-20	Weekend, no data				
27-Apr-20	3098398	238738	357167	226916	9258796
28-Apr-20	3096873	237738	397169	224435	8920696
29-Apr-20	2954449	242258	400839	258548	9043964
30-Apr-20	2937104	241047	386408	254781	9321033
1-May-20	3061479	244647	384906	343591	9182266
2-May-20	Weekend, no data				
3-May-20	Weekend, no data				
4-May-20	3063053	243547	324640	306452	9115433
5-May-20	3141317	243253	357485	302630	9023904
6-May-20	3304132	244133	349956	295350	8934067
7-May-20	3362787	243813	349198	322620	8828952
8-May-20	3353841	270653	383468	331792	8780957
9-May-20	Weekend, no data				
10-May-20	Weekend, no data				
11-May-20	3690515	269494	380976	326945	8707648
12-May-20	4675788	269824	425048	328355	8943715
13-May-20	4746827	270184	411838	314874	8898526
14-May-20	4736305	270224	405043	353466	8904478
15-May-20	4725884	270064	416912	350426	8882144
16-May-20	Weekend, no data				
17-May-20	Weekend, no data				
18-May-20	Holday, no data				
19-May-20	4802759	275542	405775	421095	8823299
20-May-20	4785763	274982	610463	421428	9003326
21-May-20	4899012	275842	588596	547473	8972975
22-May-20	5050996	275642	767296	544907	8908371
23-May-20	5038893	279322	931296	817853	8842082
24-May-20	Weekend, no data				
25-May-20	Weekend, no data				
26-May-20	5914359	282622	1031666	818977	8725340
27-May-20	5882592	282702	1093006	886097	8595770
28-May-20	5996840	292772	1198436	901089	8612592
29-May-20	6013705	302140	1196356	921561	8562511
30-May-20	Weekend, no data				
31-May-20	Weekend, no data				

Privacy Office; Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

8th September 2020

Sent via e-mail:

Re: No Responsive Records – OUR FILE# NSHA-2020-50

On 30th of August, Nova Scotia Health Authority (NSHA) received your request under the Freedom of Information and Protection of Privacy (FOIPOP) Act for a copy of the following:

Provide copies of any documents showing the source for personal protective equipment (PPE) acquired or received by the province – whether acquired directly, received from the federal government, donated/provided by third party/foreign state, etc., since March 1 2020

We have conducted a thorough search of our records, but we have not been able to locate any records responsive to your request. We purchase supplies from importers, who may be in Canada, but we have no knowledge of where their supplies came from. We do not deal directly with any manufacturers, we work with companies that are Canadian, who import the goods and sell them to us.

For supplies received from the federal government, we have no way of knowing where their supplies came from.

For donations, we may know the country where the donation came from, but not where they got the supplies from.

We are, therefore, closing your application with NSHA.

You have the right to seek a review of this decision within 60 days with the Review Officer. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca /request-a-review . Notwithstanding, within 30 days you have the right to appeal directly to the Supreme Court if there is no third party notified pursuant to section 22 of the Act.

Should you have any questions or comments, please do not hesitate to contact me at the address or telephone number provided above.
Sincerely,

Fola Adeleke
Freedom of Information Officer

c/c: to file

Privacy Office; Legal Services
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1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

Fola Adeleke, FOIPOP Officer
Nova Scotia Health

Privacy Office: Legal Services
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1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

FOIPOP 2020-56:

Please see attached your request for records for the first part of your request: *Records pertaining to the decision to cancel elective surgeries or any negative health impacts which resulted from the cancellation of elective surgeries. For example, what kinds of surgeries were canceled and how many of each kind were canceled?" I would still like to see a breakdown of delayed/canceled surgeries during the period of March 18, 2020 through July 27, 2020 by type: heart, cancer, hip/knee, etc. Perhaps a breakdown is best made according to WHO ICD-10 guidelines if the health authority already categorizes surgeries internally by the same.*

Please kindly note that data less than 5 have been redacted to prevent re-identification.

In relation to the second part of your request for *'how were the negative impacts which resulted from this policy tracked? What were these negative impacts and how many of each type of impact occurred? Examples of negative impact would include heart failure after a cancelled surgery was scheduled to occur, permanent nerve damage which occurred after a spinal surgery was scheduled to occur, etc. Individual medical reports with redacted personal information would be helpful if no data collection has occurred'* , please kindly note that this is not data that would be tracked proactively, such events would come out of a quality review process, but would not be readily apparent in our standard datasets. FOIPOP does not apply to quality improvement information in terms of the Quality-improvement Information Protection Act.

In relation to your request for the health records of others, kindly also note that s 20 (3) of the Freedom of Information and Protection of Privacy Act prevents the disclosure of personal health information of others. In addition, the Personal Health Information Act of Nova Scotia excludes the application of FOIPOP for the disclosure of personal health information of others.

We are now closing your file with our office. You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review .

Thank you.

Fola Adeleke
Freedom of Information Unit
Privacy Office, Legal Services
FOIPOP@nshealth.ca

Privacy Office; Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

902-473-2869

March 18-July 27 2020: Surgical Cancellations (all causes) by Specialty and Procedure
Source: PAR-NS Database, as of Oct 22, 2020
Provided by: NSH Performance & Analytics

* removed = case has been removed from the wait list without being completed. This can be due to various reasons, such as patient no longer needs/wants surgery, patient moved away, patient not clinically ready for surgery, etc.

Specialty	Booked Procedure	# cancellations	% cancellations now completed	% cancellations now scheduled	% cancellations now removed *
Ophthalmology	CATARACT EXTRACTION	575	83%	1%	8%
	VITRECTOMY/VITREORETINAL PROCEDURE (removal IO lens, scleral buckle)	33	79%	0%	6%
	TRABECULECTOMY/ GLAUCOMA SURGERY	18	78%	0%	6%
	KERATOPLASTY/ CORNEAL TRANSPLANT	8	75%	0%	0%
	RECONSTRUCTION EYELID	8	75%	0%	0%
	TRABECULECTOMY - DRAINAGE DEVICES	7	100%	0%	0%
	DACRYOCYSTORHINOSTOMY (DCR)	6	50%	0%	33%
	RECONSTRUCTION / DECOMPRESSION ORBIT	[redacted]	0%	0%	20%
	ORBITECTOMY/ORBITOMY	[redacted]	100%	0%	0%
	REPAIR STRABISMUS	[redacted]	100%	0%	0%
	Total	665	82%	1%	8%
Urology	CYSTOSCOPY	271	58%	3%	15%
	EXCISION OF CYST/GANGLION/LESION/LIPOMA	[redacted]	60%	0%	40%
	CYSTOSCOPY/TURP	48	60%	0%	8%
	CYSTOSCOPY URETEROSCOPY	42	71%	5%	7%
	CYSTOSCOPY/TURB	40	88%	0%	10%
	LITHOTRIPSY/LASER/ BASKET EXTRACTION	33	85%	0%	6%
	CIRCUMCISION	21	57%	0%	5%
	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION	20	80%	0%	20%
	HYDROCELECTOMY	15	67%	0%	0%
	LAPAROSCOPIC NEPHRECTOMY	13	62%	0%	31%
	NEPHRECTOMY	11	82%	0%	0%
	CYSTOLITHOPAXY/ CYSTOLITHOTOMY	11	73%	0%	9%
	PROSTATECTOMY	11	73%	9%	0%
	ADRENALECTOMY	7	100%	0%	0%
	VASECTOMY	9	56%	0%	11%
	NEPHROLITHOTOMY	8	50%	0%	13%
	PERITONEAL CATHETER INSERTION	[redacted]	100%	0%	0%
	SURGERY FOR FEMALE INCONTINENCE	[redacted]	100%	0%	0%
	PROSTATECTOMY LAPAROSCOPIC	7	100%	0%	0%
	REPAIR PEYRONIE'S	7	57%	0%	0%
	DISSECTION LYMPH NODE PERITONEAL	[redacted]	100%	0%	0%
	DMSO/ BLADDER INSTILLATION	[redacted]	60%	0%	20%
	URETHROSCOPY/URETHROTOMY	[redacted]	100%	0%	0%
	CYSTECTOMY	[redacted]	100%	0%	0%
	SACRAL NERVE STIMULATION	[redacted]	100%	0%	0%
	EPIDIDYMECTOMY	[redacted]	100%	0%	0%
	ORCHIDECTOMY/SCROTECTOMY	[redacted]	67%	0%	0%
	OTHER	[redacted]	50%	0%	50%
	PROSTATE-BIOPSY	[redacted]	0%	33%	0%
	URETEROLITHOTOMY	[redacted]	100%	0%	0%
	URETHROPLASTY	[redacted]	100%	0%	0%
	VASECTOMY REVERSAL	[redacted]	100%	0%	0%
	EXPLORATION BODY PART GENERAL	[redacted]	50%	0%	0%
	REPAIR PHIMOSIS/PARAPHIMOSIS	[redacted]	50%	0%	50%
	SUPRAPUBIC CATHETER INSERTION	[redacted]	0%	0%	50%

Specialty	Booked Procedure	# cancellations	% cancellations now completed	% cancellations now scheduled	% cancellations now removed *
	DILATATION	[redacted]	0%	0%	0%
	NEPHROSTOMY/ILEOSTOMY TUBE PLACEMENT/REMOVAL	[redacted]	0%	0%	0%
	PENILE PROSTHESIS-INSERTION/REVISION	[redacted]	0%	0%	0%
	PYELOPLASTY	[redacted]	100%	0%	0%
	SPERMATOCELECTOMY	[redacted]	0%	0%	100%
	URETEROLYSIS	[redacted]	100%	0%	0%
	URETEROURETEROSTOMY/URETEROURECTOMY	[redacted]	100%	0%	0%
	VARICOCELECTOMY	[redacted]	100%	0%	0%
	Total	636	67%	2%	12%
General Surgery	CYSTOSCOPY	[redacted]	100%	0%	0%
	HERNIORRAPHY- INGUINAL/FEMORAL (GROIN)	109	64%	6%	10%
	LAPAROSCOPIC CHOLECYSTECTOMY	102	71%	2%	11%
	EXCISION OF CYST/GANGLION/LESION/LIPOMA	15	87%	0%	0%
	HERNIORRAPHY-UMBILICAL/ PARAUMBILICAL	49	55%	8%	6%
	EXCISION OF TUMOR	[redacted]	67%	0%	33%
	CIRCUMCISION	[redacted]	100%	0%	0%
	BOWEL RESECTION/REPAIR	22	77%	0%	9%
	THYROIDECTOMY	[redacted]	75%	25%	0%
	CARPAL TUNNEL RELEASE	[redacted]	100%	0%	0%
	HERNIORRAPHY- INCISIONAL	20	65%	0%	20%
	HYDROCELECTOMY	[redacted]	50%	0%	0%
	LAPAROSCOPIC HERNIORRAPHY- INGUINAL/ FEMORAL (GROIN)	18	56%	6%	17%
	MASTECTOMY	12	75%	0%	0%
	PACEMAKER INSERTION/EXPLOR/REMOVAL/W/WO REPLACEMENT LEAD OR BATTERY	7	43%	0%	29%
	DEBRIDEMENT	[redacted]	100%	0%	0%
	EXAM UNDER ANESTHESIA	8	50%	0%	25%
	CLOSURE COLOSTOMY/ILEOSTOMY	13	69%	8%	8%
	HEMORRHOIDECTOMY	13	54%	8%	0%
	NEPHRECTOMY	[redacted]	100%	0%	0%
	REGIONAL LYMPH NODE BIOPSY/ DISSECTION (HEAD AND NECK, ILIO INGUINAL, ETC.)	11	91%	0%	0%
	LAPAROSCOPIC HERNIORRAPHY- INCISIONAL	10	70%	0%	10%
	LIVER-LOBECTOMY	10	80%	0%	20%
	LUMPECTOMY BREAST WITH LOCALIZATION/ SENTINEL NODE/ AXILLARY DISSECTON	10	90%	0%	10%
	ADRENALECTOMY	[redacted]	0%	0%	50%
	AV FISTULA CREATION/REVISION/CLOSURE	[redacted]	0%	0%	0%
	BIOPSY	[redacted]	100%	0%	0%
	HERNIORRAPHY- VENTRAL/ EPIGASTRIC/SPIGELIAN (ABDOMINAL)	9	67%	0%	0%
	PERITONEAL CATHETER INSERTION	7	100%	0%	0%
	VARICOSE VEIN LIGATION/STRIPPING	8	75%	0%	25%
	DECOMPRESSION/TRANSPOSITION/EXPLORATION/REPAIR NERVE	[redacted]	0%	0%	100%
	LAPAROSCOPIC BOWEL RESECTION/ REPAIR	7	86%	0%	14%
	LUMPECTOMY (BREAST)	7	71%	14%	14%
	RECTAL BOWEL RESECTION/REPAIR	7	100%	0%	0%
	ABDOMINAL PERINEAL RESECTION	6	67%	0%	0%
	EXCISION OF MASS	[redacted]	75%	0%	25%
	DISSECTION LYMPH NODE PERITONEAL	[redacted]	100%	0%	0%
	LAPAROSCOPIC HERNIORRAPHY- UMBILICAL / PARAUMBILICAL	[redacted]	40%	0%	40%
	SUGARBAKER (PERITONECTOMY)	[redacted]	80%	0%	20%
	APPENDECTOMY	[redacted]	75%	0%	0%
	INSERTION/REMOVAL VASCULAR ACCESS CATHETER	[redacted]	75%	0%	25%

Specialty	Booked Procedure	# cancellations	% cancellations now completed	% cancellations now scheduled	% cancellations now removed *
	LAPAROSCOPIC HERNIORRAPHY- VENTRAL/EPIGASTRIC/ SPIGELIAN (ABDOMINAL)	[redacted]	100%	0%	0%
	LAPAROTOMY-EXPLORATORY	[redacted]	100%	0%	0%
	PANCREATECTOMY	[redacted]	100%	0%	0%
	PILONIDAL CYSTECTOMY	[redacted]	50%	0%	50%
	WEIGHT LOSS SURGERY (GASTRIC BYPASS, LAP BAND)	[redacted]	100%	0%	0%
	COLOSTOMY	[redacted]	67%	0%	33%
	ILEOSTOMY	[redacted]	100%	0%	0%
	LAPAROSCOPIC-NISSEN FUNDOPLICATION	[redacted]	50%	0%	0%
	WHIPPLE PROCEDURE	[redacted]	100%	0%	0%
	CHOLECYSTECTOMY-OPEN	[redacted]	100%	0%	0%
	COLONOSCOPY	[redacted]	100%	0%	0%
	FISTULOTOMY ANAL	[redacted]	50%	50%	0%
	LAPAROSCOPIC CLOSURE COLOSTOMY/ILEOSTOMY	[redacted]	100%	0%	0%
	POLYPECTOMY	[redacted]	100%	0%	0%
	REMOVAL WART (CONDOLYOMA)	[redacted]	100%	0%	0%
	SPHINCTEROTOMY	[redacted]	100%	0%	0%
	BLEEDING CONTROL/EVACUATION HEMATOMA	[redacted]	100%	0%	0%
	EXENTERATION AND RECONSTRUCTION	[redacted]	100%	0%	0%
	HERNIORRAPHY -DIAPHRAGMATIC /HIATAL/ PARAESOPHAGEAL (CHEST)	[redacted]	100%	0%	0%
	LAPAROSCOPIC SPLENECTOMY	[redacted]	100%	0%	0%
	RECONSTRUCTION ABDOMINAL WALL	[redacted]	100%	0%	0%
	RECTAL OR STOMA DILATION/REVISION	[redacted]	0%	0%	0%
	REPAIR RECTAL PROLAPSE	[redacted]	100%	0%	0%
	Total	576	70%	3%	10%
Orthopaedic	KNEE ARTHROPLASTY	143	74%	4%	6%
	HIP ARTHROPLASTY	80	79%	8%	5%
	KNEE ARTHROSCOPY	55	53%	0%	16%
	EXCISION OF CYST/GANGLION/LESION/LIPOMA	[redacted]	0%	0%	100%
	SHOULDER ARTHROSCOPY	52	60%	0%	10%
	EXCISION OF TUMOR	[redacted]	50%	0%	25%
	HARDWARE REMOVAL	18	67%	6%	11%
	REPAIR/RECONSTRUCTION LIGAMENT/TENDON/MUSCLE/FASCIA	8	63%	0%	13%
	SPINE: LUMBAR DISCECTOMY	6	100%	0%	0%
	CARPAL TUNNEL RELEASE	[redacted]	100%	0%	0%
	KNEE ARTHROPLASTY PARTIAL	17	65%	12%	0%
	HIP ARTHROSCOPY	15	87%	0%	0%
	FOOT/TOE ARTHRODESIS (FUSION)	14	86%	0%	0%
	SHOULDER ARTHROPLASTY	13	77%	0%	0%
	HAND/FINGER ARTHROPLASTY	[redacted]	100%	0%	0%
	KNEE ACL RECONSTRUCTION	11	55%	0%	9%
	HAND/WRIST ARTHRODESIS (FUSION)	9	56%	0%	0%
	BIOPSY	7	43%	0%	0%
	ARTHROPLASTY HIP REVISION	8	75%	0%	0%
	DECOMPRESSION/TRANSPOSITION/EXPLORATION/REPAIR NERVE	[redacted]	100%	0%	0%
	KNEE ARTHROPLASTY REVISION	6	67%	0%	17%
	SPINE: CERVICAL FUSION ANTERIOR	[redacted]	100%	0%	0%
	SPINE: FUSION WITH INSTRUMENTATION	6	50%	0%	33%
	SPINE: LAMINECTOMY/DISCECTOMY/DECOMPRESSION	6	100%	0%	0%
	EXCISION BONE/EXOSTOSIS	[redacted]	80%	0%	0%
	AMPUTATION	[redacted]	100%	0%	0%

Specialty	Booked Procedure	# cancellations	% cancellations now completed	% cancellations now scheduled	% cancellations now removed *
	BUNIONECTOMY	[redacted]	50%	0%	25%
	OPEN REDUCTION INTERNAL FIXATION FRACTURE (ORIF)	[redacted]	100%	0%	0%
	SHOULDER ARTHROTOMY	[redacted]	75%	0%	25%
	ANKLE ARTHROPLASTY	[redacted]	67%	0%	33%
	ANKLE ARTHROSCOPY	[redacted]	100%	0%	0%
	FOOT ARTHROPLASTY	[redacted]	33%	0%	67%
	ANKLE ARTHRODESIS (FUSION)	[redacted]	100%	0%	0%
	ANKLE OSTEOTOMY	[redacted]	100%	0%	0%
	DISCECTOMY/LAMINECTOMY W/WO FUSION/STABILIZATION	[redacted]	100%	0%	0%
	FASCIOTOMY UPPER EXTREMITY	[redacted]	0%	0%	0%
	LEG: IM NAILING	[redacted]	100%	0%	0%
	ORTHO BIOPSY	[redacted]	50%	0%	0%
	REMOVAL WART (CONDOLYOMA)	[redacted]	0%	0%	0%
	ELBOW ARTHROTOMY	[redacted]	100%	0%	0%
	EXCISION-MORTON'S NEUROMA	[redacted]	0%	0%	0%
	HALLUX RELEASE	[redacted]	100%	0%	0%
	INCISION & DRAINAGE	[redacted]	0%	0%	100%
	MANIPULATION EXTREMITY	[redacted]	0%	0%	100%
	OSTEOTOMY UPPER EXTREMITY	[redacted]	100%	0%	0%
	SHOULDER ARTHROPLASTY PARTIAL	[redacted]	100%	0%	0%
	Unknown Procedure	[redacted]	100%	0%	0%
	WRIST ARTHROSCOPY	[redacted]	0%	0%	0%
	Total	535	70%	3%	8%
Obstetrics/Gynaecology	HYSTERECTOMY (All Types)	78	79%	0%	10%
	CESAREAN SECTION WITH OR WITHOUT TUBAL LIGATION	52	79%	0%	17%
	OPERATIVE HYSTEROSCOPY	47	89%	2%	4%
	OOPHORECTOMY/SALPINGECTOMY	21	67%	0%	10%
	EXCISION/BIOPSY LESION CERVIX	19	58%	0%	21%
	TUBAL LIGATION	15	60%	13%	7%
	ABLATION ENDOMETRIAL	12	83%	0%	17%
	REGIONAL LYMPH NODE BIOPSY/ DISSECTION (HEAD AND NECK, ILIO INGUINAL, ETC.)	[redacted]	100%	0%	0%
	EXCISION VULVAR LESION (SKINNING/WIDE LOCAL EXCISION	9	78%	0%	0%
	OPERATIVE LAPAROSCOPIC	9	78%	11%	0%
	PELVIC FLOOR REPAIR SURGERY	8	50%	13%	25%
	SURGERY FOR FEMALE INCONTINENCE	6	83%	0%	0%
	D&C	6	67%	17%	0%
	OVARIAN CYSTECTOMY	6	33%	0%	50%
	LAPAROSCOPY-DIAGNOSTIC	[redacted]	25%	0%	75%
	LAPAROTOMY-EXPLORATORY	[redacted]	100%	0%	0%
	INSERTION/REMOVAL IUD	[redacted]	33%	0%	67%
	VULVECTOMY	[redacted]	0%	0%	33%
	CAUTERY	[redacted]	100%	0%	0%
	LAPAROSCOPY CYST DRAINAGE/LYSIS ADHESIONS	[redacted]	100%	0%	0%
	THERAPEUTIC ABORTION	[redacted]	100%	0%	0%
	Total	303	74%	2%	13%
Otolaryngology (ENT)	EXCISION OF CYST/GANGLION/LESION/LIPOMA	10	100%	0%	0%
	MAXILLOFACIAL DEFORMITIES	[redacted]	100%	0%	0%
	EXCISION OF TUMOR	[redacted]	0%	0%	100%
	THYROIDECTOMY	18	78%	0%	6%
	SEPTOPLASTY	18	83%	6%	0%

Specialty	Booked Procedure	# cancellations	% cancellations now completed	% cancellations now scheduled	% cancellations now removed *
	FUNCTIONAL ENDOSCOPIC SINUS SURGERY (FESS)	16	63%	13%	6%
	DEBRIDEMENT	[redacted]	100%	0%	0%
	EXAM UNDER ANESTHESIA	[redacted]	60%	0%	40%
	LARYNGOSCOPY WITH TREATMENT	14	86%	0%	0%
	MYRINGOTOMY WITH TUBES	14	50%	14%	7%
	PARATHYROIDECTOMY	14	86%	0%	7%
	BIOPSY	[redacted]	100%	0%	0%
	TONSILLECTOMY AND ADENOIDECTOMY	9	78%	0%	11%
	TYMPANOMASTOIDECTOMY/MASTOIDECTOMY (ALL TYPES)	8	100%	0%	0%
	EXCISION OF MASS	[redacted]	50%	0%	50%
	SEPTOPLASTY AND FUNCTIONAL ENDOSCOPIC SINUS SURGERY(FESS)	6	67%	17%	17%
	TONSILLECTOMY	6	67%	0%	0%
	TUBOPLASTY/ TUBALPLASTY	6	100%	0%	0%
	ADENOIDECTOMY AND MYRINGOTOMY WITH TUBES	[redacted]	100%	0%	0%
	DIVERTICULECTOMY, MECKEL'S/ZENKER'S	[redacted]	100%	0%	0%
	EXCISION SUBMANDIBULAR/SUBLINGUAL GLAND	[redacted]	20%	0%	60%
	COCHLEAR IMPLANTATION OR REMOVAL	[redacted]	100%	0%	0%
	LARYNGECTOMY	[redacted]	50%	0%	50%
	NECK DISSECTION (ANY TYPE)	[redacted]	67%	0%	0%
	TURBINECTOMY	[redacted]	100%	0%	0%
	GLOSSECTOMY	[redacted]	50%	0%	0%
	PAROTIDECTOMY	[redacted]	100%	0%	0%
	SEPTORHINOPLASTY	[redacted]	50%	0%	0%
	THYROGLOSSAL DUCT CYST EXCISION	[redacted]	50%	0%	50%
	TYMPANOPLASTY (W/WO GRAFTING, CANALPLASTY, OSSICULOPLASTY)	[redacted]	100%	0%	0%
	VOCAL CORD AUGMENTATION	[redacted]	100%	0%	0%
	ADENOIDECTOMY	[redacted]	0%	100%	0%
	ESOPHAGOSCOPY	[redacted]	100%	0%	0%
	FACE: HYPOGLOSSAL FACIAL NERVE ANAS.N	[redacted]	100%	0%	0%
	INTUBATION/EXTUBATION	[redacted]	100%	0%	0%
	LARYNGOSCOPY	[redacted]	100%	0%	0%
	PANAENDOSCOPY	[redacted]	100%	0%	0%
	SEPTAL FLAP/PERFORATION REPAIR OR CLOSURE	[redacted]	100%	0%	0%
	TRACHEAL RESECTION/RECONSTRUCTION/TRACHEOPLASTY	[redacted]	0%	0%	100%
	UVULOPALATOPHARYNGOPLASTY	[redacted]	100%	0%	0%
	Total	203	76%	3%	9%
Plastic Surgery	EXCISION OF CYST/GANGLION/LESION/LIPOMA	20	45%	0%	45%
	EXCISION OF TUMOR	14	86%	0%	0%
	BREAST REDUCTION MAMMOPLASTY	22	73%	0%	9%
	REPAIR/RECONSTRUCTION LIGAMENT/TENDON/MUSCLE/FASCIA	14	71%	0%	0%
	SEPTOPLASTY	[redacted]	67%	0%	33%
	CARPAL TUNNEL RELEASE	15	40%	13%	20%
	MASTECTOMY	6	83%	0%	0%
	EXCISION DUPUYTREN'S CONTRACTURE(PALMAR FASCIA)	17	65%	0%	12%
	DEBRIDEMENT	10	70%	0%	0%
	HAND/FINGER ARTHROPLASTY	10	60%	0%	0%
	HAND/WRIST ARTHRODESIS (FUSION)	[redacted]	0%	0%	0%
	EXCISION MELANOMA	9	89%	0%	11%
	DECOMPRESSION/TRANSPOSITION/EXPLORATION/REPAIR NERVE	[redacted]	75%	0%	0%
	ABDOMINOPLASTY	[redacted]	60%	0%	0%

Specialty	Booked Procedure	# cancellations	% cancellations now completed	% cancellations now scheduled	% cancellations now removed *
	RECONSTRUCTION BREAST W/ WO TISSUE EXPANDER	[redacted]	60%	0%	20%
	INSERTION BREAST/SCALP TISSUE EXPANDER	[redacted]	100%	0%	0%
	OPEN REDUCTION INTERNAL FIXATION FRACTURE (ORIF)	[redacted]	100%	0%	0%
	RECONSTRUCTION BREAST FLAP	[redacted]	50%	25%	0%
	REMOVAL BREAST IMPLANT	[redacted]	100%	0%	0%
	BLEPHAROPLASTY	[redacted]	50%	0%	0%
	CLOSURE OF WOUNDS	[redacted]	50%	0%	0%
	FASCIOTOMY UPPER EXTREMITY	[redacted]	0%	0%	0%
	MASTECTOMY WITH BREAST RECONSTRUCTION	[redacted]	50%	0%	0%
	SKIN GRAFT	[redacted]	0%	0%	100%
	FACELIFT/LIFT	[redacted]	0%	100%	0%
	REPAIR ECTROPIAN/ENTROPIAN	[redacted]	0%	0%	0%
	RHINOPLASTY	[redacted]	0%	0%	0%
	Total	179	64%	2%	12%
Cardiac Surgery	CORONARY ARTERY BYPASS GRAFT WITHOUT VALVES	67	64%	0%	24%
	VALVE REPLACEMENT/REPAIR	35	83%	0%	14%
	HARDWARE REMOVAL	[redacted]	0%	0%	100%
	PACEMAKER INSERTION/EXPLOR/REMOVAL/W/WO REPLACEMENT LEAD OR BATTERY	9	44%	0%	33%
	REPAIR ANEURYSM	[redacted]	33%	0%	0%
	ENDOVASCULAR AORTIC ANEURYSM REPAIR (EVAR)	[redacted]	0%	0%	100%
	CORONARY ARTERY BYPASS GRAFT WITH VALVES	7	71%	0%	0%
	AORTIC SURGERY ASCENDING	[redacted]	40%	0%	0%
	CORONARY ARTERY BYPASS GRAFT WITH VALVES, REPEAT	[redacted]	75%	0%	25%
	OPEN REDUCTION INTERNAL FIXATION FRACTURE (ORIF)	[redacted]	100%	0%	0%
	INSERTION OF DEFIBRILLATOR	[redacted]	33%	0%	67%
	CONGENITAL HEART DEFECT SURGERY	[redacted]	100%	0%	0%
	Total	139	65%	0%	22%
Oral Maxillofacial	DENTAL RESTORATIONS	22	77%	0%	9%
	EXCISION OF CYST/GANGLION/LESION/LIPOMA	[redacted]	100%	0%	0%
	MAXILLOFACIAL DEFORMITIES	45	84%	7%	4%
	DENTOALVEOLAR SURGERY (EXTRACTIONS, APICOECTOMY)	31	26%	16%	3%
	TEMPEROMANDIBULAR JOINT	25	56%	8%	16%
	HARDWARE REMOVAL	[redacted]	100%	0%	0%
	DEBRIDEMENT	[redacted]	100%	0%	0%
	BONE/ CARTILAGE GRAFT	[redacted]	0%	50%	0%
	OTHER	[redacted]	0%	100%	0%
	GINGIVOPLASTY/STOMATOPLASTY	[redacted]	100%	0%	0%
	ORO-ANTRAL FISTULA REPAIR	[redacted]	0%	0%	0%
	Total	138	62%	9%	7%
Vascular Surgery	VEIN STRIPPING/LIGATION (NOT VARICOSE)	12	33%	42%	0%
	ANGIOPLASTY	11	36%	0%	45%
	AV FISTULA CREATION/REVISION/CLOSURE	8	63%	0%	25%
	REPAIR ANEURYSM	6	83%	0%	17%
	ENDOVASCULAR AORTIC ANEURYSM REPAIR (EVAR)	7	71%	14%	0%
	BYPASS GRAFT	[redacted]	80%	0%	0%
	AMPUTATION	[redacted]	100%	0%	0%
	ENDARTERECTOMY	[redacted]	75%	0%	25%
	VEIN HARVESTING	[redacted]	33%	0%	0%
	ENDARTERECTOMY CAROTID	[redacted]	50%	0%	50%
	Total	61	57%	10%	16%

Specialty	Booked Procedure	# cancellations	% cancellations now completed	% cancellations now scheduled	% cancellations now removed *
Neurosurgery	SPINE: LUMBAR DISCECTOMY	15	80%	0%	7%
	SPINE: CERVICAL FUSION ANTERIOR	[redacted]	100%	0%	0%
	SPINE: FUSION	6	83%	0%	0%
	HEAD: DEEP BRAIN STIM REPLACE PULSE GEN	[redacted]	100%	0%	0%
	HEAD TUMOUR BIOPSY	[redacted]	100%	0%	0%
	HEAD: CRANIOTOMY	[redacted]	100%	0%	0%
	HEAD: CRANIOTOMY FOR ANEURYSM	[redacted]	100%	0%	0%
	HEAD: CRANIOTOMY FOR TUMOR	[redacted]	100%	0%	0%
	SPINE: CERVICAL LAMINECTOMY	[redacted]	67%	0%	33%
	Embolization	[redacted]	50%	0%	0%
	HEAD: TRIGEMINAL NERVE COMPRESSION	[redacted]	100%	0%	0%
	HEAD: CRANIOPLASTY	[redacted]	100%	0%	0%
	HEAD: STEREOTACTIC SURGERY	[redacted]	0%	0%	0%
	SPINE: CERVICAL ORIF WITH INSTRUMENTATON	[redacted]	0%	0%	0%
	SPINE: INSERT BACLOFEN/INTRATHECAL PUMP	[redacted]	100%	0%	0%
	SPINE: INSERT/REMOVE SPINE STIMULATOR	[redacted]	100%	0%	0%
	SPINE: REMOVAL BACLOFEN/INTRATHECAL PUMP	[redacted]	100%	0%	0%
	SPINE: SPINAL CORD TUMOUR EXCISION	[redacted]	100%	0%	0%
	Total	57	86%	0%	4%
Thoracic Surgery	EXCISION OF CYST/GANGLION/LESION/LIPOMA	[redacted]	100%	0%	0%
	VATS APICAL RESECTION	24	83%	0%	8%
	THORACOSCOPY/PLEUROSCOPY	[redacted]	80%	0%	20%
	LAPAROTOMY-EXPLORATORY	[redacted]	100%	0%	0%
	LAPAROSCOPIC-NISSEN FUNDOPLICATION	[redacted]	0%	0%	0%
	LOBECTOMY	[redacted]	67%	0%	33%
	ESOPHAGOTOMY	[redacted]	100%	0%	0%
	THYMECTOMY	[redacted]	100%	0%	0%
	ESOPHAGECTOMY	[redacted]	100%	0%	0%
	GASTRECTOMY	[redacted]	100%	0%	0%
	STERNOTOMY/THORACOTOMY	[redacted]	100%	0%	0%
	Total	42	83%	0%	10%
Dental	DENTAL RESTORATIONS	35	46%	11%	6%
	EXAM UNDER ANESTHESIA	[redacted]	0%	0%	0%
	Total	36	44%	11%	6%
Anesthesia	BLOCK	[redacted]	0%	0%	0%
	Total	[redacted]	0%	0%	0%
Grand Total		3 571	71%	3%	10%

- *the costs of all of the equipment, materials and test kits used (swabs, test tubes, and anything necessary to facilitate a COVID-19 test)*

FOIPOP Request -January - October 2020

Lab Equipment for COVID Testing	$1,143,202.96
Information Technology (IT) Equipment/Material Costs (ie equipment, computer leases and software fees)	$251,335.00
Testing Centres (supplies and equipment)	$928,686.00

Prepared by Finance in consultation with Laboratory Services and IT
Updated: 24 November 2020

Privacy Office
Legal Services
Centennial 1-031
1276 South Park Street
Halifax NS B3H 2Y9
Telephone: (902)473-2869
Fax: (902)473-7850

December 23, 2020

Re: Partial Access – OUR FILE# NSHA-2020-69

On 2020/11/27 Nova Scotia Health received your request under the Freedom of Information and Protection of Privacy (FOIPOP) Act for a copy of the following:

Please provide data on the number of patients that died while on a waiting list for a surgical procedure in fiscal year 2019-20. Please break the data out by procedure and case info - date the patient was referred to a specialist, decision date, date for the procedure and date of cancellation. Please also note the government's target time for providing the procedure in question. (Note: many hospitals/health regions were able to identify such cases as they track the reason for cancelled operations)

Attached / Enclosed, please find a copy of the records located in response to your request. Please kindly note that we have withheld the dates requested in your request due to the possibility of identification of patients. Portions of these records have been withheld pursuant to sections 20 (personal information) of the FOIPOP Act.

In relation to your request for:

Please provide data on the number of patients that died while on a waiting list for either a diagnostic scan or a consultation with a specialist in fiscal year 2019-20. Please break the data out by procedure and case info- date the patient went on the waiting list, date for the meeting with the specialist or date for diagnostic scan (if scheduled), and date of cancellation. Please also note the government's target time for providing the meeting or scan in question. (Note: many hospitals/health regions were able to identify such cases as they track the reason for cancelled operations)

Please kindly note that we have no dataset that captures this kind of information. We are now closing your application with our office.

Should you have any questions or comments, please do not hesitate to contact me at the address or telephone number provided above.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review

Sincerely,
Fola Adeleke

For: The Privacy Office
Nova Scotia Health Authority

c/c: to file

Priority	Target Wait In Days	Number of Days Waiting	Days Past Target	Procedure
V - Within 26 weeks	182	978	-796	ABDOMINAL PERINEAL RESECTION
V - Within 26 weeks	182	390	-208	AMPUTATION
IIa - Within 7 days	7	21	-14	AMPUTATION
IV - Within 13 weeks	91	16	75	ANGIOPLASTY
V - Within 26 weeks	182	850	-668	ARTHROPLASTY HIP REVISION
V - Within 26 weeks	182	1609	-1427	ARTHROPLASTY HIP REVISION
III - Within 6 weeks	42	72	-30	AV FISTULA CREATION/REVISION/CLOSURE
III - Within 6 weeks	42	522	-480	AV FISTULA CREATION/REVISION/CLOSURE
IIa - Within 7 days	7	316	-309	AV FISTULA CREATION/REVISION/CLOSURE
IIb - Within 3 weeks	21	1214	-1193	BIOPSY
III - Within 6 weeks	42	39	3	BOWEL RESECTION/REPAIR
III - Within 6 weeks	42	110	-68	BOWEL RESECTION/REPAIR
IIa - Within 7 days	7	54	-47	BYPASS GRAFT
IV - Within 13 weeks	91	590	-499	CATARACT EXTRACTION
IV - Within 13 weeks	91	590	-499	CATARACT EXTRACTION
IV - Within 13 weeks	91	548	-457	CATARACT EXTRACTION
IV - Within 13 weeks	91	244	-153	CATARACT EXTRACTION
IV - Within 13 weeks	91	244	-153	CATARACT EXTRACTION
IV - Within 13 weeks	91	548	-457	CATARACT EXTRACTION
IV - Within 13 weeks	91	539	-448	CATARACT EXTRACTION
IV - Within 13 weeks	91	539	-448	CATARACT EXTRACTION
V - Within 26 weeks	182	981	-799	CATARACT EXTRACTION
IV - Within 13 weeks	91	954	-863	CATARACT EXTRACTION
IV - Within 13 weeks	91	121	-30	CATARACT EXTRACTION
IV - Within 13 weeks	91	121	-30	CATARACT EXTRACTION
IV - Within 13 weeks	91	86	5	CATARACT EXTRACTION
IV - Within 13 weeks	91	86	5	CATARACT EXTRACTION
IV - Within 13 weeks	91	493	-402	CATARACT EXTRACTION
IV - Within 13 weeks	91	493	-402	CATARACT EXTRACTION
IV - Within 13 weeks	91	558	-467	CATARACT EXTRACTION
IV - Within 13 weeks	91	558	-467	CATARACT EXTRACTION
III - Within 6 weeks	42	233	-191	CATARACT EXTRACTION
IV - Within 13 weeks	91	144	-53	CATARACT EXTRACTION
IV - Within 13 weeks	91	144	-53	CATARACT EXTRACTION
IV - Within 13 weeks	91	344	-253	CATARACT EXTRACTION
IV - Within 13 weeks	91	1120	-1029	CATARACT EXTRACTION
IV - Within 13 weeks	91	84	7	CATARACT EXTRACTION
IV - Within 13 weeks	91	84	7	CATARACT EXTRACTION
IV - Within 13 weeks	91	270	-179	CATARACT EXTRACTION
IV - Within 13 weeks	91	270	-179	CATARACT EXTRACTION
V - Within 26 weeks	182	155	27	CATARACT EXTRACTION

Priority	Target Wait In Days	Number of Days Waiting	Days Past Target	Procedure
IV - Within 13 weeks	91	326	-235	CATARACT EXTRACTION
IV - Within 13 weeks	91	25	66	CATARACT EXTRACTION
IV - Within 13 weeks	91	25	66	CATARACT EXTRACTION
V - Within 26 weeks	182	454	-272	CATARACT EXTRACTION
V - Within 26 weeks	182	454	-272	CATARACT EXTRACTION
IV - Within 13 weeks	91	46	45	CATARACT EXTRACTION
IV - Within 13 weeks	91	46	45	CATARACT EXTRACTION
VI - Within 52 weeks	365	107	258	CATARACT EXTRACTION
IV - Within 13 weeks	91	29	62	CATARACT EXTRACTION
IV - Within 13 weeks	91	29	62	CATARACT EXTRACTION
V - Within 26 weeks	182	11	171	CATARACT EXTRACTION
V - Within 26 weeks	182	11	171	CATARACT EXTRACTION
V - Within 26 weeks	182	131	51	CATARACT EXTRACTION
V - Within 26 weeks	182	131	51	CATARACT EXTRACTION
V - Within 26 weeks	182	20	162	CATARACT EXTRACTION
V - Within 26 weeks	182	20	162	CATARACT EXTRACTION
VI - Within 52 weeks	365	53	312	CATARACT EXTRACTION
IV - Within 13 weeks	91	216	-125	CATARACT EXTRACTION
IV - Within 13 weeks	91	304	-213	CATARACT EXTRACTION
IV - Within 13 weeks	91	1203	-1112	CATARACT EXTRACTION
VI - Within 52 weeks	365	191	174	CATARACT EXTRACTION
V - Within 26 weeks	182	109	73	CATARACT EXTRACTION
V - Within 26 weeks	182	109	73	CATARACT EXTRACTION
IV - Within 13 weeks	91	235	-144	CATARACT EXTRACTION
IV - Within 13 weeks	91	235	-144	CATARACT EXTRACTION
IV - Within 13 weeks	91	23	68	CATARACT EXTRACTION
IV - Within 13 weeks	91	768	-677	CATARACT EXTRACTION
IV - Within 13 weeks	91	48	43	CATARACT EXTRACTION
IV - Within 13 weeks	91	1537	-1446	CATARACT EXTRACTION
IV - Within 13 weeks	91	258	-167	CATARACT EXTRACTION
IV - Within 13 weeks	91	258	-167	CATARACT EXTRACTION
IV - Within 13 weeks	91	106	-15	CATARACT EXTRACTION
IV - Within 13 weeks	91	106	-15	CATARACT EXTRACTION
IV - Within 13 weeks	91	21	70	CATARACT EXTRACTION
IV - Within 13 weeks	91	21	70	CATARACT EXTRACTION
IV - Within 13 weeks	91	148	-57	CATARACT EXTRACTION
IV - Within 13 weeks	91	148	-57	CATARACT EXTRACTION
IV - Within 13 weeks	91	143	-52	CATARACT EXTRACTION
IV - Within 13 weeks	91	143	-52	CATARACT EXTRACTION
IV - Within 13 weeks	91	234	-143	CATARACT EXTRACTION
IV - Within 13 weeks	91	1306	-1215	CATARACT EXTRACTION
IV - Within 13 weeks	91	1306	-1215	CATARACT EXTRACTION
IV - Within 13 weeks	91	935	-844	CATARACT EXTRACTION
IV - Within 13 weeks	91	34	57	CATARACT EXTRACTION

Priority	Target Wait In Days	Number of Days Waiting	Days Past Target	Procedure
V - Within 26 weeks	182	56	126	CATARACT EXTRACTION
V - Within 26 weeks	182	56	126	CATARACT EXTRACTION
IV - Within 13 weeks	91	119	-28	CATARACT EXTRACTION
IV - Within 13 weeks	91	110	-19	CATARACT EXTRACTION
IV - Within 13 weeks	91	110	-19	CATARACT EXTRACTION
III - Within 6 weeks	42	37	5	CATARACT EXTRACTION
V - Within 26 weeks	182	34	148	CATARACT EXTRACTION
V - Within 26 weeks	182	34	148	CATARACT EXTRACTION
IV - Within 13 weeks	91	295	-204	CATARACT EXTRACTION
IV - Within 13 weeks	91	295	-204	CATARACT EXTRACTION
IV - Within 13 weeks	91	19	72	CATARACT EXTRACTION
IV - Within 13 weeks	91	19	72	CATARACT EXTRACTION
IV - Within 13 weeks	91	151	-60	CATARACT EXTRACTION
VI - Within 52 weeks	365	-164	529	CATARACT EXTRACTION
IV - Within 13 weeks	91	219	-128	CATARACT EXTRACTION
IV - Within 13 weeks	91	219	-128	CATARACT EXTRACTION
IV - Within 13 weeks	91	456	-365	CATARACT EXTRACTION
IV - Within 13 weeks	91	289	-198	CATARACT EXTRACTION
IV - Within 13 weeks	91	289	-198	CATARACT EXTRACTION
IV - Within 13 weeks	91	53	38	CATARACT EXTRACTION
IV - Within 13 weeks	91	53	38	CATARACT EXTRACTION
IV - Within 13 weeks	91	64	27	CATARACT EXTRACTION
IV - Within 13 weeks	91	64	27	CATARACT EXTRACTION
IV - Within 13 weeks	91	1215	-1124	CATARACT EXTRACTION
III - Within 6 weeks	42	84	-42	CATARACT EXTRACTION
IV - Within 13 weeks	91	877	-786	CATARACT EXTRACTION
IV - Within 13 weeks	91	241	-150	CATARACT EXTRACTION
V - Within 26 weeks	182	467	-285	CATARACT EXTRACTION
VI - Within 52 weeks	365	53	312	CATARACT EXTRACTION
V - Within 26 weeks	182	1039	-857	CATARACT EXTRACTION
V - Within 26 weeks	182	1039	-857	CATARACT EXTRACTION
IV - Within 13 weeks	91	12	79	CATARACT EXTRACTION
IV - Within 13 weeks	91	139	-48	CATARACT EXTRACTION
IV - Within 13 weeks	91	139	-48	CATARACT EXTRACTION
IV - Within 13 weeks	91	613	-522	CATARACT EXTRACTION
IV - Within 13 weeks	91	613	-522	CATARACT EXTRACTION
V - Within 26 weeks	182	187	-5	CATARACT EXTRACTION
V - Within 26 weeks	182	187	-5	CATARACT EXTRACTION
IV - Within 13 weeks	91	248	-157	CATARACT EXTRACTION
VI - Within 52 weeks	365	212	153	CATARACT EXTRACTION
IV - Within 13 weeks	91	41	50	CATARACT EXTRACTION
IV - Within 13 weeks	91	18	73	CATARACT EXTRACTION
IV - Within 13 weeks	91	257	-166	CATARACT EXTRACTION
IV - Within 13 weeks	91	257	-166	CATARACT EXTRACTION

Priority	Target Wait In Days	Number of Days Waiting	Days Past Target	Procedure
V - Within 26 weeks	182	104	78	CATARACT EXTRACTION
V - Within 26 weeks	182	104	78	CATARACT EXTRACTION
IV - Within 13 weeks	91	95	-4	CATARACT EXTRACTION
IV - Within 13 weeks	91	346	-255	CATARACT EXTRACTION
IV - Within 13 weeks	91	346	-255	CATARACT EXTRACTION
IV - Within 13 weeks	91	408	-317	CATARACT EXTRACTION
VI - Within 52 weeks	365	422	-57	CATARACT EXTRACTION
IV - Within 13 weeks	91	199	-108	CATARACT EXTRACTION
IV - Within 13 weeks	91	447	-356	CATARACT EXTRACTION
IV - Within 13 weeks	91	157	-66	CATARACT EXTRACTION
IV - Within 13 weeks	91	157	-66	CATARACT EXTRACTION
IV - Within 13 weeks	91	421	-330	CATARACT EXTRACTION
IV - Within 13 weeks	91	421	-330	CATARACT EXTRACTION
IV - Within 13 weeks	91	1395	-1304	CATARACT EXTRACTION
IV - Within 13 weeks	91	399	-308	CATARACT EXTRACTION
IV - Within 13 weeks	91	399	-308	CATARACT EXTRACTION
IV - Within 13 weeks	91	260	-169	CATARACT EXTRACTION
IV - Within 13 weeks	91	260	-169	CATARACT EXTRACTION
VI - Within 52 weeks	365	179	186	CATARACT EXTRACTION
IV - Within 13 weeks	91	31	60	CATARACT EXTRACTION
VI - Within 52 weeks	365	198	167	CATARACT EXTRACTION
IV - Within 13 weeks	91	1333	-1242	CATARACT EXTRACTION
V - Within 26 weeks	182	58	124	CATARACT EXTRACTION
V - Within 26 weeks	182	58	124	CATARACT EXTRACTION
V - Within 26 weeks	182	217	-109	CATARACT EXTRACTION
V - Within 26 weeks	182	217	-109	CATARACT EXTRACTION
IV - Within 13 weeks	91	1292	-1201	CATARACT EXTRACTION
V - Within 26 weeks	182	169	13	CATARACT EXTRACTION
IV - Within 13 weeks	91	112	-21	CATARACT EXTRACTION
IV - Within 13 weeks	91	456	-365	CATARACT EXTRACTION
IV - Within 13 weeks	91	145	-54	CATARACT EXTRACTION
IV - Within 13 weeks	91	145	-54	CATARACT EXTRACTION
IV - Within 13 weeks	91	74	17	CATARACT EXTRACTION
IV - Within 13 weeks	91	74	17	CATARACT EXTRACTION
IV - Within 13 weeks	91	158	-67	CATARACT EXTRACTION
IV - Within 13 weeks	91	158	-67	CATARACT EXTRACTION
IV - Within 13 weeks	91	68	23	CATARACT EXTRACTION
V - Within 26 weeks	182	99	83	CATARACT EXTRACTION
IV - Within 13 weeks	91	124	-33	CATARACT EXTRACTION
IV - Within 13 weeks	91	124	-33	CATARACT EXTRACTION
VI - Within 52 weeks	365	265	100	CATARACT EXTRACTION
IV - Within 13 weeks	91	439	-348	CATARACT EXTRACTION
VI - Within 52 weeks	365	899	-534	CATARACT EXTRACTION
IV - Within 13 weeks	91	20	71	CATARACT EXTRACTION

Priority	Target Wait In Days	Number of Days Waiting	Days Past Target	Procedure
III - Within 6 weeks	42	154	-112	CIRCUMCISION
V - Within 26 weeks	182	555	-373	CIRCUMCISION
V - Within 26 weeks	182	104	78	CLOSURE COLOSTOMY/ILEOSTOMY
VI - Within 52 weeks	365	269	96	COCHLEAR IMPLANTATION OR REMOVAL
IIb - Within 3 weeks	21	379	-358	CYSTECTOMY
IIb - Within 3 weeks	21	24	-3	CYSTECTOMY
III - Within 6 weeks	42	46	-4	CYSTOLITHOPAXY/ CYSTOLITHOTOMY
NULL	NULL	1070	NULL	CYSTOSCOPY
NULL	NULL	740	NULL	CYSTOSCOPY
NULL	NULL	574	NULL	CYSTOSCOPY
NULL	NULL	1221	NULL	CYSTOSCOPY
NULL	NULL	1137	NULL	CYSTOSCOPY
NULL	NULL	731	NULL	CYSTOSCOPY
NULL	NULL	689	NULL	CYSTOSCOPY
IV - Within 13 weeks	91	112	-21	CYSTOSCOPY
IV - Within 13 weeks	91	132	-41	CYSTOSCOPY
IV - Within 13 weeks	91	1593	-1502	CYSTOSCOPY
NULL	NULL	1780	NULL	CYSTOSCOPY
NULL	NULL	1599	NULL	CYSTOSCOPY
NULL	NULL	1522	NULL	CYSTOSCOPY
IV - Within 13 weeks	91	281	-190	CYSTOSCOPY
IIb - Within 3 weeks	21	55	-34	CYSTOSCOPY
V - Within 26 weeks	182	131	51	CYSTOSCOPY
NULL	NULL	182	NULL	CYSTOSCOPY
NULL	NULL	934	NULL	CYSTOSCOPY
III - Within 6 weeks	42	348	-306	CYSTOSCOPY
IV - Within 13 weeks	91	15	76	CYSTOSCOPY
IIb - Within 3 weeks	21	84	-63	CYSTOSCOPY
IV - Within 13 weeks	91	258	-167	CYSTOSCOPY
NULL	NULL	477	NULL	CYSTOSCOPY
V - Within 26 weeks	182	532	-350	CYSTOSCOPY
V - Within 26 weeks	182	448	-266	CYSTOSCOPY
NULL	NULL	269	NULL	CYSTOSCOPY
NULL	NULL	22	NULL	CYSTOSCOPY
IV - Within 13 weeks	91	44	47	CYSTOSCOPY
IIb - Within 3 weeks	21	467	-446	CYSTOSCOPY
V - Within 26 weeks	182	150	32	CYSTOSCOPY
VI - Within 52 weeks	365	44	321	CYSTOSCOPY
IIb - Within 3 weeks	21	74	-53	CYSTOSCOPY
NULL	NULL	65	NULL	CYSTOSCOPY
IV - Within 13 weeks	91	702	-611	CYSTOSCOPY
NULL	NULL	257	NULL	CYSTOSCOPY
IV - Within 13 weeks	91	202	-111	CYSTOSCOPY
IIb - Within 3 weeks	21	17	4	CYSTOSCOPY

Priority	Target Wait In Days	Number of Days Waiting	Days Past Target	Procedure
VI - Within 52 weeks	365	113	252	CYSTOSCOPY
NULL	NULL	538	NULL	CYSTOSCOPY
IV - Within 13 weeks	91	221	-130	CYSTOSCOPY
IV - Within 13 weeks	91	212	-121	CYSTOSCOPY
IV - Within 13 weeks	91	438	-347	CYSTOSCOPY
NULL	NULL	888	NULL	CYSTOSCOPY
IV - Within 13 weeks	91	37	54	CYSTOSCOPY
IIb - Within 3 weeks	21	24	-3	CYSTOSCOPY
V - Within 26 weeks	182	273	-91	CYSTOSCOPY
IV - Within 13 weeks	91	14	77	CYSTOSCOPY
VI - Within 52 weeks	365	306	59	CYSTOSCOPY
VI - Within 52 weeks	365	96	269	CYSTOSCOPY
V - Within 26 weeks	182	69	113	CYSTOSCOPY
IV - Within 13 weeks	91	49	42	CYSTOSCOPY
VI - Within 52 weeks	365	60	305	CYSTOSCOPY
IIb - Within 3 weeks	21	167	-146	CYSTOSCOPY
IV - Within 13 weeks	91	10	81	CYSTOSCOPY
IV - Within 13 weeks	91	97	-6	CYSTOSCOPY
IV - Within 13 weeks	91	86	5	CYSTOSCOPY
IV - Within 13 weeks	91	39	52	CYSTOSCOPY
IV - Within 13 weeks	91	53	38	CYSTOSCOPY
IV - Within 13 weeks	91	159	-68	CYSTOSCOPY
NULL	NULL	395	NULL	CYSTOSCOPY
IIb - Within 3 weeks	21	41	-20	CYSTOSCOPY
IV - Within 13 weeks	91	103	-12	CYSTOSCOPY
NULL	NULL	719	NULL	CYSTOSCOPY
IV - Within 13 weeks	91	59	32	CYSTOSCOPY
IV - Within 13 weeks	91	297	-206	CYSTOSCOPY
IV - Within 13 weeks	91	313	-222	CYSTOSCOPY
IIa - Within 7 days	7	2	5	CYSTOSCOPY
IIb - Within 3 weeks	21	93	-72	CYSTOSCOPY
III - Within 6 weeks	42	416	-374	CYSTOSCOPY
IIb - Within 3 weeks	21	50	-29	CYSTOSCOPY
NULL	NULL	702	NULL	CYSTOSCOPY
V - Within 26 weeks	182	286	-104	CYSTOSCOPY
VI - Within 52 weeks	365	473	-108	CYSTOSCOPY
V - Within 26 weeks	182	1274	-1092	CYSTOSCOPY
NULL	NULL	809	NULL	CYSTOSCOPY
V - Within 26 weeks	182	180	2	CYSTOSCOPY
IV - Within 13 weeks	91	54	37	CYSTOSCOPY
III - Within 6 weeks	42	89	-47	CYSTOSCOPY URETEROSCOPY
IIb - Within 3 weeks	21	153	-132	CYSTOSCOPY/TURB
III - Within 6 weeks	42	55	-13	CYSTOSCOPY/TURB
IIb - Within 3 weeks	21	68	-47	CYSTOSCOPY/TURB

Priority	Target Wait In Days	Number of Days Waiting	Days Past Target	Procedure
III - Within 6 weeks	42	63	-21	CYSTOSCOPY/TURB
III - Within 6 weeks	42	23	19	CYSTOSCOPY/TURB
III - Within 6 weeks	42	282	-240	CYSTOSCOPY/TURP
IV - Within 13 weeks	91	134	-43	CYSTOSCOPY/TURP
III - Within 6 weeks	42	94	-52	CYSTOSCOPY/TURP
III - Within 6 weeks	42	87	-45	CYSTOSCOPY/TURP
III - Within 6 weeks	42	141	-99	CYSTOSCOPY/TURP
V - Within 26 weeks	182	128	54	CYSTOSCOPY/TURP
VI - Within 52 weeks	365	87	278	CYSTOSCOPY/TURP
IV - Within 13 weeks	91	103	-12	DEBRIDEMENT
IIa - Within 7 days	7	93	-86	DEBRIDEMENT
IV - Within 13 weeks	91	591	-500	DENTOALVEOLAR SURGERY (EXTRACTIONS, APICOECTOMY)
IV - Within 13 weeks	91	219	-128	DENTOALVEOLAR SURGERY (EXTRACTIONS, APICOECTOMY)
IIa - Within 7 days	7	476	-469	DMSO/ BLADDER INSTILLATION
IIb - Within 3 weeks	21	12	9	ENDOVASCULAR AORTIC ANEURYSM REPAIR (EVAR)
IIb - Within 3 weeks	21	131	-110	ESOPHAGECTOMY
III - Within 6 weeks	42	38	4	EXCHANGE/ INSERTION INTRAOCULAR LENS
IIb - Within 3 weeks	21	56	-35	EXCISION MELANOMA
III - Within 6 weeks	42	555	-513	EXCISION OF CYST/GANGLION/LESION/LIPOMA
III - Within 6 weeks	42	181	-139	EXCISION OF CYST/GANGLION/LESION/LIPOMA
V - Within 26 weeks	182	25	157	EXCISION OF CYST/GANGLION/LESION/LIPOMA
IIb - Within 3 weeks	21	399	-378	EXCISION OF CYST/GANGLION/LESION/LIPOMA
IIb - Within 3 weeks	21	142	-121	EXCISION OF CYST/GANGLION/LESION/LIPOMA
IIb - Within 3 weeks	21	-6	27	EXCISION OF CYST/GANGLION/LESION/LIPOMA
III - Within 6 weeks	42	27	15	EXCISION OF CYST/GANGLION/LESION/LIPOMA
III - Within 6 weeks	42	17	25	EXCISION OF TUMOR
IV - Within 13 weeks	91	93	-2	FOREIGN BODY REMOVAL
VI - Within 52 weeks	365	367	-2	FUNCTIONAL ENDOSCOPIC SINUS SURGERY (FESS)
V - Within 26 weeks	182	26	156	FUNCTIONAL ENDOSCOPIC SINUS SURGERY (FESS)
IV - Within 13 weeks	91	116	-25	FUNCTIONAL ENDOSCOPIC SINUS SURGERY (FESS)

Priority	Target Wait In Days	Number of Days Waiting	Days Past Target	Procedure
V - Within 26 weeks	182	194	-12	HAND/FINGER ARTHROPLASTY
VI - Within 52 weeks	365	320	45	HAND/FINGER ARTHROPLASTY
V - Within 26 weeks	182	45	137	HEAD: CRANIOTOMY FOR ANEURYSM
VI - Within 52 weeks	365	692	-327	HERNIORRAPHY - PARASTOMAL
V - Within 26 weeks	182	187	-5	HERNIORRAPHY- INGUINAL/FEMORAL (GROIN)
IV - Within 13 weeks	91	609	-518	HERNIORRAPHY- INGUINAL/FEMORAL (GROIN)
III - Within 6 weeks	42	108	-66	HERNIORRAPHY- INGUINAL/FEMORAL (GROIN)
VI - Within 52 weeks	365	938	-573	HERNIORRAPHY- INGUINAL/FEMORAL (GROIN)
III - Within 6 weeks	42	160	-118	HERNIORRAPHY- INGUINAL/FEMORAL (GROIN)
V - Within 26 weeks	182	63	119	HERNIORRAPHY- INGUINAL/FEMORAL (GROIN)
V - Within 26 weeks	182	193	-11	HERNIORRAPHY-UMBILICAL/ PARAUMBILICAL
V - Within 26 weeks	182	442	-260	HIP ARTHROPLASTY
IV - Within 13 weeks	91	168	-77	HIP ARTHROPLASTY
VI - Within 52 weeks	365	1889	-1524	HIP ARTHROPLASTY
VI - Within 52 weeks	365	834	-469	HIP ARTHROPLASTY
VI - Within 52 weeks	365	556	-191	HIP ARTHROPLASTY
V - Within 26 weeks	182	102	80	HIP ARTHROPLASTY
IV - Within 13 weeks	91	56	35	HIP ARTHROPLASTY
VI - Within 52 weeks	365	549	-184	HIP ARTHROSCOPY
III - Within 6 weeks	42	15	27	HYDROCELECTOMY
IIa - Within 7 days	7	203	-196	INSERTION/REMOVAL VASCULAR ACCESS CATHETER
IIb - Within 3 weeks	21	53	-142	INSERTION/REMOVAL VASCULAR ACCESS CATHETER
IV - Within 13 weeks	91	742	-651	KERATOPLASTY/ CORNEAL TRANSPLANT
V - Within 26 weeks	182	83	99	KNEE ARTHROPLASTY
III - Within 6 weeks	42	304	-262	KNEE ARTHROPLASTY
V - Within 26 weeks	182	1311	-1129	KNEE ARTHROPLASTY
IV - Within 13 weeks	91	1147	-1056	KNEE ARTHROPLASTY
V - Within 26 weeks	182	59	123	KNEE ARTHROPLASTY
V - Within 26 weeks	182	130	52	KNEE ARTHROPLASTY
V - Within 26 weeks	182	159	23	KNEE ARTHROPLASTY
V - Within 26 weeks	182	159	23	KNEE ARTHROPLASTY
V - Within 26 weeks	182	80	102	KNEE ARTHROPLASTY
V - Within 26 weeks	182	32	150	KNEE ARTHROPLASTY
V - Within 26 weeks	182	455	-273	KNEE ARTHROPLASTY
V - Within 26 weeks	182	283	-101	KNEE ARTHROPLASTY

Priority	Target Wait In Days	Number of Days Waiting	Days Past Target	Procedure
IV - Within 13 weeks	91	186	-95	KNEE ARTHROPLASTY
V - Within 26 weeks	182	630	-448	KNEE ARTHROPLASTY
V - Within 26 weeks	182	630	-448	KNEE ARTHROPLASTY
IV - Within 13 weeks	91	262	-171	LAPAROSCOPIC BOWEL RESECTION/ REPAIR
III - Within 6 weeks	42	1191	-1149	LAPAROSCOPIC BOWEL RESECTION/ REPAIR
IIb - Within 3 weeks	21	15	6	LAPAROSCOPIC BOWEL RESECTION/ REPAIR
IV - Within 13 weeks	91	984	-893	LAPAROSCOPIC CHOLECYSTECTOMY
V - Within 26 weeks	182	20	162	LAPAROSCOPIC CHOLECYSTECTOMY
IIa - Within 7 days	7	451	-444	LAPAROSCOPIC CHOLECYSTECTOMY
IV - Within 13 weeks	91	140	-49	LAPAROSCOPIC CHOLECYSTECTOMY
IV - Within 13 weeks	91	2136	-2045	LAPAROSCOPIC HERNIORRAPHY- INCISIONAL
VI - Within 52 weeks	365	2283	-1918	LAPAROSCOPIC HERNIORRAPHY- INCISIONAL
VI - Within 52 weeks	365	1707	-1342	LAPAROSCOPIC HERNIORRAPHY- INGUINAL/ FEMORAL (GROIN)
IV - Within 13 weeks	91	159	-68	LAPAROSCOPIC HERNIORRAPHY- INGUINAL/ FEMORAL (GROIN)
III - Within 6 weeks	42	140	-98	LAPAROSCOPIC HERNIORRAPHY- INGUINAL/ FEMORAL (GROIN)
IV - Within 13 weeks	91	578	-487	LAPAROSCOPIC HERNIORRAPHY- INGUINAL/ FEMORAL (GROIN)
IV - Within 13 weeks	91	437	-346	LAPAROSCOPIC-NISSEN FUNDOPLICATION
III - Within 6 weeks	42	661	-619	LAPAROSCOPY-DIAGNOSTIC
IV - Within 13 weeks	91	39	52	LARYNGECTOMY
IIb - Within 3 weeks	21	1230	-1209	MANIPULATION EXTREMITY
III - Within 6 weeks	42	113	-71	MASTECTOMY
IV - Within 13 weeks	91	322	-231	MAXILLOFACIAL DEFORMITIES
III - Within 6 weeks	42	70	-28	NECK DISSECTION (ANY TYPE)
IIb - Within 3 weeks	21	48	-27	NECK DISSECTION (ANY TYPE)
IIb - Within 3 weeks	21	23	-2	OOPHORECTOMY/SALPINGECTOMY
IIb - Within 3 weeks	21	30	-9	OPEN REDUCTION INTERNAL FIXATION FRACTURE (ORIF)
IIa - Within 7 days	7	944	-937	ORTHO BIOPSY
III - Within 6 weeks	42	21	21	ORTHO BIOPSY
III - Within 6 weeks	42	59	-17	PACEMAKER INSERTION/EXPLOR/REMOVAL/W/WO REPLACEMENT LEAD OR BATTERY

Priority	Target Wait In Days	Number of Days Waiting	Days Past Target	Procedure
IV - Within 13 weeks	91	5	86	PACEMAKER INSERTION/EXPLOR/REMOVAL/W/WO REPLACEMENT LEAD OR BATTERY
III - Within 6 weeks	42	98	-56	PACEMAKER INSERTION/EXPLOR/REMOVAL/W/WO REPLACEMENT LEAD OR BATTERY
III - Within 6 weeks	42	56	-14	PANAENDOSCOPY
V - Within 26 weeks	182	785	-603	PARATHYROIDECTOMY
V - Within 26 weeks	182	974	-792	PARATHYROIDECTOMY
VI - Within 52 weeks	365	307	58	PAROTIDECTOMY
VI - Within 52 weeks	365	264	101	RECONSTRUCTION / DECOMPRESSION ORBIT
VI - Within 52 weeks	365	32	333	RECONSTRUCTION EYELID
IV - Within 13 weeks	91	630	-539	RECTAL BOWEL RESECTION/REPAIR
V - Within 26 weeks	182	414	-232	REMOVAL BREAST IMPLANT
IV - Within 13 weeks	91	194	-103	REPAIR ANEURYSM
VI - Within 52 weeks	365	945	-580	REPAIR/RECONSTRUCTION LIGAMENT/TENDON/MUSCLE/FASCIA
III - Within 6 weeks	42	61	-19	REVISION SCAR
V - Within 26 weeks	182	489	-307	SHOULDER ARTHROPLASTY
VI - Within 52 weeks	365	462	-97	SHOULDER ARTHROPLASTY
V - Within 26 weeks	182	1795	-1613	SHOULDER ARTHROPLASTY
VI - Within 52 weeks	365	249	116	SHOULDER ARTHROPLASTY
V - Within 26 weeks	182	65	117	SHOULDER ARTHROSCOPY
VI - Within 52 weeks	365	135	230	SHOULDER ARTHROSCOPY
V - Within 26 weeks	182	666	-484	SHOULDER ARTHROSCOPY
V - Within 26 weeks	182	198	-16	SHOULDER ARTHROSCOPY
VI - Within 52 weeks	365	464	-99	SHOULDER ARTHROSCOPY
VI - Within 52 weeks	365	1226	-861	SHOULDER ARTHROSCOPY
VI - Within 52 weeks	365	110	255	SKIN GRAFT
IV - Within 13 weeks	91	246	-155	SPINE: CERVICAL FUSION ANTERIOR
III - Within 6 weeks	42	280	-238	STERNOTOMY/THORACOTOMY
IV - Within 13 weeks	91	47	44	SUPRAPUBIC CATHETER INSERTION
IIb - Within 3 weeks	21	708	-687	SUPRAPUBIC CATHETER INSERTION
IV - Within 13 weeks	91	87	4	SURGERY FOR FEMALE INCONTINENCE
VI - Within 52 weeks	365	154	211	TEMPEROMANDIBULAR JOINT
IIa - Within 7 days	7	168	-161	TEMPORAL ARTERY BIOPSY
IIb - Within 3 weeks	21	31	-10	THORACOSCOPY/PLEUROSCOPY
VI - Within 52 weeks	365	720	-355	THYROPLASTY
VI - Within 52 weeks	365	349	16	THYROPLASTY
IV - Within 13 weeks	91	95	-4	THYROPLASTY
IV - Within 13 weeks	91	79	12	THYROPLASTY
V - Within 26 weeks	182	170	12	THYROPLASTY
III - Within 6 weeks	42	94	-52	TONSILLECTOMY

Priority	Target Wait In Days	Number of Days Waiting	Days Past Target	Procedure
IIb - Within 3 weeks	21	398	-377	TRABECULECTOMY/ GLAUCOMA SURGERY
IIb - Within 3 weeks	21	19	2	TRACHEOSTOMY
V - Within 26 weeks	182	111	71	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
IIb - Within 3 weeks	21	18	3	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
V - Within 26 weeks	182	114	68	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
IV - Within 13 weeks	91	107	-16	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
IV - Within 13 weeks	91	243	-152	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
IIb - Within 3 weeks	21	18	3	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
V - Within 26 weeks	182	-26	208	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
IIb - Within 3 weeks	21	32	-11	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
IIb - Within 3 weeks	21	4	17	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
IIb - Within 3 weeks	21	7	14	URETEROLITHOTOMY
IIa - Within 7 days	7	2	5	VALVE REPLACEMENT/REPAIR
IIa - Within 7 days	7	10	-3	VALVE REPLACEMENT/REPAIR
IIb - Within 3 weeks	21	65	-44	VALVE REPLACEMENT/REPAIR
IIb - Within 3 weeks	21	71	-50	VALVE REPLACEMENT/REPAIR
VI - Within 52 weeks	365	535	-170	VARICOSE VEIN LIGATION/STRIPPING
III - Within 6 weeks	42	24	18	VATS APICAL RESECTION
IIb - Within 3 weeks	21	300	-279	VATS APICAL RESECTION
IIb - Within 3 weeks	21	67	-46	VATS APICAL RESECTION
V - Within 26 weeks	182	207	-25	VITRECTOMY/VITREORETINAL PROCEDURE (removal IO lens, scleral buckle)
V - Within 26 weeks	182	207	-25	VITRECTOMY/VITREORETINAL PROCEDURE (removal IO lens, scleral buckle)
IV - Within 13 weeks	91	260	-169	VITRECTOMY/VITREORETINAL PROCEDURE (removal IO lens, scleral buckle)
IV - Within 13 weeks	91	89	-216	VITRECTOMY/VITREORETINAL PROCEDURE (removal IO lens, scleral buckle)
IIa - Within 7 days	7	749	-742	VITRECTOMY/VITREORETINAL PROCEDURE (removal IO lens, scleral buckle)

Priority	Target Wait In Days	Number of Days Waiting	Days Past Target	Procedure
IV - Within 13 weeks	91	65	26	VITRECTOMY/VITREORETINAL PROCEDURE (removal IO lens, scleral buckle)
IV - Within 13 weeks	91	2242	-2151	VITRECTOMY/VITREORETINAL PROCEDURE (removal IO lens, scleral buckle)
IV - Within 13 weeks	91	852	-761	VITRECTOMY/VITREORETINAL PROCEDURE (removal IO lens, scleral buckle)
IV - Within 13 weeks	91	190	-99	VITRECTOMY/VITREORETINAL PROCEDURE (removal IO lens, scleral buckle)
IV - Within 13 weeks	91	222	-131	VOCAL CORD AUGMENTATION
III - Within 6 weeks	42	16	26	VOCAL CORD AUGMENTATION

Interpretation of Data

In the attached dataset we can see that 424 patients died while waiting for surgery among over 25,000 patients who were on the waiting list for surgery during the calendar year 2019. This is a consistent figure over the past several years. The great majority (391/424) of deaths occurred in patients awaiting procedures that would not be anticipated to change the probability of death. For example, 160 deaths occurred among patients awaiting cataract surgery. Other examples of procedures not anticipated to be implicated in mortality include cystoscopy; orthopaedic procedures for arthritis; dental surgery; and other procedures that do not involve either cancer treatment or cardiovascular procedures. Thirty three (7.8%) of all deaths on the waiting list involved procedures where delays in treatment might reasonably be implicated causally. Among these are bowel resections; angioplasty; pacemaker insertion; cancer resections and abdominal aneurysm surgery. Among these, just under two thirds were waiting beyond the recommended wait times for the procedure in question. At this point we do not have precise data around cause of death for these patients and cannot comment on the probability of death avoidance if surgery were performed.

It is worthwhile noting that this data is based on our PARNS booking system and there are sometimes patients inappropriately left on the system even though a decision has been made by patient and surgeon not to pursue surgery, thus the mortality rate among those waiting may be falsely high.

Finally, the mortality rate generally in Nova Scotia is generally just below 1% (0.97% for 2019) while the mortality rate among those queued for surgery is about 1.7%. The average age of patients waiting for surgery is likely considerably higher than the average age in Nova Scotia (43 years of age) such that the death rate among patients waiting for surgery may be very close to that of an age matched group of Nova Scotians.

Privacy Office
Legal Services
Centennial 1-031
1276 South Park Street
Halifax NS B3H 2Y9
Telephone: (902)473-2626
Fax: (902)473-7850

January 22, 2021

Sent via e-mail

Re: Full Disclosure – OUR FILE# NSHA-2020-80

On 23 December 2020, Nova Scotia Health Authority (NSHA) received your request under the Freedom of Information and Protection of Privacy (FOIPOP) Act for a copy of the following:

Staff infected with COVID-19 at Northwood outbreak - numbers and breakdown by position.

Please find below the response to your request. These records are being provided to you in their entirety. We are now closing your application with our Office.

2 RNs were deemed COVID-19 positive.

Should you have any questions or comments, please do not hesitate to contact me at the address or telephone number provided above.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review

Sincerely,

Fola Adeleke

For: The Privacy Office
Nova Scotia Health Authority

c/c: to file

PLM Blood Collection Capacity Pre and Post COVID-19 Pandemic

Please Note:

In order to more accurately portray the capacity, a full week of data was used versus 1 day due to flucutations in hours of operation and staffing.

Recent post pandemic data was used to reflect the most up to date capacity

The provincial volume of laboratory testing is at approximately 75-80% compared to 2019 (pre pandemic)

Current capacity is limited due to social distancing and infection control measures

Zone	Blood Collection Site	Number of Collections/Day Pre Pandemic (Jan 20-26, 2020)	Number of Collections/Day Post Pandemic (Nov 30- Dec 6, 2020)	Comments
EZ	CBRH	1868	1330	
	Glace Bay	604	505	
	New Waterford	298	280	
	Northside General	586	398	
	Victoria County	130	112	
	Sacred Heart	113	69	
	Buchanan	62	40	
	Inverness	216	188	
	Strait Richmond	385	275	
	Guysborough	98	68	
	Eastern Memoria	52	35	
	St. Mary's Memorial	67	39	
	St. Martha's Regional	516	448	
	Eskasoni	43	49	
	Wacobah	10	10	
	Wagmatcook	9	8	
	Membertou	19	18	
NZ	Colchester	980	840	
	Aberdeen	870	685	
	Cumberland Reg	485	415	
	Lillian Fraser	120	110	
	North Cumberland	90	75	
	All Saints	160	115	
	South Cumberland	85	95	
	Sutherland Harris	230	165	
	Lloyd E Matheson Ctr	465	455	
	Oxford	23	13	
	River Hebert	13	4	
	Bayview	11	16	
	Indian Brook	22	22	
WZ	South Shore	628	743	
	Yarmouth	584	605	
	Valley Regional	825	351	
	Eastern Kings	156	385	
	Western Kings	258	206	
	Soldier's Memorial	490	392	
	Queens General	269	186	
	Fishermen's Memorial	329	162	
	Roseway	203	216	
	Digby General	240	215	
	Annapolis Community HC	160	144	
	North Queens Health Ctr	30	9	
	Barrington Community HC	145	55	
	Clare Health Ctr	92	67	
	Weymouth Medical Ctr	24	18	
	Lockporte Medical Ctr	24	0	Location has not reopened post-pandemic
	Our Health Ctr	69	0	Location has not reopened post-pandemic
CZ	Bayers Road	2510	1750	
	Halifax Infirmary	798	600	
	St Margarets Bay	624	557	
	Victoria General	653	610	
	Dartmouth General	1697	1208	
	Eastern Shore Memorial	92	95	
	Musquodoboit Valley	154	140	
	Twin Oaks Memorial	323	325	
	Cobequid Community HC	1604	1100	

Hants Community Hospital	606	650
Woodlawn	648	600
Spryfield Community HC	349	1000

Privacy Office
Legal Services
Centennial 1-031
1276 South Park Street
Halifax NS B3H 2Y9
Telephone: (902)473-2869
Fax: (902)473-7850

January 26 2021

Sent via e-mail

Re: Full Disclosure – OUR FILE# NSHA-2020-81

On December 18 2020, Nova Scotia Health Authority (NSHA) received your request under the Freedom of Information and Protection of Privacy (FOIPOP) Act for a copy of the following:

Reports or briefing notes at the executive director level and above regarding blood collection during COVID-19. Timeline: March 2020 to present.

Please find attached a copy of the records located in response to your request. These records are being provided to you in their entirety. We are now closing your application with our Office.

Should you have any questions or comments, please do not hesitate to contact me at the address or telephone number provided above.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review

Sincerely,

Fola Adeleke

For: The Privacy Office
Nova Scotia Health Authority

c/c: to file

PLM Blood Collection Capacity Pre and Post COVID-19 Pandemic

Please Note:

In order to more accurately portray the capacity, a full week of data was used versus 1 day due to flucutations in hours of operation and staffing.

Recent post pandemic data was used to reflect the most up to date capacity

The provincial volume of laboratory testing is at approximately 75-80% compared to 2019 (pre pandemic)

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	Glace Bay	604	505	
	New Waterford	298	280	
	Northside General	586	398	
	Victoria County	130	112	
	Sacred Heart	113	69	
	Buchanan	62	40	
	Inverness	216	188	
	Strait Richmond	385	275	
	Guysborough	98	68	
	Eastern Memoria	52	35	
	St. Mary's Memorial	67	39	
	St. Martha's Regional	516	448	
	Eskasoni	43	49	
	Wacobah	10	10	
	Wagmatcook	9	8	
	Membertou	19	18	
NZ	Colchester	980	840	
	Aberdeen	870	685	
	Cumberland Reg	485	415	
	Lillian Fraser	120	110	
	North Cumberland	90	75	
	All Saints	160	115	
	South Cumberland	85	95	
	Sutherland Harris	230	165	
	Lloyd E Matheson Ctr	465	455	
	Oxford	23	13	
	River Hebert	13	4	
	Bayview	11	16	
	Indian Brook	22	22	
WZ	South Shore	628	743	
	Yarmouth	584	605	
	Valley Regional	825	351	
	Eastern Kings	156	385	
	Western Kings	258	206	
	Soldier's Memorial	490	392	
	Queens General	269	186	
	Fishermen's Memorial	329	162	
	Roseway	203	216	
	Digby General	240	215	
	Annapolis Community HC	160	144	
	North Queens Health Ctr	30	9	
	Barrington Community HC	145	55	
	Clare Health Ctr	92	67	
	Weymouth Medical Ctr	24	18	
	Lockporte Medical Ctr	24	0	Location has not reopened post-pandemic
	Our Health Ctr	69	0	Location has not reopened post-pandemic
CZ	Bayers Road	2510	1750	
	Halifax Infirmary	798	600	
	St Margarets Bay	624	557	
	Victoria General	653	610	
	Dartmouth General	1697	1208	
	Eastern Shore Memorial	92	95	
	Musquodoboit Valley	154	140	
	Twin Oaks Memorial	323	325	
	Cobequid Community HC	1604	1100	

Zone	Priority	Target Wait In Days	Num Days Waiting	Days Past Target	Procedure
Northern	IV - Within 13 weeks	91	377	-440	HIP ARTHROPLASTY
Central	V - Within 26 weeks	182	692	-510	HIP ARTHROPLASTY
Western	V - Within 26 weeks	182	83	99	KNEE ARTHROPLASTY
Central	IV - Within 13 weeks	91	540	-449	KNEE ARTHROPLASTY
Western	III - Within 6 weeks	42	46	-4	CYSTOLITHOPAXY/ CYSTOLITHOTOMY
Western	IV - Within 13 weeks	91	55	36	CYSTOSCOPY
Western	VI - Within 52 weeks	365	413	-48	CYSTOSCOPY
Western	V - Within 26 weeks	182	192	-10	CYSTOSCOPY
Eastern	V - Within 26 weeks	182	175	7	CYSTOSCOPY
Western	VI - Within 52 weeks	365	399	-34	CYSTOSCOPY
Western	III - Within 6 weeks	42	56	-14	CYSTOSCOPY/TURB
Northern	V - Within 26 weeks	182	256	-74	CATARACT EXTRACTION
Northern	V - Within 26 weeks	182	256	-74	CATARACT EXTRACTION
Western	IV - Within 13 weeks	91	468	-377	CATARACT EXTRACTION
Western	IV - Within 13 weeks	91	468	-377	CATARACT EXTRACTION
Northern	IV - Within 13 weeks	91	58	33	CATARACT EXTRACTION
Northern	IV - Within 13 weeks	91	58	33	CATARACT EXTRACTION
Western	IV - Within 13 weeks	91	244	-153	CATARACT EXTRACTION
Western	IV - Within 13 weeks	91	244	-153	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	1075	-984	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	632	-541	CATARACT EXTRACTION
Central	VI - Within 52 weeks	365	365	0	KERATOPLASTY/ CORNEAL TRANSPLANT
Central	IV - Within 13 weeks	91	260	-169	VITRECTOMY/VITREORETINAL PROCEDURE (removal IO lens, scleral buckle)
Central	IV - Within 13 weeks	91	-2029	2120	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	2136	-2045	LAPAROSCOPIC HERNIORRAPHY- INCISIONAL
Central	IV - Within 13 weeks	91	-1060	1151	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	-1060	1151	CATARACT EXTRACTION
Western	VI - Within 52 weeks	365	-164	529	CATARACT EXTRACTION
Eastern	IV - Within 13 weeks	91	97	-6	CYSTOSCOPY
Western	VI - Within 52 weeks	365	212	153	CATARACT EXTRACTION
Eastern	IV - Within 13 weeks	91	41	50	CATARACT EXTRACTION
Central	VI - Within 52 weeks	365	380	-15	CATARACT EXTRACTION
Eastern	IV - Within 13 weeks	91	95	-4	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	852	-761	VITRECTOMY/VITREORETINAL PROCEDURE (removal IO lens, scleral buckle)
Central	V - Within 26 weeks	182	170	12	THYROPLASTY
Central	III - Within 6 weeks	42	661	-619	LAPAROSCOPY-DIAGNOSTIC
Central	IIb - Within 3 weeks	21	32	-11	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
Western	IV - Within 13 weeks	91	297	-206	CYSTOSCOPY
Northern	IV - Within 13 weeks	91	186	-95	KNEE ARTHROPLASTY
Western	V - Within 26 weeks	182	102	80	HIP ARTHROPLASTY
Central	III - Within 6 weeks	42	452	-410	CYSTOSCOPY/TURP
Central	IV - Within 13 weeks	91	1395	-1304	CATARACT EXTRACTION
Eastern	IV - Within 13 weeks	91	313	-222	CYSTOSCOPY
Eastern	IIa - Within 7 days	7	2	5	CYSTOSCOPY

Central	VI - Within 52 weeks	365	27	338	DENTAL RESTORATIONS
Eastern	III - Within 6 weeks	42	140	-98	LAPAROSCOPIC HERNIORRAPHY- INGUINAL/ FEMORAL (GROIN)
Central	IV - Within 13 weeks	91	399	-308	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	399	-308	CATARACT EXTRACTION
Central	V - Within 26 weeks	182	630	-448	KNEE ARTHROPLASTY
Central	V - Within 26 weeks	182	630	-448	KNEE ARTHROPLASTY
Central	IV - Within 13 weeks	91	260	-169	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	260	-169	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	7	84	VITRECTOMY/VITREORETINAL PROCEDURE (removal IO lens, scleral buckle)
Western	VI - Within 52 weeks	365	179	186	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	31	60	CATARACT EXTRACTION
Eastern	IV - Within 13 weeks	91	56	35	HIP ARTHROPLASTY
Eastern	IIb - Within 3 weeks	21	93	-72	CYSTOSCOPY
Eastern	III - Within 6 weeks	42	416	-374	CYSTOSCOPY
Western	VI - Within 52 weeks	365	198	167	CATARACT EXTRACTION
Central	V - Within 26 weeks	182	58	124	CATARACT EXTRACTION
Central	V - Within 26 weeks	182	58	124	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	1333	-1242	CATARACT EXTRACTION
Central	IIb - Within 3 weeks	21	708	-687	SUPRAPUBIC CATHETER INSERTION
Eastern	IIb - Within 3 weeks	21	50	-29	CYSTOSCOPY
Central	V - Within 26 weeks	182	128	54	CYSTOSCOPY/TURP
Western	V - Within 26 weeks	182	301	-119	CYSTOSCOPY
Western	NULL	NULL	702	NULL	CYSTOSCOPY
Eastern	V - Within 26 weeks	182	414	-232	REMOVAL BREAST IMPLANT
Central	III - Within 6 weeks	42	94	-52	CYSTOSCOPY
Central	IIa - Within 7 days	7	95	-88	CYSTOSCOPY
Northern	V - Within 26 weeks	182	217	-109	CATARACT EXTRACTION
Northern	V - Within 26 weeks	182	217	-109	CATARACT EXTRACTION
Central	V - Within 26 weeks	182	169	13	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	1292	-1201	CATARACT EXTRACTION
Central	V - Within 26 weeks	182	193	-11	HERNIORRAPHY-UMBILICAL/ PARAUMBILICAL
Central	III - Within 6 weeks	42	21	21	ORTHO BIOPSY
Northern	III - Within 6 weeks	42	98	-56	PACEMAKER INSERTION/EXPLOR/REMOVAL/W/WO REPLACEMENT LEAD OR BATTERY
Central	IIa - Within 7 days	7	21	-14	AMPUTATION
Eastern	V - Within 26 weeks	182	286	-104	CYSTOSCOPY
Eastern	IV - Within 13 weeks	91	112	-21	CATARACT EXTRACTION
Central	IIb - Within 3 weeks	21	295	-274	CYSTOSCOPY/TURP
Central	VI - Within 52 weeks	365	87	278	CYSTOSCOPY/TURP
Central	VI - Within 52 weeks	365	473	-108	CYSTOSCOPY
Central	IIb - Within 3 weeks	21	56	-35	EXCISION MELANOMA
Central	III - Within 6 weeks	42	38	4	EXCHANGE/ INSERTION INTRAOCULAR LENS
Central	IV - Within 13 weeks	91	456	-365	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	145	-54	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	145	-54	CATARACT EXTRACTION
Northern	IV - Within 13 weeks	91	937	-846	CATARACT EXTRACTION

Northern	IV - Within 13 weeks	91	87	4	CATARACT EXTRACTION
Northern	IV - Within 13 weeks	91	430	-339	CATARACT EXTRACTION
Central	III - Within 6 weeks	42	46	-4	AV FISTULA CREATION/REVISION/CLOSURE
Central	IIb - Within 3 weeks	21	1382	-1361	SACRAL NERVE STIMULATION
Central	V - Within 26 weeks	182	63	119	HERNIORRAPHY- INGUINAL/FEMORAL (GROIN)
Eastern	IV - Within 13 weeks	91	578	-487	LAPAROSCOPIC HERNIORRAPHY- INGUINAL/ FEMORAL (GROIN)
Central	III - Within 6 weeks	42	16	26	VOCAL CORD AUGMENTATION
Western	IV - Within 13 weeks	91	65	26	CATARACT EXTRACTION
Western	IV - Within 13 weeks	91	65	26	CATARACT EXTRACTION
Western	NULL	NULL	1179	NULL	CYSTOSCOPY
Western	NULL	NULL	416	NULL	CYSTOSCOPY
Western	III - Within 6 weeks	42	438	-396	CYSTOSCOPY
Central	VI - Within 52 weeks	365	549	-184	HIP ARTHROSCOPY
Central	IV - Within 13 weeks	91	1050	-959	EXCISION DUPUYTREN'S CONTRACTURE(PALMAR FASCIA)
Central	IV - Within 13 weeks	91	1508	-1417	HARDWARE REMOVAL
Central	IV - Within 13 weeks	91	74	17	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	74	17	CATARACT EXTRACTION
Western	III - Within 6 weeks	42	23	19	CYSTOSCOPY/TURB
Central	V - Within 26 weeks	182	1274	-1092	CYSTOSCOPY
Western	NULL	NULL	809	NULL	CYSTOSCOPY
Central	IV - Within 13 weeks	91	1821	-1730	VITRECTOMY/VITREORETINAL PROCEDURE (removal IO lens, scleral buckle)
Northern	IV - Within 13 weeks	91	818	-727	CATARACT EXTRACTION
Central	V - Within 26 weeks	182	180	2	CYSTOSCOPY
Central	IV - Within 13 weeks	91	158	-67	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	158	-67	CATARACT EXTRACTION
Western	NULL	NULL	401	NULL	CYSTOSCOPY
Western	NULL	NULL	57	NULL	CYSTOSCOPY
Central	IV - Within 13 weeks	91	68	23	CATARACT EXTRACTION
Central	V - Within 26 weeks	182	99	83	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	190	-99	VITRECTOMY/VITREORETINAL PROCEDURE (removal IO lens, scleral buckle)
Central	IIb - Within 3 weeks	21	71	-50	VALVE REPLACEMENT/REPAIR
Central	IIb - Within 3 weeks	21	1230	-1209	MANIPULATION EXTREMITY
Western	IIb - Within 3 weeks	21	87	-66	CYSTOSCOPY/TURB
Central	VI - Within 52 weeks	365	307	58	PAROTIDECTOMY
Eastern	IV - Within 13 weeks	91	140	-49	CYSTOSCOPY
Eastern	IIb - Within 3 weeks	21	42	-21	CYSTOSCOPY
Central	IV - Within 13 weeks	91	124	-33	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	124	-33	CATARACT EXTRACTION
Eastern	IIb - Within 3 weeks	21	4	17	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
Central	V - Within 26 weeks	182	45	137	HEAD: CRANIOTOMY FOR ANEURYSM
Central	IIa - Within 7 days	7	54	-47	BYPASS GRAFT
Central	VI - Within 52 weeks	365	723	-358	SHOULDER ARTHROSCOPY
Central	VI - Within 52 weeks	365	265	100	CATARACT EXTRACTION
Northern	IIb - Within 3 weeks	21	53	-142	INSERTION/REMOVAL VASCULAR ACCESS CATHETER
Central	III - Within 6 weeks	42	89	-47	CATARACT EXTRACTION

Eastern	IV - Within 13 weeks	91	90	1	CYSTOSCOPY
Central	IV - Within 13 weeks	91	1518	-1427	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	439	-348	CATARACT EXTRACTION
Western	III - Within 6 weeks	42	113	-71	MASTECTOMY
Central	IV - Within 13 weeks	91	54	37	CYSTOSCOPY
Central	VI - Within 52 weeks	365	249	116	SHOULDER ARTHROPLASTY
Central	VI - Within 52 weeks	365	899	-534	CATARACT EXTRACTION
Central	VI - Within 52 weeks	365	1756	-1391	EXCISION OF MASS
Central	IV - Within 13 weeks	91	235	-144	RECTAL BOWEL RESECTION/REPAIR
Eastern	IV - Within 13 weeks	91	106	-15	CATARACT EXTRACTION
Western	III - Within 6 weeks	42	209	-167	CYSTOSCOPY/TURP
Western	VI - Within 52 weeks	365	34	331	CLOSURE COLOSTOMY/ILEOSTOMY
Central	IV - Within 13 weeks	91	556	-465	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	15	76	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	15	76	CATARACT EXTRACTION
Western	IV - Within 13 weeks	91	606	-515	CYSTOSCOPY/TURP
Eastern	IIb - Within 3 weeks	21	44	-23	AMPUTATION
Eastern	IIb - Within 3 weeks	21	31	-10	CYSTOSCOPY
Eastern	IIb - Within 3 weeks	21	64	-43	CYSTOSCOPY
Eastern	IV - Within 13 weeks	91	127	-36	CYSTOSCOPY
Central	IV - Within 13 weeks	91	20	71	CATARACT EXTRACTION
Eastern	IIa - Within 7 days	7	280	-273	CYSTOSCOPY/TURB
Western	IV - Within 13 weeks	91	54	37	CATARACT EXTRACTION
Western	IV - Within 13 weeks	91	54	37	CATARACT EXTRACTION
Eastern	IIb - Within 3 weeks	21	300	-279	CYSTOSCOPY
Eastern	III - Within 6 weeks	42	30	12	CYSTOSCOPY/TURB
Central	III - Within 6 weeks	42	17	25	EXCISION OF TUMOR
Western	V - Within 26 weeks	182	560	-378	KNEE ARTHROPLASTY
Western	IV - Within 13 weeks	91	470	-379	CATARACT EXTRACTION
Western	IV - Within 13 weeks	91	470	-379	CATARACT EXTRACTION
Central	V - Within 26 weeks	182	932	-750	CATARACT EXTRACTION
Central	V - Within 26 weeks	182	553	-371	RECONSTRUCTION BREAST FLAP
Central	IV - Within 13 weeks	91	33	58	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
Central	IV - Within 13 weeks	91	34	57	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	141	-50	THYROPLASTY
Central	IIa - Within 7 days	7	2057	-2050	HIP ARTHROSCOPY
Western	VI - Within 52 weeks	365	180	185	CATARACT EXTRACTION
Northern	V - Within 26 weeks	182	39	143	CATARACT EXTRACTION
Northern	V - Within 26 weeks	182	35	147	CATARACT EXTRACTION
Northern	IV - Within 13 weeks	91	699	-608	CATARACT EXTRACTION
Central	V - Within 26 weeks	182	485	-303	BOWEL RESECTION/REPAIR
Central	V - Within 26 weeks	182	485	-303	BOWEL RESECTION/REPAIR
Central	IV - Within 13 weeks	91	92	-1	HIP ARTHROPLASTY
Central	IIb - Within 3 weeks	21	102	-81	ESOPHAGECTOMY
Western	NULL	NULL	507	NULL	CYSTOSCOPY

Central	III - Within 6 weeks	42	608	-566	NEPHROSTOMY/ILEOSTOMY TUBE PLACEMENT/REMOVAL
Eastern	IIb - Within 3 weeks	21	26	-5	SUPRAPUBIC CATHETER INSERTION
Central	III - Within 6 weeks	42	56	-14	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
Western	V - Within 26 weeks	182	477	-295	HIP ARTHROPLASTY
Western	IV - Within 13 weeks	91	89	2	CYSTOSCOPY
Western	IV - Within 13 weeks	91	227	-136	HIP ARTHROPLASTY
Central	VI - Within 52 weeks	365	170	195	CYSTOSCOPY
Western	V - Within 26 weeks	182	354	-172	HIP ARTHROPLASTY
Western	III - Within 6 weeks	42	41	1	DEBRIDEMENT
Central	III - Within 6 weeks	42	1295	-1253	CARPAL TUNNEL RELEASE
Central	V - Within 26 weeks	182	1690	-1508	KNEE ARTHROPLASTY
Northern	IV - Within 13 weeks	91	217	-126	CYSTOUTHOPAXY/ CYSTOUTHOTOMY
Eastern	III - Within 6 weeks	42	339	-297	CYSTOSCOPY
Central	IV - Within 13 weeks	91	673	-582	CATARACT EXTRACTION
Western	IV - Within 13 weeks	91	157	-66	EXAM UNDER ANESTHESIA
Central	V - Within 26 weeks	182	570	-388	SACRAL NERVE STIMULATION
Central	III - Within 6 weeks	42	115	-73	CYSTOUTHOPAXY/ CYSTOUTHOTOMY
Central	IV - Within 13 weeks	91	54	37	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
Eastern	III - Within 6 weeks	42	85	-43	CATARACT EXTRACTION
Eastern	V - Within 26 weeks	182	65	117	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
Central	IV - Within 13 weeks	91	18	73	CYSTOSCOPY/TURB
Central	IV - Within 13 weeks	91	430	-339	CYSTOSCOPY/TURP
Eastern	III - Within 6 weeks	42	158	-116	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	338	-247	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	338	-247	CATARACT EXTRACTION
Central	V - Within 26 weeks	182	86	96	CATARACT EXTRACTION
Central	V - Within 26 weeks	182	86	96	CATARACT EXTRACTION
Eastern	V - Within 26 weeks	182	384	-202	FASCIOTOMY UPPER EXTREMITY
Central	IV - Within 13 weeks	91	412	-321	CATARACT EXTRACTION
Central	V - Within 26 weeks	182	489	-307	ANKLE ARTHRODESIS (FUSION)
Eastern	V - Within 26 weeks	182	134	48	DENTAL RESTORATIONS
Eastern	VI - Within 52 weeks	365	118	247	EXCISION OF CYST/GANGLION/LESION/LIPOMA
Central	IV - Within 13 weeks	91	430	-339	EXAM UNDER ANESTHESIA
Central	VI - Within 52 weeks	365	144	221	VITRECTOMY/VITREORETINAL PROCEDURE (removal IO lens, scleral buckle)
Western	IV - Within 13 weeks	91	198	-107	CATARACT EXTRACTION
Western	IV - Within 13 weeks	91	198	-107	CATARACT EXTRACTION
Western	VI - Within 52 weeks	365	136	229	CATARACT EXTRACTION
Central	VI - Within 52 weeks	365	234	131	HERNIORRAPHY- INGUINAL/FEMORAL (GROIN)
Eastern	V - Within 26 weeks	182	90	92	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
Western	IV - Within 13 weeks	91	90	1	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	28	63	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
Northern	V - Within 26 weeks	182	45	-147	CATARACT EXTRACTION
Western	III - Within 6 weeks	42	18	24	CYSTOSCOPY
Central	IV - Within 13 weeks	91	502	-411	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	502	-411	CATARACT EXTRACTION

Eastern	IV - Within 13 weeks	91	209	-118	CATARACT EXTRACTION
Western	V - Within 26 weeks	182	96	86	SHOULDER ARTHROPLASTY
Central	V - Within 26 weeks	182	666	-484	LAPAROSCOPIC HERNIORRAPHY- VENTRAL/EPIGASTRIC/ SPIGELIAN (ABDOMINAL)
Western	III - Within 6 weeks	42	92	-50	LAPAROSCOPIC NEPHRECTOMY
Central	IV - Within 13 weeks	91	143	-126	KNEE ARTHROPLASTY
Northern	V - Within 26 weeks	182	411	-257	EXCISION OF CYST/GANGLION/LESION/LIPOMA
Northern	V - Within 26 weeks	182	111	71	CATARACT EXTRACTION
Northern	V - Within 26 weeks	182	111	71	CATARACT EXTRACTION
Northern	IV - Within 13 weeks	91	56	35	CYSTOSCOPY
Central	IIa - Within 7 days	7	4	3	VALVE REPLACEMENT/REPAIR
Eastern	IV - Within 13 weeks	91	282	-191	CLOSURE COLOSTOMY/ILEOSTOMY
Central	IV - Within 13 weeks	91	450	-359	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	450	-359	CATARACT EXTRACTION
Eastern	IIa - Within 7 days	7	8	-1	CYSTOSCOPY
Central	IV - Within 13 weeks	91	146	-55	CYSTOSCOPY/TURP
Central	III - Within 6 weeks	42	48	-6	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
Central	V - Within 26 weeks	182	639	-457	HIP ARTHROPLASTY
Central	IIb - Within 3 weeks	21	162	-141	TRABECULECTOMY/ GLAUCOMA SURGERY
Northern	IIb - Within 3 weeks	21	599	-578	OTHER
Central	IV - Within 13 weeks	91	178	-87	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	178	-87	CATARACT EXTRACTION
Western	IV - Within 13 weeks	91	310	-219	CATARACT EXTRACTION
Western	IV - Within 13 weeks	91	310	-219	CATARACT EXTRACTION
Eastern	IV - Within 13 weeks	91	31	60	CYSTOSCOPY
Eastern	IIb - Within 3 weeks	21	137	-116	DISCECTOMY/LAMINECTOMY W/WO FUSION/STABILIZATION
Central	IV - Within 13 weeks	91	349	-258	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	349	-258	CATARACT EXTRACTION
Northern	IV - Within 13 weeks	91	186	-95	CYSTOLITHOPAXY/ CYSTOLITHOTOMY
Central	IV - Within 13 weeks	91	147	-56	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	474	-383	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	474	-383	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	147	-56	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	368	-277	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	368	-277	CATARACT EXTRACTION
Northern	IV - Within 13 weeks	91	259	-168	KNEE ARTHROPLASTY
Central	IV - Within 13 weeks	91	528	-437	KNEE ARTHROPLASTY
Central	V - Within 26 weeks	182	175	7	KNEE ARTHROPLASTY
Central	VI - Within 52 weeks	365	493	-128	TEMPEROMANDIBULAR JOINT
Eastern	VI - Within 52 weeks	365	225	140	CYSTOSCOPY
Western	IV - Within 13 weeks	91	324	-233	DENTOALVEOLAR SURGERY (EXTRACTIONS, APICOECTOMY)
Central	VI - Within 52 weeks	365	210	155	CATARACT EXTRACTION
Central	VI - Within 52 weeks	365	1024	-659	KNEE ARTHROPLASTY
Northern	V - Within 26 weeks	182	260	-78	CATARACT EXTRACTION
Northern	V - Within 26 weeks	182	260	-78	CATARACT EXTRACTION
Eastern	IV - Within 13 weeks	91	180	-89	CYSTOSCOPY/TURP

Eastern	IV - Within 13 weeks	91	490	-399	PARATHYROIDECTOMY
Central	V - Within 26 weeks	182	315	-133	ARTHROPLASTY HIP REVISION
Central	VI - Within 52 weeks	365	552	-187	HIP ARTHROPLASTY
Eastern	V - Within 26 weeks	182	22	160	NEPHROSTOMY/ILEOSTOMY TUBE PLACEMENT/REMOVAL
Eastern	III - Within 6 weeks	42	48	-6	CYSTOSCOPY
Central	V - Within 26 weeks	182	520	-338	CATARACT EXTRACTION
Central	III - Within 6 weeks	42	479	-437	LAPAROSCOPIC BOWEL RESECTION/ REPAIR
Central	VI - Within 52 weeks	365	487	-122	PENILE PROSTHESIS-INSERTION/REVISION
Central	IIb - Within 3 weeks	21	66	-45	CYSTOSCOPY URETEROSCOPY
Western	IIb - Within 3 weeks	21	145	-124	CYSTOSCOPY
Northern	III - Within 6 weeks	42	159	-117	SUPRAPUBIC CATHETER INSERTION
Eastern	VI - Within 52 weeks	365	40	325	CYSTOSCOPY
Central	IIa - Within 7 days	7	11	-4	CORONARY ARTERY BYPASS GRAFT WITHOUT VALVES
Eastern	IV - Within 13 weeks	91	174	-83	LAPAROSCOPIC CHOLECYSTECTOMY
Northern	IV - Within 13 weeks	91	187	-246	CYSTOSCOPY/TURP
Central	IV - Within 13 weeks	91	890	-799	CATARACT EXTRACTION
Eastern	IIb - Within 3 weeks	21	39	-18	CYSTOSCOPY
Eastern	III - Within 6 weeks	42	309	-267	CATARACT EXTRACTION
Eastern	IIb - Within 3 weeks	21	56	-35	BOWEL RESECTION/REPAIR
Central	IIb - Within 3 weeks	21	13	8	VALVE REPLACEMENT/REPAIR
Eastern	VI - Within 52 weeks	365	246	119	EXCISION OF CYST/GANGLION/LESION/LIPOMA
Eastern	III - Within 6 weeks	42	15	27	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
Central	V - Within 26 weeks	182	309	-127	THYROPLASTY
Central	VI - Within 52 weeks	365	478	-113	TYMPANOPLASTY (W/WO GRAFTING, CANALPLASTY, OSSICULOPLASTY)
Central	IV - Within 13 weeks	91	235	-144	CATARACT EXTRACTION
Central	VI - Within 52 weeks	365	255	110	HERNIORRAPHY- INCISIONAL
Western	IV - Within 13 weeks	91	60	31	HERNIORRAPHY- INGUINAL/FEMORAL (GROIN)
Western	IV - Within 13 weeks	91	201	-110	CATARACT EXTRACTION
Western	IV - Within 13 weeks	91	201	-110	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	320	-229	SHOULDER ARTHROSCOPY
Western	VI - Within 52 weeks	365	146	219	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	454	-363	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
Central	IV - Within 13 weeks	91	291	-200	CATARACT EXTRACTION
Western	III - Within 6 weeks	42	39	3	CYSTOSCOPY/TURP
Western	IV - Within 13 weeks	91	161	-70	CATARACT EXTRACTION
Western	IV - Within 13 weeks	91	161	-70	CATARACT EXTRACTION
Eastern	IV - Within 13 weeks	91	288	-197	CATARACT EXTRACTION
Eastern	IV - Within 13 weeks	91	97	-6	CYSTOSCOPY
Central	VI - Within 52 weeks	365	1787	-1422	KNEE ARTHROPLASTY
Central	IV - Within 13 weeks	91	498	-407	CATARACT EXTRACTION
Western	IV - Within 13 weeks	91	375	-284	CATARACT EXTRACTION
Western	IV - Within 13 weeks	91	375	-284	CATARACT EXTRACTION
Western	IV - Within 13 weeks	91	331	-240	CATARACT EXTRACTION
Western	IV - Within 13 weeks	91	331	-240	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	512	-421	CATARACT EXTRACTION

Central	IV - Within 13 weeks	91	512	-421	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	308	-217	CYSTOSCOPY
Eastern	IIb - Within 3 weeks	21	52	-31	CYSTOSCOPY
Northern	V - Within 26 weeks	182	319	-137	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	639	-548	KNEE ARTHROPLASTY
Eastern	IV - Within 13 weeks	91	185	-94	CATARACT EXTRACTION
Northern	V - Within 26 weeks	182	306	-124	CATARACT EXTRACTION
Northern	V - Within 26 weeks	182	319	-137	CATARACT EXTRACTION
Central	IIb - Within 3 weeks	21	1099	-1078	VITRECTOMY/VITREORETINAL PROCEDURE (removal IO lens, scleral buckle)
Central	IV - Within 13 weeks	91	597	-506	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	597	-506	CATARACT EXTRACTION
Central	III - Within 6 weeks	42	827	-785	CYSTECTOMY
Western	III - Within 6 weeks	42	191	-149	TONSILLECTOMY
Eastern	IIb - Within 3 weeks	21	45	-24	CYSTOSCOPY/TURP
Central	V - Within 26 weeks	182	1125	-943	CARPAL TUNNEL RELEASE
Eastern	IIb - Within 3 weeks	21	91	-70	CYSTOSCOPY
Eastern	III - Within 6 weeks	42	287	-245	EXCISION OF CYST/GANGLION/LESION/LIPOMA
Northern	IV - Within 13 weeks	91	308	-217	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	113	-22	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
Central	III - Within 6 weeks	42	64	-22	CYSTECTOMY
Western	V - Within 26 weeks	182	198	-16	CYSTOSCOPY
Central	III - Within 6 weeks	42	89	-47	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
Western	III - Within 6 weeks	42	196	-154	VEIN STRIPPING/LIGATION (NOT VARICOSE)
Eastern	IIb - Within 3 weeks	21	244	-223	CYSTOSCOPY
Central	IV - Within 13 weeks	91	295	-204	HIP ARTHROPLASTY
Western	V - Within 26 weeks	182	665	-483	DENTOALVEOLAR SURGERY (EXTRACTIONS, APICOECTOMY)
Western	IV - Within 13 weeks	91	258	-167	CATARACT EXTRACTION
Western	IV - Within 13 weeks	91	258	-167	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	804	-1023	CARPAL TUNNEL RELEASE
Central	V - Within 26 weeks	182	147	35	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
Eastern	V - Within 26 weeks	182	674	-492	DENTAL RESTORATIONS
Western	IV - Within 13 weeks	91	828	-737	HYSTERECTOMY (All Types)
Eastern	III - Within 6 weeks	42	34	8	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	63	28	CATARACT EXTRACTION
Central	V - Within 26 weeks	182	355	-173	CATARACT EXTRACTION
Central	V - Within 26 weeks	182	355	-173	CATARACT EXTRACTION
Eastern	IIb - Within 3 weeks	21	11	10	CYSTOSCOPY
Northern	IIb - Within 3 weeks	21	23	-2	CYSTOSCOPY
Northern	IV - Within 13 weeks	91	30	61	CYSTOSCOPY
Central	IV - Within 13 weeks	91	62	29	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	62	29	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	427	-336	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	427	-336	CATARACT EXTRACTION
Western	IV - Within 13 weeks	91	325	-234	CATARACT EXTRACTION
Western	IV - Within 13 weeks	91	325	-234	CATARACT EXTRACTION

Central	IV - Within 13 weeks	91	386	-295	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
Central	IV - Within 13 weeks	91	25	66	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
Central	VI - Within 52 weeks	365	2135	-1770	KNEE ARTHROPLASTY
Central	IV - Within 13 weeks	91	43	48	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	43	48	CATARACT EXTRACTION
Central	VI - Within 52 weeks	365	1039	-674	BONE-ANCHORED HEARING AID
Central	IV - Within 13 weeks	91	54	37	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	54	37	CATARACT EXTRACTION
Central	V - Within 26 weeks	182	355	-173	CATARACT EXTRACTION
Central	V - Within 26 weeks	182	355	-173	CATARACT EXTRACTION
Eastern	IIb - Within 3 weeks	21	101	-80	CYSTOSCOPY
Eastern	VI - Within 52 weeks	365	253	112	KNEE ARTHROSCOPY
Western	IV - Within 13 weeks	91	439	-348	CATARACT EXTRACTION
Northern	V - Within 26 weeks	182	32	150	CATARACT EXTRACTION
Northern	V - Within 26 weeks	182	32	150	CATARACT EXTRACTION
Western	V - Within 26 weeks	182	233	-51	HIP ARTHROPLASTY
Central	IIb - Within 3 weeks	21	31	-10	INSERTION/REMOVAL VASCULAR ACCESS CATHETER
Central	V - Within 26 weeks	182	3034	-2852	HAND/FINGER ARTHROPLASTY
Western	NULL	NULL	40	NULL	CYSTOSCOPY
Western	V - Within 26 weeks	182	54	128	CATARACT EXTRACTION
Northern	IV - Within 13 weeks	91	106	-15	CYSTOSCOPY/TURP
Central	V - Within 26 weeks	182	365	-183	CATARACT EXTRACTION
Western	VI - Within 52 weeks	365	384	-19	CATARACT EXTRACTION
Eastern	IV - Within 13 weeks	91	28	63	URETER- CATHETER/STENT INSERTION/REMOVAL OR DILATION
Central	V - Within 26 weeks	182	448	-266	CATARACT EXTRACTION
Central	V - Within 26 weeks	182	81	101	CATARACT EXTRACTION
Central	VI - Within 52 weeks	365	267	98	KNEE ARTHROPLASTY
Central	VI - Within 52 weeks	365	2256	-1891	KNEE ARTHROPLASTY
Central	III - Within 6 weeks	42	8	34	THYROIDECTOMY
Central	V - Within 26 weeks	182	2245	-2063	THYROIDECTOMY
Northern	III - Within 6 weeks	42	829	-787	EXCISION OF CYST/GANGLION/LESION/LIPOMA
Central	V - Within 26 weeks	182	41	141	FOOT/TOE ARTHRODESIS (FUSION)
Central	V - Within 26 weeks	182	351	-169	KNEE ARTHROPLASTY
Western	NULL	NULL	627	NULL	CYSTOSCOPY
Eastern	IV - Within 13 weeks	91	101	-10	CATARACT EXTRACTION
Central	IIb - Within 3 weeks	21	21	0	CORONARY ARTERY BYPASS GRAFT WITH VALVES
Central	IIb - Within 3 weeks	21	-3	24	ENDOVASCULAR AORTIC ANEURYSM REPAIR (EVAR)
Central	IV - Within 13 weeks	91	92	-1	CATARACT EXTRACTION
Central	IV - Within 13 weeks	91	1081	-990	CATARACT EXTRACTION
Central	V - Within 26 weeks	182	304	-122	CATARACT EXTRACTION

Response to Foipop Request: *Please provide data on the number of patients that died while on a waiting list for a surgical procedure in 2019-20. Please provide data separated by procedure and note the government's target time for providing the procedure in question.*

In the attached dataset we can see that 399 patients died while waiting for surgery among over 24,000 patients who were on the waiting list for surgery during the calendar year 2020. This is a consistent figure over the past several years. The great majority of deaths occurred in patients awaiting procedures that would not be anticipated to change the probability of death, for example cataract or joint replacement surgery. Less than 10% of the deaths occurred in patients awaiting procedures where delays in treatment might reasonably be implicated causally. Among these are bowel resections; angioplasty; pacemaker insertion; cancer resections and abdominal aneurysm surgery. Among these, just under two thirds were waiting beyond the recommended wait times for the procedure in question. At this point we do not have precise data around cause of death for these patients and cannot comment on the probability of death avoidance if surgery were performed.

It is worthwhile noting that this data is based on our PARNS booking system and there are sometimes patients inappropriately left on the system even though a decision has been made by patient and surgeon not to pursue surgery, thus the mortality rate among those waiting may be falsely high.

Finally, the mortality rate generally in Nova Scotia is generally just below 1% (0.97% for 2019) while the mortality rate among those queued for surgery is about 1.6%. The average age of patients waiting for surgery is likely considerably higher than the average age in Nova Scotia (43 years of age) such that the death rate among patients waiting for surgery may be very close to that of an age matched group of Nova Scotians.

Privacy Office; Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

1 March 2021

Sent via email

Good afternoon,

Please see attached records responsive to your requests that are within our custody and control. Please kindly note that some of your records requested are not available in the specific form requested, more clarification is needed for some requests while others are exempted from disclosure under the Freedom of Information and Protection of Personal Information Act. For more details, please below:

Testing

I am requesting statistical overviews broken down by race and gender that track COVID-19 cases amongst prisoners and prison staff, including positive tests, negative tests, inconclusive tests, deaths, recoveries and active cases, as well as memorandums and presentations on these statistics.

We do not have records on COVID-19 cases that categorises patients as prisoners or prison staff.

COVID Screening Procedures

I am requesting standing orders and policy directives documenting correctional institution COVID-19 screening procedures for prisoners, prison staff, oversight body officials, lawyers, and volunteers.

This would fall to Department of Justice except for inmates (prisoners) – that would fall to healthcare and we have a Care Directive that has been shared. There is also information on the publically accessible COVID Hub under Correctional Health Services (includes memos, protocols, etc.). This includes universal testing for all new admissions and a 14 days on a quarantine unit.

Privacy Office; Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

Health, Hygiene, Cleaning, and Distancing

I am requesting memorandums, briefing notes, information notes, statistics and powerpoint decks outlining (a) health and personal hygiene protocols issued to and measures, (b) outlining cleaning protocols issued to and measures adopted and (c) protocols issued to and measures adopted to promote social distancing in your correctional institutions related to COVID-19 pandemic prevention and management.

For the healthcare unit and cells we would follow our normal cleaning procedures for a hospital setting and adopt NSHA policies/directives with respect to masking, shields, etc. (information is available on the COVID-19 hub).

Health and Mental Health Care

I am requesting all records outlining protocols issued to and measures adopted or modified by your correctional institutions concerning health and mental health care provision to prisoners and prison staff related to COVID-19 prevention, management and treatment.

Level of care and services offered remain unchanged. We implemented universal precautions (PPE) for staff, universal testing for all new admissions to the facility, and a 14 day quarantine. Please let me know how best you want to proceed with this request and I can assist with putting information together and/or connecting us with those that can help (e.g. our IPAC practitioner).

Testing

I am requesting all records tracking COVID-19 cases amongst probationers and other individuals currently on community release, including positive tests, negative tests, inconclusive tests, deaths, recoveries and active cases.

This information is considered Personal Health Information and is protected from disclosure. By the Personal Health Information Act. If you are seeking aggregated information regarding COVID testing among a certain population please restate your request with as many specifics as possible and we will see if the information may be made available or not.

Entry and Exit Screening Procedures

I am requesting memorandums, briefing notes, information notes, statistics and powerpoint decks documenting probation office entry and exit COVID-19 screening procedures for probationers and other individuals currently on community release, prison staff, oversight body officials, lawyers, volunteers, and other parties.

Probation is a federal mandate and does not fall within the mandate of either NS Health or the NS Department of Justice.

Privacy Office; Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

Health, Cleaning, Distancing, and Contacts

Related to COVID-19 pandemic prevention and management, I am requesting all records outlining health and personal hygiene protocols, all records outlining cleaning protocols issued to and measures adopted, all records outlining protocols issue to and measures adopted, and all records outlining protocols issued to and measures adopted by your probation offices to restrict community contact for those currently on probation or other forms of community release related to COVID-19 pandemic prevention and management.

Probation is a federal mandate and does not fall within the mandate of either NS Health or the NS Department of Justice.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review

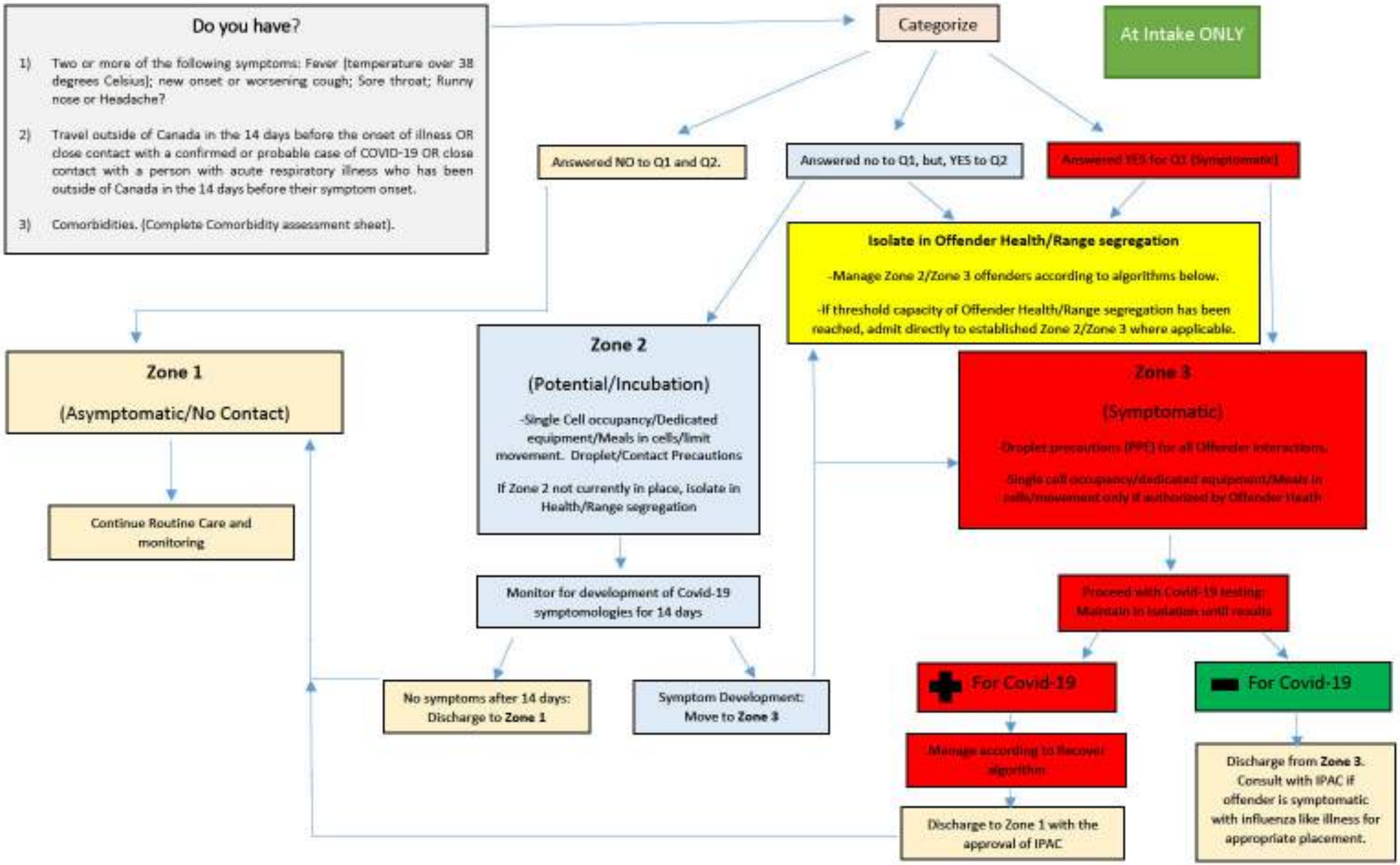
Sincerely,

Fola Adeleke

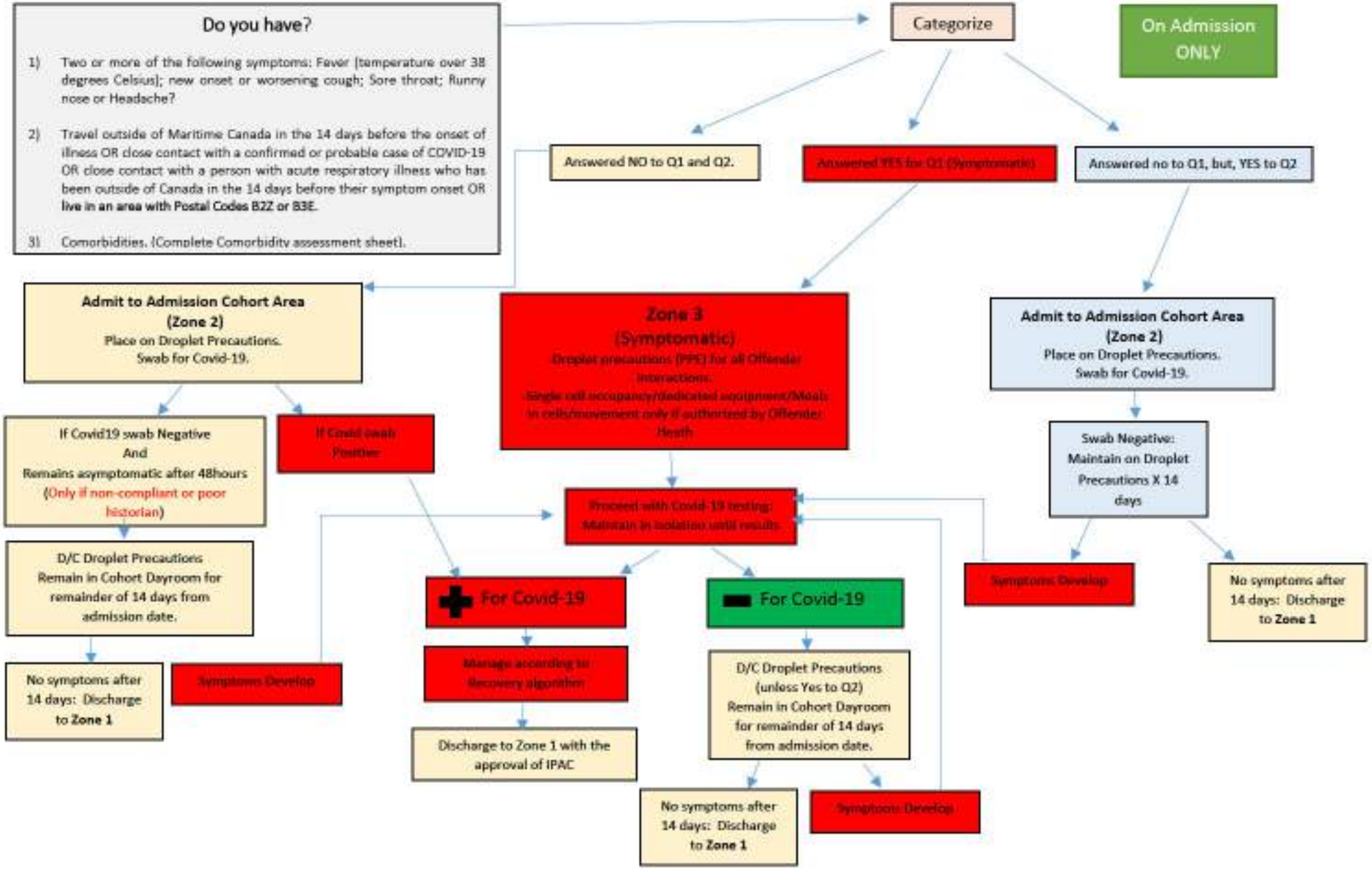
For: The Privacy Office
Nova Scotia Health Authority

c/c: to file

Nova Scotia Correctional Facility Phase II Contingency Planning: "At Intake"



Nova Scotia Correctional Facility Phase II Contingency Planning: "At Intake"



Nova Scotia Correctional Facility Phase II Contingency Planning: "In House"

During routine monitoring.

1) Two or more of the following symptoms: Fever (temperature over 38 degrees Celsius); new onset or worsening cough; Sore throat; Runny nose or Headache?
2) Has the offender been on an Area/Range/Wedge with a known and/or suspected Covid-19 person?

Categorize

While Offenders are "In-house"

Answered NO to Q1 and Q2

Answered no to Q1, but, YES to Q2

Answered YES for Q1 (Symptomatic)

Isolate in Offender Health/Range segregation

-Manage Zone 3 offenders according to algorithms below. If threshold capacity of Offender Health/Range segregation has been reached, admit directly to established Zone 3 where applicable.

Zone 1

(Asymptomatic/No Contact)

Continue Routine Care and monitoring

Zone 2

(Potential/Incubation)

-Single Cell occupancy/Dedicated equipment/Meals in cells/limit movement. Droplet/contact precautions.

Discontinuation of Zone 2 may occur if **all** suspected contact cases prove (-) for Covid-19.

Zone 3

(Symptomatic)

Droplet precautions (PPE) for all Offender interactions.

Single cell occupancy/dedicated equipment/Meals in cells/movement only if authorized by Offender Health

Monitor for development of Covid-19 symptomologies for 14 days after contact

Offender with no symptoms after 14 days: Discharge to **Zone 1**

Symptom Development: Move to **Zone 3**

Proceed with Covid-19 testing: Maintain in isolation until results

For Covid-19

Manage according to Recovery algorithm.

Discharge to Zone 1 with the approval of IPAC

For Covid-19

Discharge from **Zone 3**. Consult with IPAC if offender is symptomatic with influenza like illness for appropriate placement.

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East Coast Forensic Hospital & Offender Health

COVID–19 ASSESSMENT CHART (Version 5. 2021FEB10)

This COVID–19 Assessment Chart Applies Only to East Coast Forensic Hospital and Offender Health Services.

Patient Location: _____

Assess all admitted patients / offenders for Red Flags

Adult and Pregnancy Red Flags
Adult: Heart rate greater than 110 **Pregnancy:** Heart rate greater than 120 or less than 50
Adult: Respiration rate greater than 30 **Pregnancy:** Respiration rate equal to or greater than 30 or less than 10
Chest pain
Adult: SpO2 less than 92 % on room air **Pregnancy:** SpO2 less than 94 % on room air

Baseline Vital Signs (Note Adult Red Flag criteria page).

HR: _____ bpm RR: _____ BP: _____ / _____ SpO2 _____ on room air Temperature: _____ ° C

☐ **If Red Flags present, consult with Medical physician on–call.**

☐ **If no Red Flags, collect swab.**

PATIENT RISK COVID–19 ASSESSMENT IDENTIFICATION: _____

Assess for the following symptoms:

☐ New or worsening cough ☐ Unexplained fever: Measured temperature greater than 38.0° C (or fever like symptoms: chills or sweats)	Two or more of the following: ☐ Runny nose / nasal congestion (new or worsening) ☐ Sore throat ☐ Cough (new or exacerbation of chronic cough) ☐ Headache (new or worsening)

Has patient travelled for any reason outside of NS or PEI within the last 14 days:

☐ No ☐ Yes Location: Dates (YYYY/MON/DD): _____

Has anyone in the patient's household travelled outside of NS or PEI for any reason within the last 14 days:

☐ No ☐ Yes Location: Dates (YYYY/MON/DD): _____

In the past 14 days, has the patient been in contact with someone known to have COVID–19 or suspected (symptomatic or exposure risk) of having COVID–19?

☐ Known case ☐ Suspected case ☐ No known COVID–19 contacts

Has the patient been to any location identified by Public Health Alerts (see COVID–19 Hub) and has been instructed to self–isolate and be tested for COVID–19:

☐ No ☐ Yes

Does the patient live or work within a known facility cluster as identified on the COVID–19 Hub:

☐ Lives within a known COVID–19 facility cluster ☐ Works within a known COVID–19 facility cluster

☐ Does not live or work in a COVID–19 facility cluster

Does the patient live within a known community cluster as identified on the COVID–19 Hub:

☐ Lives within a known Covid–19 community cluster ☐ Does not live within a Covid–19 community cluster

Name of Assessor (Printed)	Signature of Assessor	Date (YYYY/MON/DD)	Time

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East Coast Forensic Hospital & Offender Health

COVID-19 ASSESSMENT CHART (Version 5. 2021FEB10)

Patients who present with symptoms but NO red flags + / - Risk Factors:

Provide education on the following.

- Drink plenty of fluids
- Direct individual to wash hands with soap
- Avoid touching face
- Cough into sleeve or into tissues and dispose of them and wash hands
- When interacting face-to-face with staff, wear **surgical mask** (don't share)
- Advise Correctional Officer or NSH nursing staff if beginning to feel unwell or if symptoms worsen and / or experience any of the following.
    1) Difficulty breathing
    2) Chest pain
    3) Palpitations or rapid heart rate
    4) Confusion
    5) Dizziness or faintness

Check all that apply:

- ❑ Swab collected.
- ❑ Instructions provided to patient as above.
- ❑ Physician assessment needed and arranged.
- ❑ In the event of transfer, ensure swab collection status is communicated to receiving department / unit / secondary assessment centre
- ❑ Additional documentation, if required, completed in nursing notes.

Name of Assessor (Printed)	Signature of Assessor	Date (YYYY/MON/DD)	Time

NSCOVIDACEC

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Novel Coronavirus COVID-2019

Overview and Personal Protective Equipment Requirements

NSHA Infection Prevention and Control

March 2020

Evolving Situation

- On December 31,2019 the World Health Organization was alerted to several cases of pneumonia in Wuhan, Hubei Province China. The virus did not match any other known virus. On January 7, 2020 China confirmed a novel coronavirus.
- There is now rapid global spread in recent weeks and the situation is being closely monitored by the Office of the Chief Medical Officer of Health, NS Department of Health and Wellness in partnership with the Public Health Agency of Canada.
- WHO declares a pandemic March 11, 2020 at that time 118,000 cases in 114 countries
- Planning is ongoing and evolves as the global situation changes.

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Coronaviruses

- Coronaviruses are a large family of viruses which may cause illness in animals or humans. These viruses cause infections of the nose, throat and lungs. They are most commonly spread from an infected person through:
  - Coughing and sneezing.
  - Close personal contact, touching or shaking hands.
  - Touching something with the virus on it, then touching your mouth, nose or eyes before washing your hands.
- Many coronaviruses cause only minor symptoms similar to those of a cold. Two specific coronaviruses have lead to severe illness in humans:
  - Severe acute respiratory syndrome coronavirus (SARS)
  - Middle East respiratory syndrome coronavirus (MERS CoV)

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Novel Coronavirus 2019

- As new Viruses are discovered, they receive names. For example H7N9, H1N1, MERSCov, etc.
- This virus has been named SARS-CO-V-2.

- COVID-19 is the name of the infectious disease caused by this most recently discovered coronavirus.

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Screening and Diagnosis

If the patient presents with:

- fever (over 38 degrees celcius) **OR**
- new onset (or exacerbation of chronic) cough **and**
- in the 14 days prior has travelled outside Canada or has been in close contact with a confirmed case of COVID-19 or
- In contact with a person with symptoms who has travelled

**Refer to current Screening Tool for up-to-date information.*

A Nasopharyngeal (NP) swab is required for testing of standard respiratory viruses and SARS-CO-V-2. It will be forwarded to the QEII Microbiology Laboratory.

- Standard respiratory virus testing is done at the QEII but the specialized testing for this novel virus occurs at the National Microbiology Lab in Winnipeg.

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Symptoms

- Those infected with COVID-19 may have little to no symptoms.
- Those hospitalized in China often had co-existing medical conditions including hypertension, diabetes, cardiovascular disease, cancer, etc.

Symptoms have included:	
Fever	Fatigue
Dry Cough	Difficulty Breathing
Myalgia	Diarrhea

- These symptoms are similar to other respiratory viruses circulating in the winter months.

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Recovery

Global statistics from the World Health Organization (February 28, 2020)

- Most people (80%) recover from the disease without needing special treatment.
- Approximately 18 % of patients who get COVID-19 become seriously ill and develop difficulty breathing. Older people with underlying medical conditions are most likely to develop serious illness.
- Approximately 2-3 % of people with the disease have died.

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Transmission

- Many of the initial cases reported in Wuhan had exposure to a live animal market selling chickens, bats, marmots and other wild animals in addition to seafood which raised concerns that this was a zoonotic disease reminiscent of SARS and MERS.

- COVID-19 is spread by **droplet and contact** routes of transmission.
  - *Droplet*: Spread from person to person is through respiratory droplets when a person with the disease coughs or exhales.
  - *Contact*: These droplets land on objects and surfaces surrounding the person. Other people then touch these surfaces and then their eyes, mouth or nose.

- It is not spread through the air.

Public Health Agency of Canada

- Provides evidence-based recommendations on healthcare-associated infections.
- Infection Prevention and Control for Coronavirus Disease (COVID-19): Interim Guidance for Acute Healthcare Settings is intended to provide guidance to healthcare organizations and healthcare workers for management of symptomatic patients.
- The guidance is based on Canadian guidance documents developed for previous coronavirus outbreaks (e.g. SARS and MERS) as well as documents from the World Health Organization (WHO).
- The guidance developed for Canadian Healthcare settings and healthcare workers may differ from guidance developed by other countries.
- NSHA develops our protocols from this guidance.

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Care of the Patient

- Place the Patient in a Private Room with the door closed.
  - An Airborne Infection Isolation Room (Negative Pressure Room) is only required when performing an Aerosol Generating Medical Procedure.
- Place on Droplet and Contact Precautions
- Dedicate Equipment and use single use disposable when possible.
- Restrict patients to their rooms unless essential diagnostic/therapeutic procedures are required. Transfer within and between facilities should be avoided.
- Clean and disinfect non-disposable patient care equipment between patients as per Routine Practices.

Care of Patient continued…

- No agency staff or students should care for these patients.
- Limit the number of staff entering the patient room to essential personnel.
- Avoid unnecessary entries into the room. Ensure you have all necessary equipment/supplies on entry, and try to batch care tasks i.e. provide personal care while in the room to deliver scheduled medications or perform vital signs.
- Visitors will be restricted to those who are essential (parent, guardian, primary caregiver) and will visit the patient directly and exit the facility after the visit. They should be screened and managed if they have signs and symptoms and exposure criteria consistent with COVID-19. They will be required to wear the same PPE as staff for their visit.

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Additional Information:

- Testing for COVID-19 requires that the nasopharyngeal swab be sent to the National Microbiology Lab in Winnipeg for confirmation. This takes a few days. Please refer to PPHLN Novel Coronavirus- lab testing if further respiratory viral testing is required.
- Staff and Physicians can engage a trained interpreter via Language Services to support patients who do not speak English fluently or understand it fully.
- Ill staff members are to contact Occupational Health Safety and Wellness

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Personal Protective Equipment (PPE) Donning and Doffing

- PPE should be used based on the risk of exposure (e.g., type of activity) and the transmission dynamics of the pathogen (e.g., contact, droplet or aerosol). COVID-19 is spread by **droplet and contact routes of transmission**.
- The required PPE for Droplet and Contact Precautions is familiar to most healthcare workers as we utilize it frequently during Flu season.
- You must put on a gown, gloves, mask and eye/facial protection when within 2 meters of the patient.
- Posters have been created with the proper sequencing of putting on and removing the required PPE.

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Aerosol-Generating Medical Procedures (AGMPs)

- AGMPs are medical procedures that can generate aerosols as a result of artificial manipulation of a person's airway. They include: bronchoscopy, intubation, suctioning, BiPap, sputum induction, nasopharyngeal aspirate in pediatric populations, etc.

- AGMPs performed on patients with Novel or Emerging Respiratory Viruses require additional measures as per PHAC guidance documents and NSHA policies:
  - IPC-RP-015 Droplet Precautions
  - IPC-RP-025 Airborne Precautions.

- AGMPs should only be performed on patients suspected to have COVID-19 when medically necessary.
  - AGMPs should be performed in a Airborne Infection Isolation Room (AIIR) when feasible. If AIIR rooms are unavailable they should be performed in a single room with the door closed and away from high risk patients.
  - The number of healthcare workers present during an AGMP should be limited to those essential for patient care.
  - A N95 respirator and facial protection are recommended for all healthcare workers present for the AGMP on a suspected or confirmed case of COVID-19).

GUIDE TO PUTTING ON PERSONAL PROTECTIVE EQUIPMENT

Droplet & Contact Precautions

1 Hand Hygiene

Perform hand hygiene.

Alcohol-based hand rub is preferred. Use soap and water if hands are visibly soiled.

3b OR N95 Respirator

- Required for aerosol-generating medical procedures (AGMP's) for patients with unknown, novel or emerging pathogens.
- Refer to manufacturer for specific donning instructions.
- Perform a 'seal check' with each use.
- N95 respirators must be 'fit tested' prior to use.

4 Face/Eye Protection

- Several types of face/eye protection are available (e.g. mask with built in visor, goggles, full face shield)
- Place over the eyes or face.
- Adjust to fit.
- **NOTE**: Eyeglasses are not considered protective eyewear.

2 Long-sleeved gown

- Select level of gown based on fluid exposure risk.
- Make sure the gown covers from neck to knees to wrist.
- Tie at back of neck and waist.

5 Gloves

- Put on gloves.
- Pull the cuffs of gloves over the cuffs of the gown.

3a Procedure/surgical mask

- Secure ties or ear loops around head or ears so the mask stays in place.
- Fit moldable band around the bridge of your nose.
- Fit snugly to face over mouth and nose and below chin.

FOR NOVEL AND EMERGING PATHOGENS: Initiate Contact & Droplet Precautions and wear gloves, gown, procedure/surgical mask and face/eye protection when within 2 meters of patient.

For more information complete- Personal Protective Equipment (PPE) LMS video
LMS Code: 0973.01

Developed by Infection Prevention & Control- Jan 31, 2020

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GUIDE TO REMOVING PERSONAL PROTECTIVE EQUIPMENT

Droplet & Contact Precautions

1 Gloves

- Use glove to glove, skin to skin technique
- Outside of gloves are contaminated
- Discard in garbage

2 Hand Hygiene

Perform hand hygiene.

Alcohol based hand rub is preferred. Use soap and water if hand are visibly soiled.

3 Long-sleeved gown

- Carefully unfasten ties.
- Grasp the outside of the gown at the back by the shoulders and pull down over the arms.
- Turn the gown inside out during removal.
- Carefully fold into bundle. Do not rip off.
- Place disposable gown in garbage or place non-disposable gown in laundry hamper

4 Hand Hygiene

Perform hand hygiene.

Alcohol based hand rub is preferred. Use soap and water if hand are visibly soiled.

5 Face/Eye Protection

- Handle only by headband or earpieces
- Carefully pull away from the face
- Place non-disposable goggles in designated area for disinfection & disposable items in waste receptacle.

6 Mask OR N95 Respirator

- Handle only by the ties.
- Undo/remove bottom tie first, then top. Allow to fall away from face.
- **N95 respirator is removed outside of the patient room.**

7 Perform Hand Hygiene

8 Exit Patient Room, remove N95 (if applicable) & perform Hand Hygiene again as needed

For more information complete- Personal Protective Equipment (PPE) LMS video
LMS Code: 0373.01

Developed by Infection Prevention & Control - Jan 31, 2020

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Helpful PPE Tips:

- Perform Hand Hygiene prior to donning and after doffing.
- The order of putting on PPE is not as critical as removing.
- The one piece to remember in donning is to put your gloves on last.
- With doffing there are a few pointers:
  - Gloves are removed first as they are considered the most soiled.
  - The back of your gown is the cleanest- remove by pulling from the back and gently forward into a bundle.
  - Perform hand hygiene before you touch your face to remove facial protection/mask.
  - Remove eye/facial protection last and away from the patient.
  - Always remove an N95 outside of the patient room

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DO's & DON'Ts

FOR WEARING **GLOVES** FOR
ROUTINE PRACTICES & ADDITIONAL PRECAUTIONS

GLOVES

NON-STERILE GLOVES

STERILE GLOVES

DO

- ✓ DO wear **gloves** to reduce the risk of contamination or exposure to blood, body fluids, exudates or secretions.
- ✓ DO clean hands before putting on gloves.
- ✓ DO clean hands after removing gloves.
- ✓ DO wear gloves when caring for or in contact with a patient on Contact Precautions or their environment.
- ✓ DO clean hands and change gloves if they become torn, damaged or contaminated.
- ✓ DO make sure that gloves fit you properly before performing any tasks.
- ✓ DO ensure the correct type of glove is available if you have any skin or sensitivity issues.
- ✓ DO wear gloves for a sterile procedure.

DON'T

- ✓ DON'T lubricate glove use for **hand hygiene**.
- ✓ DON'T use non-approved hand lotions they may impact integrity of gloves.
- ✓ DON'T wear clean gloves or glove pocket for future use.
- ✓ DON'T use gloves if they are damaged or visibly soiled.
- ✓ DON'T touch face when wearing gloves.
- ✓ DON'T wear the same pair of gloves from one patient to another.
- ✓ DON'T forget to remove gloves and dispose of gloves properly.
- ✓ DON'T re-use or wash gloves.

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DO's & DON'Ts

FOR WEARING **GOWNS** FOR
ROUTINE PRACTICES & ADDITIONAL PRECAUTIONS

GOWNS

ISOLATION GOWNS

PROCEDURE GOWNS

DO

- ✓ DO wear a gown when caring for or in contact with a patient on Contact Precautions or their environment.
- ✓ DO perform hand hygiene before putting on and removing all PPE.
- ✓ DO wear a gown if you may come in blood or body fluids.
- ✓ DO wear a gown when performing a surgical or invasive procedure.
- ✓ DO secure the gown by the ties at the neck and waist.
- ✓ DO make sure the gown covers your clothing in front and back.
- ✓ DO make sure the gown fits securely around your wrists with gloves pulled over the cuffs.
- ✓ DO remove gown by slowly rolling it inside out and away from your body. Keep contaminated front and sleeves inside bundle.
- ✓ DO remove gown in the patient room or designated area (e.g. airlock).
- ✓ DO dispose of gown in designated waste or laundry receptacle (if reusable).

DON'T

- ✓ DON'T re-use the gown for the same or different patient. Gowns are single use.
- ✓ DON'T push or roll up sleeves on your forearm.
- ✓ DON'T allow contaminated gown to hang out of laundry bin or garbage.
- ✓ DON'T wear contaminated gown outside of patient room.

DO's & DON'Ts

FOR WEARING **MASKS & FACE PROTECTION** FOR
ROUTINE PRACTICES & ADDITIONAL PRECAUTIONS

MASKS & FACE PROTECTION

PROCEDURE MASK

FACE PROTECTION

DO

- ✓ DO wear **mask and face protection** when you may be at risk of splashes/sprays of blood, body fluids, excretions or secretions.
- ✓ DO wear mask and face protection when caring for or in contact with patients on Droplet Precautions.
- ✓ DO check to make sure mask and face protection has no defects, such as tear in face strap or ear loop.
- ✓ DO ensure mask covers your mouth & nose.
- ✓ DO remain mask when no longer in clinical space and patient intervention is complete.
- ✓ DO remove mask correctly pull away from face in downward motion.
- ✓ DO dispose of mask into waste receptacle by touching only ear loops or ties.
- ✓ DO perform hand hygiene before and after removing mask & face protection.

DON'T

- ✓ DON'T use a procedure mask when caring for patients on Airborne Precautions (use N95 respirator).
- ✓ DON'T reuse! Discard after use (exception: reusable goggles).
- ✓ DON'T wear if wet or moist, pull on a new mask.
- ✓ DON'T allow mask to hang or dangle around your neck.
- ✓ DON'T touch the front of the mask or face protection when wearing or during removal.

DO's & DON'Ts

FOR WEARING **N95 RESPIRATORS**

N95 RESPIRATOR

FIT TESTING

DO

- ✓ DO wear N95 Respirator when caring for or in contact with patients on Airborne Precautions OR for aerosol-generating medical procedures (AGMPs) on patients with a novel or emerging pathogen.
- ✓ DO follow manufacturer's instructions for donning and removal of respirator.
- ✓ DO check to make sure respirator has no defects, such as tears, holes or torn straps.
- ✓ DO perform hand hygiene before and after removing respirator.
- ✓ DO complete a 'fit or seal check' every time you wear a respirator to ensure a tight seal.
- ✓ DO remain mask when no longer in patient room/clinical space.
- ✓ DO remove respirator correctly: tilt head forward & remove by pulling bottom strap over back of head, followed by top strap without touching front of mask, pull away from face in downward motion.
- ✓ DO discard respirator in waste receptacle.

DON'T

- ✓ DON'T wear a mask that you have **not been fit tested for.**
- ✓ DON'T wear if wet or soiled, put on a new respirator.
- ✓ DON'T reuse! Discard after use.
- ✓ DON'T allow respirator to hang or dangle around your neck.
- ✓ DON'T touch the front of the respirator when wearing or during removal.
- ✓ DON'T let patients or visitors wear respirators unless they have been fit tested to wear it.

Mask Myths...I should wear a mask all of the time to protect myself

- Health care workers caring for individuals who have respiratory symptoms such as a cough and fever should wear a mask and eye protection while caring for them (within 2 meters).
- Symptomatic patients who are outside of their room i.e. being transported to diagnostic imaging, another care unit/facility should wear a mask for this time frame to help contain any droplets. They should also wear a mask while in a waiting room if there is a delay to placing them in a private room.
- Some Immunosuppressed patient populations (e.g. patients undergoing cancer treatment or dialysis) may benefit from wearing a mask while in public spaces...this is normal practice for this group.

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Pandemic

- A pandemic is the worldwide spread of a new disease.
- It can easily spread between people leading to a worldwide outbreak.
- In the past many pandemics have been caused by new Influenza viruses.
- During pandemic activity, personal protective equipment is in high demand across the globe. It is often challenging to acquire a large amount of supplies in a short time frame.

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Resources

- NSHA and IWK Policies on Additional Precautions
- Public Health Agency of Canada (2020). Infection prevention and control for coronavirus disease (COVID-19): Interim guidance for acute healthcare settings.
- Province of Nova Scotia. (2019). Respiratory Response Plan for Public Health 2019-2020.
- World Health Organization (WHO). Coronavirus disease (COVID-19) outbreak website.
- Coronavirus Update button on the NSHA intranet page. "One Source of Truth"
  - Infection Prevention and Control tools
  - Occupational Health Safety and Wellness
  - Public Health Lab testing information and other resources.

  The information housed on this page is updated as new information is learned about this novel virus.

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Last updated July 08, 2020 1400 hrs (check OP3 to ensure this is the most current version)

MENTAL HEALTH & ADDICTIONS SERVICES
Care Directive

Title:	ECFH & OHS Screening for COVID-19 by Swab Collection	Number:	CD-ECF-001
Sponsor:	Senior Director Mental Health & Addictions	Page:	1 of 5
Approved by:	Emergency Operations Center HAMAC	Approval Date: Effective Date:	March 20, 2020 March 20, 2020
Applies to:	East Coast Forensic Hospital & Offender Health Services: RNs, LPNs, ACPs and CCPs		

This Care Directive Applies only to East Coast Forensic Hospital (ECFH) and Offender Health Services (OHS). The ECFH & OHS has been deemed a high priority site based on its co-location with Nova Scotia Correctional Facilities.

PURPOSE

This care directive provides the conditions under which the Registered Nurse (RN), Licensed Practice Nurse (LPN), Advanced and Critical Care Paramedics (ACP and CCP), can assess and swab patients presenting with concern of COVID-19 / SARS-CoV-2 infection.

POLICY

1. If patient presents with Red Flags +/- Risk Factors: Consult with the medical physician on-duty/call using SBAR to discuss clinical assessment and interventions needed to manage clinical presentation.
   1.1. When red flags are present, the priority is to manage the clinical presentation.
   1.2. If required to transfer patient to an Emergency Department for further assessment, ensure transport as per local protocol or activate EHS.
   1.3. If unable to obtain swab before transfer, ensure swab collection status is communicated to receiving department/unit.

1.4. Red flags include:

Adult and Pregnancy Red Flags
Adult: Heart rate greater than 110 **Pregnancy:** Heart rate greater than 120 or less than 50
Adult: Respiration rate greater than 30 **Pregnancy:** Respiration rate equal to or greater than 30 or less than 10
Chest pain
Adult: SpO2 less than 92% on room air **Pregnancy**: SpO2 less than 94% on room air

2. If no Red Flags, the RN and LPN are authorized to collect a nasopharyngeal or throat/nare swab on all patients admitted to ECFH and OHS.

> **Note:** During the Pandemic, LPNs are only authorized to independently enact the **collection of COVID-19 swabs** using a care directive. (See Nova Scotia College of Nursing Statement)

3. The ACP/CCP is not authorized to autonomously implement this CD and must collaborate with RN or medical physician on-duty/call.
4. The name of the AP must be included on the lab requisition for COVID-19.
    4.1. Dr. Lisa Barrett, Assistant Professor, Infectious Disease/ Microbiology and Immunology is the AP for the ECF and OHS.

PROCEDURE

Admission

1. Admit all patients/offenders, place on droplet precautions, and swab for COVID-19.
    1.1. In addition to routine practices initiate:
        - IPC-RP-015 Droplet Precautions and IPC-RP-010 Contact Precautions.
2. If the patient has red flags +/- risk factors, consult the medical physician on duty/call to determine patient disposition.

Swab

3. Nasopharyngeal swabs are the preferred sample choice. Refer to IPC-SC-001 Nasopharyngeal Swab Collection and Screening for Respiratory Illness.
    - Throat and nares collection is the alternate choice. Refer to Instructions

for the alternate collection of Throat and Nares for COVID-19 testing 2020-03-19

NOTE: If collection supplies are low or unavailable, contact the lab for further direction and refer to the **Laboratory Updates** on the Coronavirus Intranet Page.

4. Ordering and requisition requirements:

   4.1. Complete Microbiology requisition or for Meditech Order Entry, follow COVID-19 Process for Ordering as posted.

   4.2. Include the name of the AP (Dr. Elsa Barrett), on the lab requisition; for review and follow-up.

   4.3. Ensure the top of the specimen container is tightened and that the requisition is not placed in the bag with the specimen.

   4.4. Send swabs promptly to the local laboratory.

   - For sites that require off-site transport to the local laboratory, follow Procedure - Off Site Viral Swab Packaging for Transport and Job Aid - Off Site Viral Swab Packaging.
   - All swabs will be transported to the Central Zone Laboratory at the QEII Health Sciences Centre.

Educate

5. Educate the patient as per COVID-19 Assessment Chart.

Document

6. Use COVID-19 Assessment Chart for East Coast Forensic Hospital and Offender Health Services.

   6.1. If additional documentation is required then follow site procedure to ensure documentation is completed and properly labelled.

RELATED DOCUMENTS

Coronavirus Disease (COVID-19)

COVID-19 Process for Ordering

Correction Facilities Lab Requisition

Novel Coronavirus - Lab testing

COVID-19 Assessment Chart for ECFH and OHS

Procedure for Sampling Covid-19 Using HOLOGIC Swabs

Instructions for the alternate collection of Throat and Nares for COVID-19 testing 2020-03-19P

Policies

IPC-CD-001 Outbreak Management

IPC-CD-030 Reporting Notifiable Diseases and Conditions

IPC-SC-001 Nasopharyngeal Swab Collection and Screening for Respiratory Illness

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VERSION HISTORY

Major Revisions (e.g. Standard 4 year review)	Minor Revisions (e.g. spelling correction, wording changes, etc.)
March 19, 2020 New	
March 25, 2020 – Updated Screening Criteria	
April 09, 2020 Updated to include new symptom Criteria and red flags.	
April 21, 2020 Updated to reflect new admission criteria, etc.	
April 22, 2020 Updated 4.1 page 3	
April 23, 2020 Updated 4.0 page 3	
April 29, 2020 Revised Procedure #3 and #4	
June 04, 2020 Revised Policy Statement Section	
July 08, 2020 1. Removed Procedure statements 3 and 4 under the "Admission" heading. 2. Revised Red Flags.	

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COVID-19 RISK ASSESSMENT (Version 16. 2021FEB10)

For patients receiving healthcare service within NS Health

Date (YYYY/MON/DD):

The following risk assessment must be completed for every patient who receives face to face services or is admitted.

The COVID-19 Risk Assessment should be placed in the front of the patient's chart when completed or placed in a location and communicated to team members who are caring for the patient. The Risk Assessment is used to facilitate patient, staff and physician safety.

It is the responsibility of the Most Responsible Provider to ensure that the assessment is completed and signed at the time of healthcare interaction or admission.

COVID-19 RISK FACTORS: (Completed by any healthcare worker)

If the patient meets any of the boxes below have the patient wash / sanitize their hands and put on a surgical mask.

Do you currently have the following symptoms:

❑ An unexplained fever (measured temperature greater than 38.0) or fever like symptoms: chills or sweats OR

❑ A new or worsening cough OR

Two or more of the following symptoms (new or worsening): ❑ Sore throat ❑ Runny nose ❑ Headache ❑ Shortness of breath

❑ No symptoms

Non-symptomatic risk factors:

In the past 14 days, has the patient or anyone in their household traveled outside of NS or PEI:

❑ Yes, patient ❑ Yes, household member ❑ No

In the last 14 days, has the patient been in close contact with someone who has COVID-19 or suspected of having COVID 19:

❑ Known case ❑ Suspected case ❑ No Known COVID-19 contacts

In the last 14 days, has the patient been to any location identified by Public Health Alert (see COVID-19 Hub) and instructed to self isolate and be tested for COVID-19:

❑ Yes ❑ No

Does the patient live or work within a known facility cluster as identified on the COVID-19 Hub:

❑ Lives within a known COVID-19 facility cluster ❑ Works within a known COVID-19 facility cluster

❑ Does not live or work in a facility cluster

Does the patient live within a known community cluster as identified on the COVID-19 Hub:

❑ COVID-19 community cluster ❑ Does not live within a community cluster

Most Responsible Provider must verify the above (or complete if not done by another team member) and complete the boxes below

PATIENT RISK COVID-19 ASSESSMENT:

IDENTIFIED COVID-19 RISK (See page 2 for actions)	NO IDENTIFIED COVID-19 RISK
Confirmed case OR symptomatic (unexplained fever, OR new or worsening cough, OR two or more symptoms (new or worsening): sore throat, runny nose, headache, shortness of breath) / other acute respiratory illness consistent with infection OR patient / someone in their household traveled outside of NS or PEI OR contact with known or suspected COVID-19 case OR resides in a known community / facility cluster or works in a facility cluster OR Public Health Alert exposure OR symptoms / exposure cannot be determined due to physical and / or mental status	Asymptomatic and no identified non-symptomatics risk factors of COVID-19
☐	☐

COVID-19 SWAB HISTORY (*see page 2):

Has the person been tested for COVID-19:

❑ Not Indicated ❑ Done; Date of swab (YYYY/MON/DD): _____ ❑ POS ❑ NEG ❑ pending (check SHARE for pending swab)

Verified by (PMB # if applicable): _____ Signature: _____

Updated by (if applicable): _____ Signature: _____

please print

nova scotia health

COVID–19 RISK ASSESSMENT (Version 18, 2021FEB10)

Guidance in caring for patient IDENTIFIED RISK for COVID–19:

All healthcare providers and physicians should have a surgical mask on as per universal masking practice or surgical mask and eye protection (universal pandemic precautions) if working in a facility where UPP has been implemented.

- If the patient has been swabbed (i.e. for surveillance or pre-procedural screening) but does not have any risk factors listed on page 1, the patient DOES NOT require additional precautions.

Ambulatory Services:

- If the patient has COVID–19 or is symptomatic (unexplained fever or cough OR two of the following symptoms: shortness of breath, sore throat, runny nose, headache), have the patient wash / sanitize their hands and put a surgical mask on. The healthcare provider should don droplet and contact precautions. After the appointment, disinfect all equipment used. The room needs to be cleaned as per droplet and contact precautions protocol after the appointment.
- If the patient is asymptomatic but has an identified COVID–19 non–symptom risk factor, have the patient wash / sanitize their hands and put a surgical mask on. After the appointment use disinfectant wipes to clean all equipment and high touch surfaces.
- If the patient is asymptomatic and has identified as having non–symptomatic risk factors ask them to call 811 for advice around testing. Patients whose ONLY risk factor is residence in a community cluster, DO NOT need to call 811 or be tested.

  Complete the Risk Assessment in advance of the ambulatory care appointment. It is not necessary to test a patient for COVID–19 before coming to their ambulatory care appointment.

Emergency Department Services:

- If the patient has an **identified COVID–19 Risk**, please have the patient wash / sanitize their hands and put a surgical mask on:
  - UPP facility: If patient's ONLY risk factor is residence in a community cluster, patient does not need droplet and contact precautions, UPP is sufficient.
  - Non–UPP facility: Place patient on droplet and contact precautions.
- Disinfect all equipment used. If the patient required droplet and contact precautions, the room needs to be cleaned as per droplet and contact precautions protocol after the patient leaves.
- If the patient is asymptomatic but has travelled or resides in facility cluster or has been in close contact and has not been swabbed for COVID–19, please swab the patient and provide them with "*COVID–19 Patient Information Sheet*".
- If patient's ONLY risk factor is residence in a community cluster and the patient is **NOT** being admitted, they DO NOT need to have a COVID–19 test.

Patient requiring admission and has an identified COVID–19 Risk: *See NS Health COVID–19 Admission Pathway.*

- Swab patient for COVID–19 (if not already done).
- Patients who are admitted should have the COVID–19 Risk Assessment reviewed and updated if patient's status changes.
- If patient is symptomatic, they are admitted on droplet and contact precautions (see zone or facility specific COVID–19 admission pathways).
- In the event that it is not possible to assess a patient's risk of COVID–19 because the patient's physical or mental health precludes them from providing a history of symptoms or exposure, the patient is to be placed on droplet and contact precautions, tested for and managed as a suspect COVID–19 for 48h. If asymptomatic at 48h, exposure risk has been determined to be negative, and COVID–19 swab is negative, patient can be removed from droplet and contact precautions and managed with routine practices.
- If the patient is a close contact of a person with COVID–19 or has traveled / has a household member who has traveled outside of NS or PEI in the last 14 days for any reason or resides / works in a facility cluster or is part of Public Health Alert exposure, place the patient on droplet and contact precautions, swab the patient (if not already done so), keep the patient on droplet and contact precautions for 14 days and monitor for symptoms as per inpatient symptoms monitoring (*COVID–19 ILI symptoms monitoring for inpatients*)
- If the patient's ONLY risk factor is residence in a community cluster;
  - UPP facility: If patient's ONLY risk factor is residence in a community cluster, patient does not need droplet and contact precautions. UPP is sufficient.
  - Non–UPP facility: Place patient on droplet and contact precautions.

Patients requiring resuscitation (Code Blue) and has COVID–19 or an identified COVID–19 Risk.

- Use **airborne** precautions for AGMP's.

  Mask and eye protection are to be used by the first responders in a Code Blue situations, regardless of COVID–19. If patient has COVID–19 or an identified COVID–19 risk factor and manual ventilation or intubation is required, all responders should be donned in airborne precautions.

Let us help

MORNEAU SHEPELL

Access your Employee and Family Assistance Program (EFAP) 24/7 by phone, web or mobile app.

1.800.461.5558 TTY: 1.877.338.0275
workhealthlife.com

Download My EAP app now at your device app store or scan the QR code.

Laissez-nous vous aider

MORNEAU SHEPELL

Accédez à votre programme d'aide aux employés et à la famille (PAEF) en tout temps, par téléphone, sur le Web ou à l'aide de votre appareil mobile.

1.800.461.5558 ATS-ATME : 1.877.338.0275
travailsantevie.com

Téléchargez l'application Mon PAE à partir de la boutique d'applications de votre appareil ou balayez le code QR ci-contre.

Mental Health Connections for Health Care Workers - Self-Care

As a health care worker you may be experiencing fear, anxiety, and a sense of powerlessness. There could even be aspects such as rage and anger toward those who have not followed public health advice. There can also be compassion fatigue.

Taking time to focus on self-care and your own mental health before the stress gets too high can help you cope during this time.

Relax

- Take a mental break and sit quietly for a few minutes.
- Relax with easy and quick techniques (belly breath, stretches, visualization) to destress.
- Challenge "what if" thoughts and focus on the things you can control.

Treat Your Body Well

- Take care of your body. When you can, drink water and eat healthy.
- Moving your body or getting some fresh air can improve your mood and decrease stress.
- Be aware of your level of substance use – including smoking, vaping, and alcohol.

Connect and Connect Again

- Emotional support and healthy problem solving are vital to your health and well-being.
- Connect with people both in your personal and work lives (phone calls, virtual meetings, etc.).
- Explore, follow or join a new social network around a hobby or interest.

Unplug, If That's Helpful

- Don't feel like you have to be constantly productive. Doing what makes you laugh or provides an escape (binge watch a show, listen to music you like, read a book) is good for your well-being. There is no shame in needing to relax, laugh or take time for yourself.
- Decide how much time you're going to devote to checking reliable news and social media sources. If media and news brings you down- consider giving it a time limit in your day.

Still having difficulty coping. Now what?

Mindwell U is a free, mindfulness challenge that only takes five minutes per day. It challenges you to take a part out of your day to learn the basics in mindfulness, a practice that allows a person to focus their attention and be fully present in a moment.

If you still feel significant distress around COVID-19 and feel you are not coping well, you may need extra support.

Reach out to NSHA resources like:

- Our **Intake line**, call toll free **1-855-922-1122** self-refer to Community Mental Health and Addictions clinics, Withdrawal Management Services, or Opioid Replacement and Treatment Program,
- The **Provincial Mental Health Crisis Line** is available 24/7 by calling toll free **1-888-429-8167.**
- **Employee Assistance Programs** offer important support and assistance.

Mental Health and Wellness Connections
for Colleagues and Peers

Lots of us are feeling **worried** and **stressed** about the ongoing coronavirus outbreak.

You don't need to be an expert on mental health to be there for colleagues and peers.

Top Five Ways to Support Each Other

1 Check In

You might not be able to meet face-to-face, but picking up the phone, having a video call, starting a group chat or messaging someone on social media lets them know you are there to talk and ready to listen.

2 Listen & Reflect

If someone opens up to you, remember that you don't need to fix things or offer advice. Often just listening, and showing you take them seriously, can help someone to manage.

3 Ask Questions

Asking how people are managing can help someone to open up and explore what they're feeling. Ask again if you're worried they aren't sharing the full picture.

4 Avoid Making Assumptions

Don't try to guess what symptoms a co-worker might have and how these might affect their life or their ability to do their job – many people are able to manage mental illness and perform their role to a high standard.

5 Respect Confidentiality

Remember mental health information is confidential and sensitive. Don't pass on information. A breach of trust could also negatively impact someone's mental health.

If you feel they are experiencing a mental health crisis direct them to the **Provincial Mental Health Crisis** line **1-888-429-8167** or **call 911** if it is an emergency.

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New eMH Tools in Your Toolbox

You may have heard about three new online eMH services we have launched in MHAP. Nova Scotians can now self-refer and enroll for free (descriptions of each below). Accessible through the Mental Health and Addictions Public Website at https://www.nshealth.ca/content/online-mental-health-services

Clinicians are not required to create or manage any client accounts or monitor client's activities in any of these programs.

ICAN (Conquer Anxiety and Nervousness)

Many adults experience mild-to moderate anxiety and depression at some point. In this program, people work with a coach to learn about anxiety and the valuable life-skills that have been proven to overcome nervousness.

This service is private and confidential and offered through the Strongest Families Institute- a charity that provides proven services to those seeking help for issues impacting health and mental well-being.

With weekly telephone support from a coach, individuals work through materials in a manual or via a secure website. The program offers skill demonstration videos, practice activities and follows a client-centered program that is customized to their needs. People can access the program from the comfort and privacy of their own home.

Adults can now self-refer to this program here https://login.strongestfamilies.com/folder/1963/

Therapy Assisted Online (TAO) Self-Help

TAO is a free and private online resource available in French and English. It includes interactive activities and videos for people having challenges with their mental health. Each person can choose which topics they want to explore and go at their own pace. Topics include:

- Calming your worry
- Let go and be well
- Interpersonal relationships and communication
- Leave Your Blues Behind
- Improving Your Mood
- Evaluating Alcohol and Drug Use
- Pain Management

TAO Self-Help has many videos, skill tips and short activities. As individuals engage with the interactive components, they gain knowledge, self-awareness, and skills to achieve their mental health goals. Some of the skills TAO focuses on are:

- stress management,
- mindfulness,
- problem solving
- strategies to avoid dwelling on your concerns, and
- develop more helpful thinking patterns

For more information, or to sign up for TAO please visit: https://taoconnect.org/what_is_tao/ns/

MINDWELL•U

Mindwell U

Mindwell U is a free online 30-day challenge that takes just five minutes a day. Accessible on any device at any time of day in French and English.

In brief 5 mins modules the challenge teaches basics in mindfulness: how to focus your attention and be fully present in a moment. This practice lowers stress and increases resilience.

The Challenge focuses on practicing 'mindfulness-in-action' so people don't need to stop what they are doing to become calmer, present and more focused.

Everyone who registers for the Challenge can invite a buddy to take the training with them if they choose as a way to help keeping on track and support one another.

How does it work?

1) Visit https://app.mindwellu.com/novascotia to sign up.
2) Complete your short profile, invite a buddy (optional but recommended)
3) Each day for 30 days you recieve an email that guides you through a "Take 5" session

The Challenge starts every Tuesday but you can sign up anytime.

Please watch this short video to learn more about Mindwell Challenge

What we need from you:

Your support and involvement in sharing information about these new tools will help the programs get into the hands of Nova Scotians who may benefit. For additional information on the tools you can watch the overview videos so you are informed about what the programs offer

We'd also ask you to share broadly with clients who you think could benefit from building these skills and share the online links in your personal networks and with colleagues. Let them know these tools have been evaluated and have been to reduce stress and increase resilience

Thank you for your help making these new services an impactful experience for all!

Coping with COVID-19

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For many of us, COVID-19 is creating an uncertain future. People worry about their own health, the health of their loved ones, school, work, or finances. This is an anxious and stressful time for everyone. It's okay to take time for your mental health – good mental health and positive wellbeing can help you better cope during this time.

Take Action

Being proactive can help you take back control and reduce anxiety. Look to trusted organizations and agencies like the **Nova Scotia Government**, **Health Canada** and **World Health Organization** for information about how to reduce your risk of getting sick or passing the illness on to others.

Take Care of Yourself

 Eat as well as possible.

 Exercise regularly.

 Make time for hobbies.

 Get enough sleep.

Stay Connected with Family and Friends

Isolating yourself from others can affect your mood. Find ways to connect with people you care about in other ways - you can still reach out by phone, text, or video call.

Help Others if You Can

Ask friends, family members, or neighbours if they need anything, such as groceries or other household needs. Simply checking in regularly by phone, text, or video call can make a big difference.

Cut Back on Social Media and the News

Constantly checking for updates or reading sensationalized stories can really take a toll on your mental health. Try to avoid excessive exposure and limit yourself if social media or news stories increase your anxiety. If you need to limit conversations, it's okay to tell family, friends, and co-workers that you can't participate.

Explore Self-Management Strategies

Explore self-management strategies like mindfulness, yoga, meditation, art, or relaxation techniques to manage anxious thoughts.

You can find self-management strategies for anxiety from Anxiety Canada and Kids Help Phone.

Anxiety Canada

Kids Help Phone

Have a Plan

It's hard to predict exactly what will happen next, but preparing for situations like self-isolation can help reduce some uncertainty about the future.

People with preexisting mental health conditions and/or substance use disorders should continue with their treatment as much as possible and be aware of new or worsening symptoms.

The Mental Health Provincial Crisis Line is available **24 hours a day, 7 days a week** to anyone experiencing a mental health or addictions crisis or someone concerned about them, by calling **1-888-429-8167** (toll free).

For information and updates, visit: www.novascotia.ca/coronavirus

Staff Support - Offerings
November –December 2020

Care for the Caregiver

Honouring Your Mental Health & Wellness

Dear NSHA Team Members:

Below is a list of offerings available to all clinical and support staff, supporting our mental health and wellbeing. During these difficult, uncertain times you may need a little extra support. The Provincial Mental Health Crisis Line is available 24/7, toll-free 1-888-429-8167 as is your EFAP provider 1-800-461-5558. Thank you for all that you do.

CONTINUOUS OFFERINGS

By Request – *All Formal Leaders*

MicroCoaching for Leaders: Brief (15-20 minute), focused, just-in-time coaching for individual leaders. Email: basia.solarz@nshealth.ca to request this service.

SCHEDULED OFFERINGS

Nova Scotia Health in Collaboration with Community Partners:

Grief: Yours, Mine & Ours Leading into the Holidays

With a grief and trauma informed care lens, we would like to invite you to participate in the upcoming wellness forum for all Healthcare & Community Partners leading into the holiday season. Beginning November 19th, 2020 the forum will take place each week and will be web based from 12:00-1:00PM. Moderated by Serena Lewis, Provincial Grief and Bereavement Lead and Pam MacLean, Workplace Health Promotion Consultant, each session will be an opportunity to share and reflect with our diverse helping community. Please feel free to attend all or a single session.

Nov 26, 2020: Managing our Fatigue: Compassion Satisfaction and Resilience
Pam MacLean & Roy Ellis, Bereavement Coordinator
To join: https://nshealth.webex.com/nshealth/j.php?MTID=mf5ff9b7186c575383da6d3556265fd97

Dec 3, 2020: Finding Peace in the Season
David Maginley, Spiritual and Religious Care & Linden Hardie, Hospice Halifax
To Join: https://nshealth.webex.com/nshealth/j.php?MTID=mf5ff9b7186c575383da6d3556265fd97

Dec 10, 2020: Coping through Adversity: A deeper dive into self-awareness
Danielle Leblanc, Clinical Manager MHA & Brian Brooks, Jr and Sr High School Counsellor – L'nu Spipuk Kina'muokuom
To Join: https://nshealth.webex.com/nshealth/j.php?MTID=mf5ff9b7186c575383da6d3556265fd97

Dec 17th, 2020: Mindfulness for Times of Stress
Basia Solarz, Consultant, Communication and Conflict Competence, T&OD
To Join: https://nshealth.webex.com/nshealth/j.php?MTID=mf5ff9b7186c575383da6d3556265fd97

Dec 21, 2020: Transitions & Expectations- 2020-2021
Pam MacLean & Serena Lewis
To Join: https://nshealth.webex.com/nshealth/j.php?MTID=m937f66976c92d80863bde03604f52600

***These sessions will not be recorded to maintain confidentiality.*

For more information, feedback or suggestions, please contact:
Pam MacLean Workplace Health Promotion Consultant, OHSW pamelac.maclean@nshealth.ca
Visit the OHSW Site @ http://intra.nshealth.ca/ohsw/SitePages/Home.aspx and/or T&OD Site - http://intra.nshealth.ca/tod/SitePages/Home.aspx

nova scotia health authority

Memorandum

To: Zone Leadership

From: COVID-19 NSHA EOC

Date: April 7, 2020

Subject: Change in Practice re Masking

We appreciate all you are doing to plan, prepare, and care for patients with COVID-19; we know these are extraordinary times. After careful consideration, NSHA will be implementing a new practice around masking during the COVID-19 pandemic. Specifically, all staff who provide patient care or work in patient care areas will be asked to wear a procedure mask throughout their entire shift (refer to FAQ for more detailed information).

We need your help in working with staff to implement this strategy on the patient care area(s) you oversee. Site leads will work to set up a process for distribution of masks for staff on your site. One procedure mask per shift will be distributed to staff at the beginning of their shift. Staff will be able access additional masks should they be required.

Information is available to share with staff in the attached *Frequently Asked Questions* document.

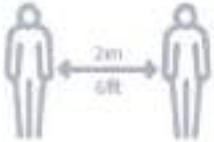
We know and are grateful for the important role you are playing in leading and supporting staff during this remarkable time. Thank you for always making quality and safe care of patients and staff safety priorities.

GUIDELINES FOR GATHERINGS WITHIN NSH FACILITIES

nova scotia health

Healthcare worker and learner education are core pieces of NSH operations, the following guidelines have been developed to ensure the care and safety of healthcare workers and patients. During gatherings:

in clinical areas:



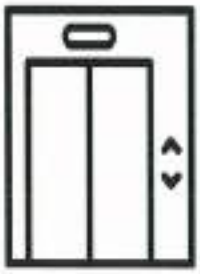
- limit learners and healthcare workers essential to patient care in patient rooms
- ensure physical distancing during team rounds, patient discussions, hand-offs, and post conferences
- virtual technology should be utilized whenever possible
- stagger break times to ensure physical distancing and minimize contacts
- mandatory universal masking is required at all times

in non-clinical areas

- virtual technology should be utilized whenever possible
- rooms shall be set up to maintain physical distancing
- mandatory universal masking is required during in-person gatherings
- regardless of room capacity, in-person classroom sessions shall be limited to 20 (10 in CZ) including instructors/presenters
- maintain group rotation of breaks/sessions to limit the number of contacts in each group
- communal food and drink are not permitted arrange for individual/pre-packaged food and drink choices
- ensure frequent cleaning of high touch surfaces

in common areas

- ensure physical distancing is maintained at all times including lunch and break times
- when sharing a meal/break consider seating arrangements to minimize face to face interactions and/or ensure physical distancing
- ensure physical distancing on benches/picnic tables
- limit number of persons in elevator to maintain physical distancing



Infection Prevention & Control
Occupational Health Safety & Wellness
Interprofessional Practice & Learning

Revised: 2020 11 25

POINT OF CARE RISK ASSESSMENT

Before each patient/resident/client interaction, the health care worker completes a 'Point of Care Risk Assessment' (PCRA) by asking the following questions to determine the risk of exposure and appropriate Routine Practices and Additional Precautions required for safe care:

- **What are the patient's symptoms?**
- **What is the degree of contact?**
- **What is the degree of contamination?**
- **What is the patient's level of understanding and cooperation?**
- **What is the degree of difficulty of the procedure being performed and the experience level of the care provider?**
- **What is my risk of exposure to blood, body fluids, excretions, secretions, non-intact skin and mucous membranes?**

The PCRA allows the health care worker to determine what personal protective equipment (PPE) to select and wear for that interaction. PCRA should be performed even if the patient has been placed on Additional Precautions as more PPE may be required.

Will my hands be exposed to blood, excretions, secretions, tissues, non-intact skin or contaminated items in the environment?	· If YES, perform hand hygiene and wear gloves
Will my face be exposed to a splash, spray, cough or sneeze? Will I be within 2 metres of a coughing patient?	· If YES, wear facial protection (includes mask and protective eyewear)
Will my skin or clothing be exposed to splashes or items contaminated with blood, body fluids excretions, secretions or non-intact skin?	· If YES, wear a gown
Does the patient have a suspected or confirmed airborne illness (e.g. measles, tuberculosis chicken pox)? Am I performing an aerosol-generating medical procedure (AGMP) on a patient with a suspected or confirmed novel or emerging respiratory pathogen?	· If YES, wear a respirator (N95)

REMEMBER: Perform Hand Hygiene before and after PPE use so you do not introduce germs to patients or yourself.

IWK Health Centre

nova scotia health authority

Privacy Office
Legal Services
Centennial 1-031
1276 South Park Street
Halifax NS B3H 2Y9
Telephone: (902)473-2869
Fax: (902)473-7850

March 23, 2021

Sent via e-mail

Re: Full Disclosure – OUR FILE# NSHA-2021-33

Nova Scotia Health Authority (NSHA) received your request under the Freedom of Information and Protection of Privacy (FOIPOP) Act for various datasets relating to COVID-19 testing.

Please find attached our response. These records are being provided to you in their entirety. We are now closing your application with our Office.

Should you have any questions or comments, please do not hesitate to contact me at the address or telephone number provided above.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review

Sincerely,

Fola Adeleke

For: The Privacy Office
Nova Scotia Health Authority

c/c: to file

Laboratory	SARS CoV 2 Test	Ct value
QEII	In house assay based on BCCDC primers for RdRp on ABI 7500 fast	RdRp CT <35 = positive RdRp CT 35 -38 = indeterminate
	Hologic Panther Aptima SARS CoV 2 assay	Positive based on manufacturer's criteria. Assay does not produce a Ct value
	GeneXpert Xpert Xpress SASR-COV-2/Flu/RSV	Ct<37 = positive Ct ≥ 37 = indeterminate
	Roche 6800 – Cobas SARS CoV 2 assay	Ct<38 = positive Ct ≥ 38 = indeterminate
IWK	Biofire Respiratory 2.1 panel	Positive based on manufacturer's criteria - Ct value not reported by the instrument and cut off not defined by manufacturer
	GeneXpert Xpert Xpress SASR-COV-2/Flu/RSV	Ct<37 = positive Ct ≥ 37 = indeterminate
Cape Breton Regional	Hologic Panther Aptima SARS CoV 2 assay	Positive based on manufacturer's criteria. Assay does not produce a Ct value
	GeneXpert Xpert Xpress SASR-COV-2/Flu/RSV	Ct<37 = positive Ct ≥ 37 = indeterminate
St Martha's Hospital	GeneXpert Xpert Xpress SASR-COV-2/Flu/RSV	Ct<37 = positive Ct ≥ 37 = indeterminate
Aberdeen Hospital	GeneXpert Xpert Xpress SASR-COV-2/Flu/RSV	Ct<37 = positive Ct ≥ 37 = indeterminate
Colchester Regional	GeneXpert Xpert Xpress SASR-COV-2/Flu/RSV	Ct<37 = positive Ct ≥ 37 = indeterminate
Cumberland Regional Health Care Center	Biofire Respiratory 2.1 panel	Positive based on manufacturer's criteria - Ct value not reported by the instrument and cut off not defined by manufacturer
	GeneXpert Xpert Xpress SASR-COV-2/Flu/RSV	Ct<37 = positive Ct ≥ 37 = indeterminate
Valley Regional Hospital	GeneXpert Xpert Xpress SASR-COV-2/Flu/RSV	Ct<37 = positive Ct ≥ 37 = indeterminate
	Biofire Respiratory 2.1 panel	Positive based on manufacturer's criteria - Ct value not reported by the instrument and cut off not defined by manufacturer
Yarmouth Regional Hospital	GeneXpert Xpert Xpress SASR-COV-2/Flu/RSV	Ct<37 = positive Ct ≥ 37 = indeterminate

1. *Confirmation of the cycle threshold used in Nova Scotia to determine a positive case of covid-19. Several sources have indicated this to be 35 but would like official confirmation from public health. Has the cycle threshold always been the same, or has it changed since March of 2020? If it's ever changed, please provide the date(s) of change and what the value was before and after the change*

   The early assay and Ct values were refined over time based on ongoing validation and quality assurance. The current cut offs have been in place since mid-first wave. Exact dates are not available

2. *What is the average number of PCR amplification cycles that has been required to determine a positive Covid-19 test in Nova Scotia to date, since March 2020? As in, if you add up the total cycles for each positive case (1659 to date) and divide by 1659, what is that number? If you have raw data you can send, that would be preferable and then I am happy to work it out myself. Of course I am not looking for any identifying information, just the number of amplification cycles associated with each positive test*

   Average Ct of all positive test was 26.9

3. *Of the total positive Covid-19 tests in NS to date, how many (or what percentage) of them required greater than or equal to 30 PCR amplification cycles? As per my last point, if you are able to provide the requested data I can easily work this out for myself. A simple spreadsheet showing the cycle threshold for each positive case would suffice (again, no identifying information is being requested, column A could simply say "positive case #1" all the way to "positive case #1659" (as of today) and column B would just have the PCR amplification value associated with that case/test)*

   Proportion of specimens with Ct > 30 = 35%

4. *Of the 65 Covid-19 related deaths that have occurred to date in NS since March 2020, what is the PCR amplification cycle that was required to detect each case and determine a positive Covid-19 result? If you are able to send the data as indicated already, an additional column simply indicating which of the tests was associated with a case that ended in death would suffice, or in any manner of your choosing that allows me to calculate this information. A document that simply has 65 values on it would be sufficient. It for some reason this data cannot be provided, the average PCR amplification cycles for each test that ended up in death would be sufficient, though having the data over a simple average is preferable*

   The PCR values are not linked directly to patient clinical outcomes, we do not have this data for you.

1. *Please provide all lab names and locations in Nova Scotia which are conducting the COVID-19 RT-PCR tests for SARS-CoV2 for the Nova Scotia Government for determining cases of COVID-19 in Nova Scotia. I also require at how many Cycle thresholds (Ct) each lab is using for the RT-PCR COVID-19 submitted for determining cases of COVID-19 in Nova Scotia.*

Laboratory	SARS CoV 2 Test	Ct value
QEII	In house assay based on BCCDC primers for RdRp on ABI 7500 fast	RdRp CT <35 = positive RdRp CT 35 -38 = indeterminate
	Hologic Panther Aptima SARS CoV 2 assay	Positive based on manufacturer's criteria. Assay does not produce a Ct value
	GeneXpert Xpert Xpress SASR-COV-2/Flu/RSV	Ct<37 = positive Ct ≥ 37 = indeterminate
	Roche 6800 – Cobas SARS CoV 2 assay	Ct<38 = positive Ct ≥ 38 = indeterminate
IWK	Biofire Respiratory 2.1 panel	Positive based on manufacturer's criteria - Ct value not reported by the instrument and cut off not defined by manufacturer
	GeneXpert Xpert Xpress SASR-COV-2/Flu/RSV	Ct<37 = positive Ct ≥ 37 = indeterminate
Cape Breton Regional	Hologic Panther Aptima SARS CoV 2 assay	Positive based on manufacturer's criteria. Assay does not produce a Ct value
	GeneXpert Xpert Xpress SASR-COV-2/Flu/RSV	Ct<37 = positive Ct ≥ 37 = indeterminate
St Martha's Hospital	GeneXpert Xpert Xpress SASR-COV-2/Flu/RSV	Ct<37 = positive Ct ≥ 37 = indeterminate
Aberdeen Hospital	GeneXpert Xpert Xpress SASR-COV-2/Flu/RSV	Ct<37 = positive Ct ≥ 37 = indeterminate
Colchester Regional	GeneXpert Xpert Xpress SASR-COV-2/Flu/RSV	Ct<37 = positive Ct ≥ 37 = indeterminate
Cumberland Regional Health Care Center	Biofire Respiratory 2.1 panel	Positive based on manufacturer's criteria - Ct value not reported by the instrument and cut off not defined by manufacturer
	GeneXpert Xpert Xpress SASR-COV-2/Flu/RSV	Ct<37 = positive Ct ≥ 37 = indeterminate
Valley Regional Hospital	GeneXpert Xpert Xpress SASR-COV-2/Flu/RSV	Ct<37 = positive Ct ≥ 37 = indeterminate
	Biofire Respiratory 2.1 panel	Positive based on manufacturer's criteria - Ct value not reported by the instrument and cut off not defined by manufacturer
Yarmouth Regional Hospital	GeneXpert Xpert Xpress SASR-COV-2/Flu/RSV	Ct<37 = positive Ct ≥ 37 = indeterminate

2. *Please provide the genome sequence for SARS-CoV2 that each of the above requested labs are using to identify COVID-19 when conducting the RT-PCR COVID-19 tests to determine cases in Nova Scotia.*

Assay	Gene	Primer sequence
In house assay (ABI 7500 fast)	RdRp	**RdRP_Lee_Forward -** TGCCGATAAGTATGTCCGCA **RdRP_Lee_Reverse –** CAGCATCGTCAGAGAGTATCATCATT **RdRp probe -** FAM-MGB TTGACACAGACTTTGTGAATG
Hologic Panther Aptima SARS CoV 2 assay	ORF 1a/b	Not available - proprietary
GeneXpert Xpert Xpress SASR-COV-2/Flu/RSV	E N2	Not available - proprietary
Roche 6800 – Cobas SARS CoV 2 assay	E ORF1	Not available - proprietary
Biofire Respiratory 2.1 panel	S M	Not available - proprietary

Privacy Office; Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

May 21, 2021

Re: Full Disclosure – OUR FILE# NSHA-2021-060

On May 11, 2021 Nova Scotia Health (NSH) received your request under the *Freedom of Information and Protection of Privacy Act* (*FOIPOP Act*).

We understand your application to be for a copy of the following:
Please provide the following data for the following dates -
April 20 - May 10, Number of positive covid-19 test results by DATE test conducted.
No new records need be created. You can redact all non-relevant/personal information.
(Date Range for Record Search: From 04/19/2021 To 05/09/2021)

Please find below the records located in response to your request. We are providing these records to you in their entirety. We are now closing your file.

Please note that the results are listed by date of specimen collection and represents first positive tests for distinct individuals by collected date. Any re-tests have been removed.

Day of Specimen Collection	Number of all Positive Results
20-Apr-21	43
21-Apr-21	41
22-Apr-21	68
23-Apr-21	73
24-Apr-21	85
25-Apr-21	93
26-Apr-21	116
27-Apr-21	120
28-Apr-21	179
29-Apr-21	173
30-Apr-21	178
01-May-21	145
02-May-21	140
03-May-21	126
04-May-21	148
05-May-21	170
06-May-21	149
07-May-21	112
08-May-21	108
09-May-21	95

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1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

10-May-21	122

Should you have any questions, please do not hesitate to contact me.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review.

Sincerely,
Katie Smith
Freedom of Information Officer
Nova Scotia Health Authority
Halifax, Nova Scotia

Privacy Office: Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

July 12, 2021

Sent via e-mail

Re: Full Disclosure – OUR FILE# NSHA-2021-062

On July 12, 2021 Nova Scotia Health (NSH) received your request under the *Freedom of Information and Protection of Privacy Act* (*FOIPOP Act*).

We understand your application to be for a copy of the following:

1) List of all brands of COVID test used since start of 2020
2) The type of test for each COVID test in use (PCR, Other)
3) Statement of Government approval for all tests.
4) For non PCR tests, claimed margin of error.
5) For PCR test number of cycles used, if it varies a list of labs and the varied levels.
6) Cost of each type of test and the number administer during the requested period.
(Date Range for Record Search: From 12/31/2019 To 05/12/2021)

Please find a copy of the records located in response to your request. We are providing these records to you in their entirety. We are now closing your file.

Should you have any questions, please do not hesitate to contact me.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review.

Sincerely,
Katie Smith
Freedom of Information Officer
Nova Scotia Health Authority
Halifax, Nova Scotia

IVD Rx Only 2 °C 30 °C

REF 256082
500048916(05)
2021-01

BD

Veritor™ System
For Rapid Detection of SARS-CoV-2

Kit configured for testing nasal swab samples freshly collected, processed and dispensed directly onto assay test device.

For use under an Emergency Use Authorization only, in the United States.

30
Determinations

bd.com/e-labeling

Becton, Dickinson and Company
7 Loveton Circle
Sparks, Maryland 21152 USA

BD Veritor™ System
For Rapid Detection of SARS-CoV-2

Kit configured for testing nasal swab samples freshly collected, processed and dispensed directly onto assay test device.

For *In Vitro* Diagnos ic Use.
For use with the BD Veritor™ Plus Analyzer running firmware version 5.4 or later.
For use under an Emergency Use Authorization only in the United States.

Please read these instructions completely before beginning to test specimens.

INTENDED USE

The BD Veritor™ System for Rapid Detec ion of SARS-CoV-2 is a chromatographic digital immunoassay intended for the direct and qualitative detection of SARS-CoV-2 nucleocapsid an igens in nasal swabs from individuals who are suspected of COVID-19 by heir healthcare provider within the first five days of the onset of symptoms. In the United States, testing is limited to laboratories cer ified under he Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a, that meet the requirements to perform moderate, high, or waived complexity tests. This test is authorized for use at the Point of Care (POC), i.e., in patient care settings opera ing under a CLIA Certificate of Waiver, Cer ificate of Compliance, or Certificate of Accreditation.

Results are for the identifica ion of SARS-CoV-2 nucleocapsid antigen. This antigen is generally detectable in upper respiratory samples during the acute phase of infection. Positive results indicate the presence of viral antigens, but clinical correlation with patient history and other diagnostic information is necessary to determine infec ion status. Posi ive results do not rule out bacterial infection or co-infection wi h other viruses. The agent detected may not be the definite cause of disease. Laboratories within the United States and its territories are required to report all positive results to the appropriate public health au horities.

Nega ive results should be treated as presumptive, do not rule out SARS-CoV-2 infection and should not be used as the sole basis for treatment or patient management decisions, including infection control decisions. Negative results should be considered in the context of a patient's recent exposures, history and the presence of clinical signs and symptoms consistent with COVID-19, and confirmed with a molecular assay, if necessary, for patient management.

The BD Veritor™ System for Rapid Detec ion of SARS-CoV-2 is intended for use in point of care settings and operated by healthcare professionals or trained users specifically instructed in the use of he BD Veritor™ System and proper infection control procedures. In he United States, the BD Veritor™ System for Rapid Detec ion of SARS-CoV-2 is only for use under the Food and Drug Administration's Emergency Use Authorization.

SUMMARY AND EXPLANATION OF THE TEST

A novel coronavirus (2019-nCoV) was identified in December 2019,[1] which has resulted in hundreds of thousands of confirmed human infections worldwide. Cases of severe illness and deaths have been reported. On February 11, 2020 the International Committee for Taxonomy of Viruses (ICTV) renamed he virus SARS-CoV-2.

The median incubation ime is estimated to be approximately 5 days[2] with symptoms es imated to be present wi hin 12 days of infec ion. The symptoms of COVID-19 are similar to o her viral respiratory diseases and include fever, cough, and shortness of breath.

The BD Veritor™ System for Rapid Detec ion of SARS-CoV-2 is a rapid (approximately 15 minutes) chromatographic digital immunoassay for the direct detec ion of the presence or absence of SARS-CoV-2 an igens in respiratory specimens taken from patients with signs and symptoms who are suspected of COVD-19. The test is intended for interpretation in both laboratory and near patient tes ing environments only wi h the BD Veritor™ Plus Analyzer Instrument. The test is not intended to be interpreted visually. Procedures to evaluate test devices depend on the BD Veritor™ Plus Analyzer workflow configuration chosen. In **Analyze Now mode**, the instrument evaluates assay devices after manual timing of their development. In **Walk Away mode**, devices are inserted immediately after application of the specimen, and timing of assay development and analysis is automated. Additionally, connec ion of a BD Veritor™ Plus Analyzer to a printer or IT system is possible if desired. Additional result documentation capabilities are possible wi h the integra ion of a BD Veritor™ Barcode Scanning Enabled module. Please refer to he BD Veritor™ Plus Analyzer Instructions for Use for details on how to implement these features.

PRINCIPLES OF THE PROCEDURE

The BD Veritor™ System consists of a dedicated opto-electronic interpretation instrument and immunochromatographic assays for the qualitative detection of antigens from pathogenic organisms in samples processed from respiratory specimens. The BD Veritor™ System for Rapid Detection of SARS-CoV-2 is designed to detect the presence or absence of SARS-CoV-2 nucleocapsid proteins in respiratory samples from patients wi h signs and symptoms of infection who are suspected of COVID-19. When specimens are processed and added to he test device, SARS-CoV-2 antigens present in the specimen bind to antibodies conjugated to detector particles in the test strip. The antigen-conjugate complexes migrate across the test strip to the reaction area and are captured by a line of antibodies bound on he membrane. A positive result is determined by the BD Veritor™ Plus Analyzer when antigen-conjugate is deposited at he Test "T" position and the Control "C" position on he assay device. The instrument analyzes and corrects for non-specific binding and detects positives not recognized by the unaided eye to provide an objective result.

REAGENTS

The following components are included in the BD Veritor™ System for Rapid Detection of SARS-CoV-2 kit.

Materials Provided:

KIT COMPONENT	QUANTITY	DESCRIPTION
BD Veritor™ System Test Devices	30 single use test devices	Foil pouched test device containing one reactive strip. Each strip has one line of murine anti-SARS coronavirus monoclonal antibody on the test line, and one of biotin coupled to bovine protein on he positive control line. Murine and Leporine anti-SARS coronavirus and anti-biotin monoclonal antibodies conjugated to detector reagents are bound in the sample delivery area.
Extrac ion Reagent	30 single use reac ion tubes, each with 325 µL extraction reagent and having an integral dispensing tip	Detergent solution with less than 0.1% sodium azide (preservative).
Specimen sampling swabs	30 sterile, single use specimen sampling swabs	For sample collection and transfer.
SARS-CoV-2 (+) Control Swab	1 each – individually wrapped for single use	Non-infectious, recombinant viral protein antigen wi h less than 0.1% sodium azide.
SARS-CoV-2 (–) Control Swab	1 each – individually wrapped for single use	Buffer wi h less than 0.1% sodium azide.
Assay documentation	1 each - Instruc ions for use 1 each - Quick reference instruction card 1 each - Nasal sampling instructions	

MATERIALS REQUIRED BUT NOT PROVIDED	OPTIONAL EQUIPMENT
• BD Veritor™ Plus Analyzer (Catalog number 256066) • BD Veritor™ System InfoScan Module (Catalog Number 256068)* • Timer • Tube rack for specimens • Any necessary personal protective equipment	• USB Printer cable for BD Veritor Plus Analyzer (Catalog number 443907) • Epson Printer model TM-T20 II • BD Veritor™ Plus Connect (contact your BD representative for details)

* If necessary to configure instrument display language

WARNINGS AND PRECAUTIONS

1. For *in vitro* diagnostic use. Only for use under an Emergency Use Au horization in the United States.
2. In the USA, this product has not been FDA cleared or approved; but has been authorized by FDA under an EUA for use by authorized laboratories; use by laboratories certified under the CLIA, 42 U.S.C. §263a, that meet requirements to perform moderate, high, or waived complexity tests and at the Point of Care (POC), i e., in patient care settings opera ing under a CLIA Certificate of Waiver, Certificate of Compliance, or Cer ificate of Accreditation.
3. This product has been authorized only for he detection of proteins from SARS-CoV-2, not for any o her viruses or pathogens; and, in the USA, this product is only au horized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostics for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declara ion is terminated or authorization is revoked sooner.
4. Do not use this kit beyond he expiration date printed on he outside carton.
5. Do not use the kit to evaluate patient specimens if either the positive control swab or negative control swab fail to give expected results.
6. Test results are not meant to be visually determined. All test results must be determined using he BD Veritor™ Plus Analyzer.
7. To avoid erroneous results, specimens must be processed as indicated in the assay procedure sec ion.
8. Do not reuse any BD Veritor™ System test device or kit components.
9. Do not use components from any other BD Veritor test with the BD Veritor System for Rapid Detection of SARS-CoV-2. While components from o her BD Veritor tests may appear similar, they are not the same.
10. When collecting a nasal swab sample, use the nasal swab supplied in the kit.
11. Other than the swabs used for specimen collection, kit components should not make contact with he patient.
12. Proper specimen collec ion, storage and transport are critical to the performance of this test.

13. Specific training or guidance is recommended if operators are not experienced with specimen collection and handling procedures. Wear protective clo hing such as laboratory coats, disposable gloves, and eye protection when specimens are collected and evaluated.
14. Pathogenic microorganisms, including hepatitis viruses and Human Immunodeficiency Virus, may be present in clinical specimens. Standard precautions and institutional guidelines should always be followed in handling, storing, and disposing of all specimens and all items contaminated with blood or other body fluids.
15. The SARS-CoV-2 posi ive control swabs have been prepared from recombinant viral proteins and do not contain infectious material.
16. Dispose of used BD Veritor™ System test devices and reagents as biohazardous waste in accordance with federal, state and local requirements.
17. Reagents contain sodium azide, which is harmful if inhaled, swallowed or exposed to skin. If there is contact with skin, wash immediately with plenty of water. Contact with acids produces very toxic gas. Dispose of used BD Veritor™ System test devices and reagents in accordance with federal, state and local requirements in an approved biohazard waste container. Do not flush reagents down the drain.
18. Test devices used in a laminar flow hood or in areas with high air flow should be covered during test development to ensure proper sample flow.
19. For additional information on hazard symbols, safety, handling and disposal of he components within this kit, please refer to the Safety Data Sheet (SDS) located at bd.com.

STORAGE

Kits may be stored at 2–30 °C. DO NOT FREEZE. **Reagents and devices must be at room temperature (15–30 °C) when used for testing**.

SPECIMEN COLLECTION AND HANDLING

Specimen Collection and Preparation

Acceptable specimens for testing with his kit include nasal swab specimens obtained by the dual nares collection method. It is essen ial hat correct specimen collection and prepara ion methods be followed. Specimens obtained early during symptom onset will contain the highest viral iters; specimens obtained after five days of symptoms are more likely to produce negative results when compared to an RT-PCR assay. Inadequate specimen collection, improper specimen handling and/or transport may yield a falsely negative result; therefore, training in specimen collection is highly recommended due to the importance of specimen quality for generating accurate test results.

Specimen Transport and Storage

Freshly collected specimens should be processed as soon as possible, but no later than one hour after specimen collection. It is essential that correct specimen collection and preparation me hods be followed.

Nasal Swab Specimen Collection

1. Insert swab into one nostril of the patient. The swab tip should be inserted up to 2.5 cm (1 inch) from the edge of the nostril. Roll the swab 5 times along the mucosa inside the nostril to ensure that both mucus and cells are collected. Take approximately 15 seconds to collect the sample.
2. Using the same swab, repeat this process for the other nostril to ensure that an adequate sample is collected from both nasal cavities.
3. Withdraw the swab from he nasal cavity. The sample is now ready for processing using the BD Veritor™ System SARS-CoV-2 kit. The swab should be processed in the extraction reagent vial within one hour.

NOTE: The BD Veritor™ System Kit includes swabs for nasal specimen collection.

DO'S AND DON'TS OF SPECIMEN COLLECTION

- Do collect sample as soon as possible after onset of symptoms
- Do test sample immediately.
- Use only swabs provided with the kit.
- In the United States, refer to: Interim Guidelines for Collec ing, Handling and Testing Clinical Specimens from persons for COVID-19 at https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html.
- Outside the United States, refer to applicable guidelines from o her national or local authorities.

TEST PROCEDURE

Reagents, specimens and devices must be at room temperature (15–30 °C) for testing.

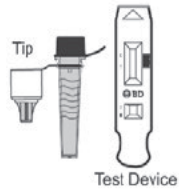
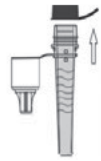
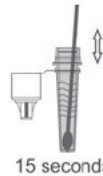
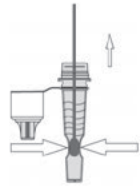
This BD Veritor™ System assay kit is only intended for nasal swab specimens that are collected and tested directly (i.e., swabs that have NOT been placed in transport media). The kit includes a pre-diluted processing reagent in a ready to use "unitized" tube. This kit IS NOT INTENDED for testing liquid samples such as wash or aspirate samples or swabs in transport media as results can be compromised by over dilution.

Getting Ready To Test

The following steps assume that the BD Veritor™ Plus Analyzer is ready to use. To choose or change any BD Veritor™ Plus Analyzer settings, see the BD Veritor™ Plus Analyzer Instructions for Use. A printer is not necessary to display results. However, if your facility has chosen to connect the BD Veritor™ Plus Analyzer to a printer, check that the BD Veritor™ Plus Analyzer is plugged into a power source, paper supply is adequate and any necessary network connections are enabled before testing.

Once the nasal swab has been collected from the nostrils, the swab should be processed within one hour.

Procedural steps for Nasal Swabs or control swabs:

1 • Remove one extraction reagent tube/tip and one BD Veritor™ System test device from its foil pouch immediately before testing or within 5 minutes of opening. If uncovered, debris may land on the device read window and interfere with line interpretation causing false positive or invalid results. • Label one test device and one extraction reagent tube for each specimen or control to be tested. • Place he labeled extraction reagent tube(s) in a rack in the designated area of the workspace.	
2 Remove and discard the cap from the extraction reagent tube.	
3 Insert he swab into he tube and plunge the swab up and down in the fluid for a minimum of 15 seconds, taking care not to splash contents out of the tube.	
4 Remove he swab while squeezing the sides of the tube to extract the liquid from the swab.	
5 Press the attached ip firmly onto the extrac ion reagent tube containing the processed sample (hreading or twisting is not required). Mix horoughly by swirling or flicking the bottom of he tube.	

NOTE: Do not use tubes or tips from any o her product, including other products from BD or o her manufacturers.

Once the swab has been processed in the extraction reagent and the tube has been capped, the sample should be added to the test device within 30 minutes.

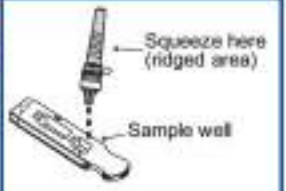
After step 5, choose from the BD Veritor™ Plus Analyzer workflow option below before continuing to step 6:				
	BD Veritor™ Plus Analyzer in **Analyze Now** mode	BD Veritor™ Plus Analyzer in **Walk Away** mode	BD Veritor™ Plus Analyzer with the BD Veritor™ Barcode Scanning Enabled Module	
			in **Analyze Now** mode	in **Walk Away** mode
Instructions in section:	**A**	**B**	**C**	**D**

A Using a BD Veritor™ Plus Analyzer in "*Analyze Now*" mode*:

6A **Adding the specimen to the test device (If testing in batches, jump to Step 6A-Batch)**

- Invert the extraction reagent tube and hold it vertically (approximately one inch above the sample well).
- Gently squeeze the ridged body of the tube, dispensing three (3) drops of the processed specimen into the sample well.
- Excess volume remains for retesting if necessary.

NOTE: Squeezing the tube too close to the tip may cause leakage. This could result in contamination or insufficient sample to run the assay, potentially resulting in a false positive or invalid result.



7A **Timing test development**

- After adding the sample, allow the test to run for **15 minutes but no longer than 20 minutes** before inserting the test device into the BD Veritor™ Plus Analyzer.
- During incubation time, turn the BD Veritor™ Plus Analyzer on by pressing the blue power button once.

NOTE: Test devices used in a laminar flow hood or in areas with high air flow should be covered during test development to prevent sample evaporation and incomplete sample flow which may produce an erroneous false negative false positive result or control invalid result.

CAUTION: Incorrect results may occur if development time is less than 15 minutes. Some lines may appear on the device sooner. Do not read device visually. Do not read test devices before 15 minutes as this could result in a false negative or invalid result. Do not read devices after 20 minutes as false negative, false positive or invalid results may occur.

8A **Using the BD Veritor™ Plus Analyzer**

- The BD Veritor™ Plus Analyzer will complete a self-test before it is ready for use. After the self-test the display window shows "INSERT TEST DEVICE OR DOUBLE-CLICK BUTTON FOR WALK AWAY MODE".
- INSERT THE TEST DEVICE when the 15-minute assay development time is complete.
- The status of the assay analysis process appears in the display window. Follow the on-screen prompts to complete the procedure. Do not touch the instrument or remove the test device until the result appears.
- When analysis is complete, the test result appears in the display window.

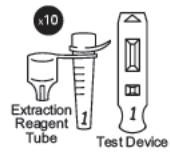
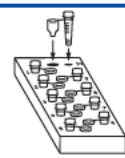
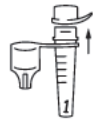
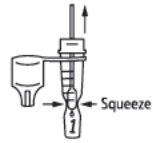
9A **Record the result before removing the test device.**

"ATTENTION TEST Results are NOT maintained in the display window when the device is removed or if the BD Veritor™ Plus Analyzer is left unattended for more than 15 minutes(60 minutes if AC power adapter is connected).

Instructions for Batch Testing

Processing errors that result in false positive or false negative results may occur when inadequate time is planned between multiple specimens in batch mode. Allow adequate time for each specimen to process in the test device and for obtaining and recording Analyzer results. Follow CDC Guidelines for changing gloves and cleaning work area between specimen handling and processing. https://www.cdc.gov/coronavirus/2019-nCoV/lab/lab-biosafety-guidelines.html. The following recommendations were developed based upon a single replicate of 12 specimens tested by professional operators within 30 minutes. Untrained or inexperienced operators may not be able to accurately process as many specimens in batch mode. Each institu ion should develop a batch testing protocol to ensure that patient specimens can be tested accurately and in accordance wi h the instructions for use.

A-Batch Batch Sample Collection (10 Tests):

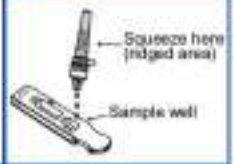
6A Batch	**Gather 10 sets of test materials.** • Open test device pouches. • Label each set with patient ID (extraction reagent tube and test device).	
7A Batch	**Label the tube tray with the patient ID.** • Set each tube in the tray with the matching patient ID.	
8A Batch	Select extraction reagent tube and remove cap.	
9A Batch	**Insert patient sample swab** and vigorously plunge the swab up and down for 15 seconds taking care not to splash contents out of the tube.	
10A Batch	**Remove swab** while squeezing to extract liquid. Properly dispose of swab.	
11A Batch	Press dispensing tip on the tube firmly. **Mix** he sample by swirling the bottom of the tube.	
12A Batch	Place tube back in tray with matching patient ID. • Repeat steps 8A–12A until all remaining tubes have been prepared. • Specimen processed in the reagent vial must be **run within 30 minutes** on the test device.	

A-Batch Batch Preparation and Analysis (10 Tests):

13A Batch

Select the extracted Sample and the matching test device for each specimen. **Add 3 drops of the processed sample** to the test device sample well.

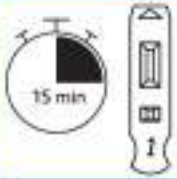
NOTE: Squeezing the tube too close to the tip may cause leakage. This could result in contamination or insufficient sample to run the assay.



14A Batch

Activate a 15-minute timer. Each test device **must incubate for 15 minutes** before it can be analyzed.

NOTE Do not read test devices before 15 minutes as this could result in a false negative or invalid result. Do not read devices after 20 minutes as false positive, false negative or invalid results may occur.



15A Batch

Repeat steps 13A–14A until all remaining devices **have been prepared and are incubating**, with a timer running staggering each test by 30 seconds.

16A Batch

Power on the BD Veritor™ Plus Analyzer by pressing the blue start button once. The device is now ready to be inserted into the Analyzer. Analyzer may remain on until all testing is completed.

17A Batch

When prompted, **insert the test device to read.**

18A Batch

If using the optional bar code reader module, follow the screen prompts to scan operator ID and kit lot number to start the test analysis.

After scans are completed, the BD Veritor™ Plus Analyzer displays a countdown time and test analysis begins.

19A Batch

Result will appear on screen and will be stored in the BD Veritor™ Plus Analyzer.

- Record result.
- Remove test device and properly dispose.
- Continue with the next device once it has incubated for 15 minutes.

***ATTENTION TEST Results are NOT maintained in the display window when the device is removed or if the BD Veritor™ Plus Analyzer is left unattended for more than 15 minutes(60 minutes if AC power adapter is connected).**

B Using the BD Veritor™ Plus Analyzer in "*Walk Away*" mode*: with no barcode scanning module installed

To use Walk Away mode - connect the AC power adapter to the Analyzer and a power source

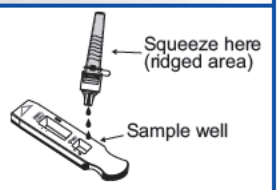
6B **Starting Walk Away Mode**

- Turn the BD Veritor™ Plus Analyzer on by pressing the blue power button once
- When the display window reads: "INSERT TEST DEVICE OR DOUBLE-CLICK FOR WALK AWAY MODE", Double-click the blue power button.
- The display window reads "ADD SPECIMEN TO TEST DEVICE AND INSERT IMMEDIATELY".

7B **Adding the specimen to the test device**

- Invert the extraction reagent tube and hold it vertically (approximately one inch above the sample well).
- Gently squeeze the ridged body of the tube, dispensing three (3) drops of the processed specimen into the sample well.
- Excess volume remains for retesting if necessary.

NOTE: Squeezing the tube too close to the tip may cause leakage.This could result in contamination or insufficient sample to run the assay, potentially resul ing in a false posi ive or invalid result.



CAUTION: A countdown timer displays the time remaining for test insertion. Walk Away mode must be activated again when this timer expires. Confirm timer is visible and Walk Away mode is activated before inserting test device.

8B **Starting the development and reading sequence**

- Insert the test device into the slot on the right side of the BD Veritor™ Plus Analyzer.

The test device must remain horizontal to prevent spilling the specimen out of the sample well, potentially contaminating the workspace and compromising the integrity of the result.

- "DO NOT DISTURB TEST IN PROGRESS" appears in the display window. Automatic timing of the assay development, image processing and result analysis begins.The status of the assay analysis process appears in the display window. Follow the on-screen prompts to complete the procedure. Do not touch the instrument or remove the test device until the result appears.
- The display window shows the remaining analysis time.

Do not touch the BD Veritor™ Plus Analyzer or remove the test device during this process. Doing so will abort the assay analysis. If this happens within 5 minutes of starting the assay, restart the BD Veritor™ Plus Analyzer, select Walk-Away Now mode and insert the device again for a 15-minute read. If this occurs after 5 minutes and if there is sufficient remaining extracted sample, re-apply the extracted sample to a new device and re-analyze after 15 minutes. If there is insufficient extracted sample, a new swab specimen will be needed.

9B **Record the result before removing the test device.**

- When analysis is complete, he test result appears in he display window. Record the result and discard the test device appropriately.

***ATTENTION TEST Results are NOT maintained in the display window when the device is removed or if the BD Veritor™ Plus Analyzer is left unattended for more than 15 minutes(60 minutes if AC power adapter is connected).**

C Using the BD Veritor™ Plus Analyzer in "*Analyze Now*" mode with a barcode scanning module installed

6C **Adding the specimen to the test device**

- Invert the extraction reagent tube and hold it vertically (approximately one inch above the sample well).
- Gently squeeze the ridged body of the tube, dispensing three (3) drops of the processed specimen into the sample well.
- Excess volume remains for retesting if necessary.

NOTE Squeezing the tube too close to the tip may cause leakage. This could result in contamination or insufficient sample to run the assay, potentially resulting in a false positive or invalid result.

7C **Timing test development**

- After adding the sample, allow the test to run for **15 minutes but no longer than 20 minutes** before inserting the test device into the BD Veritor™ Plus Analyzer.

NOTE Test devices used in a laminar flow hood or in areas with high air flow should be covered during test development to prevent sample evaporation and incomplete sample flow which may produce an erroneous false negative, false positive result or control invalid result.

CAUTION **Do not read test device visually. Some lines may appear on the device before the end of the incubation time. Do not read test devices before 15 minutes as this could result in a false negative or invalid result . Do not read devices after 20 minutes as false negative, false positive or invalid results may occur.**

8C **Using the BD Veritor™ Plus Analyzer**

During the test device incubation time, turn on the BD Veritor™ Plus Analyzer by pressing the blue button once.

The display window briefly shows "SCAN CONFIG BARCODE." This is an opportunity to change the configuration of the BD Veritor™ Plus Analyzer. Ignore this message and postpone this process when an assay is awaiting analysis. Please refer to the BD Veritor™ Plus Analyzer Instructions for Use for configuration steps.

- When assay development time is complete and the BD Veritor™ Plus Analyzer display window reads "INSERT TEST DEVICE OR DOUBLE-CLICK FOR WALK AWAY MODE", insert the BD Veritor™ System SARS-CoV-2 device into the slot on the right side of the BD Veritor™ Plus Analyzer.

9C **Using the barcode scanner**

Follow the prompts on the display screen to complete any required barcode scans of:

— OPERATOR ID

— SPECIMEN ID and/or

— KIT LOT NUMBER

- **Prompts for each scanning step appear in the display window for only 30 seconds. Failure to complete scans during that time will cause the BD Veritor™ Plus Analyzer to default to the beginning of step 8C. To restart this step, remove and reinsert the test device to initiate a new reading sequence.**
- **Move barcodes slowly toward the window until a confirmation tone sounds. The scanned barcode value appears in the next display window.**
- **The BD Veritor™ Plus Analyzer can record the Kit Lot Number and expiration date in the test record but does not restrict the use of expired or inappropriate reagents. Management of expired materials is the responsibility of the user.**

After required scans are completed, the BD Veritor™ Plus Analyzer displays a countdown timer and test analysis begins.

- **Do not touch the BD Veritor™ Plus Analyzer or remove the test device during this process. Doing so will abort the assay analysis.**
- When analysis is complete a result appears in the display window. If configured to display, the specimen ID barcode value also appears. If a printer is connected, specimen ID and result are automatically printed.

If the printer is not connected, record the result before removing the assay device.

ATTENTION **TEST Results are NOT maintained in the display window when the device is removed or if the BD Veritor™ Plus Analyzer is left unattended for more than 15 minutes (60 minutes if AC power adapter is connected).**

10C **Removing the test device**

Remove and then discard the test device appropriately. The display will show "INSERT TEST DEVICE OR DOUBLE-CLICK BUTTON FOR WALK AWAY MODE" to indicate the BD Veritor™ Plus Analyzer is ready to perform another test.

If the BD Veritor™ Plus Analyzer is connected to an LIS, a steady ENVELOPE symbol will appear to indicate that results are awaiting transmission. If a network connection is not detected while the ENVELOPE symbol is still displayed, the BD Veritor™ Plus Analyzer will queue all untransmitted results and attempt to transmit them when reconnected. If it is powered off during this time, it will attempt to transmit as soon as power is restored, and connection is re-established. A flashing envelope indicates that data are in the process of being transmitted.

D Using the BD Veritor™ Plus Analyzer In "*Walk Away*" mode with a barcode scanning module installed

To use Walk Away mode - connect the AC power adapter to the BD Veritor™ Plus Analyzer and a power source

6D

Starting Walk Away Mode

- Turn the BD Veritor™ Plus Analyzer on by pressing the blue power button once. The display window will briefly show "SCAN CONFIG BARCODE". This is an opportunity to change the configuration of the BD Veritor™ Plus Analyzer. Please refer to the BD Veritor™ Plus Analyzer Instructions for Use for configuration steps. Ignore this message and postpone this process when an assay is awaiting analysis.
- When the display window reads: "INSERT TEST DEVICE OR DOUBLE-CLICK FOR WALK AWAY MODE", Double-click the blue power button.

7D

Using the barcode scanner

- Follow the prompts on the display screen to complete any required barcode scans of:

— OPERATOR ID
— SPECIMEN ID and/or
— KIT LOT NUMBER

- **Prompts for each scanning step appear in the display window for only 30 seconds. Failure to complete scans during that time will cause the BD Veritor™ Plus Analyzer to default to the beginning of step 6D. To restart this step, remove and reinsert the test device to initiate a new reading sequence.**
- **Move barcodes slowly toward the window until a confirmation tone sounds. The scanned barcode value appears in the next display window.**
- **The BD Veritor™ Plus Analyzer can record the Kit Lot Number and expiration date in the test record but does not restrict the use of expired or inappropriate reagents. Management of expired materials is the responsibility of the user.**

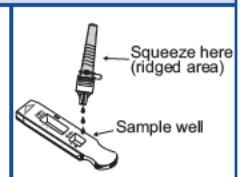
8D

Adding the specimen to the test device

- When the display window reads: "ADD SPEC MEN TO TEST DEVICE AND NSERT IMMEDIATELY":

— Invert the tube, holding it vertically (approximately one inch above the BD Veritor™ System SARS-CoV-2 device sample well).
— Gently squeeze the ridged portion of the tube, dispensing three (3) drops of the processed specimen into the sample well.
— Excess volume remains for retesting if necessary.

NOTE: Squeezing the tube too close to the tip may cause leakage. This could result in contamination or insufficient sample to run the assay, poten ially resulting in a false positive or invalid result..



CAUTION: A countdown timer displays the time remaining for test insertion. Walk Away mode must be activated again when this timer expires. Confirm timer is visible and Walk Away mode is activated before inserting test device.

9D

Starting the development and reading sequence

- Insert the test device into the slot on the right side of the BD Veritor™ Plus Analyzer. The test device must remain horizontal to prevent spilling the specimen out of the sample well.
- "DO NOT DISTURB TEST IN PROGRESS" appears in the display window. Automatic timing of the assay development, image processing and result analysis begins.
- The display window shows the remaining analysis time.

Do not touch the BD Veritor™ Plus Analyzer or remove the test device during this process. Doing so will abort the assay analysis.

- When analysis is complete, a result appears in the display window. If configured to display, the Specimen D barcode value also appears. If a printer is connected, specimen ID and result are automatically printed.

If the printer is not connected, record the result before removing the assay device.

ATTENTION TEST Results are NOT maintained in the display window when the device is removed or if the BD Veritor™ Plus Analyzer is left unattended for more than 15 minutes (60 minutes if AC power adapter is connected).

10D

Removing the test device

Remove and then discard the test device appropriately. The display will show "INSERT TEST DEVICE OR DOUBLE-CLICK BUTTON FOR WALK AWAY MODE" to indicate the BD Veritor™ Plus Analyzer is ready to perform another test. Note that the BD Veritor™ Plus Analyzer returns to Analyze Now mode at the conclusion of each read sequence.

If the BD Veritor™ Plus Analyzer is connected to an LIS, a steady ENVELOPE symbol will appear to indicate that results are awaiting transmission. If a network connection is not detected while the ENVELOPE symbol is still displayed, the BD Veritor™ Plus Analyzer will queue all untransmitted results and attempt to transmit them when reconnected. If it is powered off during this time, it will attempt to transmit as soon as power is restored, and connection is re-established. A flashing envelope indicates that data are in the process of being transmitted.

INTERPRETATION OF RESULTS

The BD Veritor™ Plus Analyzer (provided separately) must be used for interpreta ion of all test results. Operators should not attempt to interpret assay results directly from the test strip contained within the BD Veritor™ assay device.

Display	Interpretation
CoV2: +	Positive Test for SARS-CoV-2 (antigen detected)
CoV2: -	Presumptive Negative Test for SARS-CoV-2 (no antigen detected)
CONTROL INVAL D	Test Invalid.* Repeat the test.

*Invalid Test – If he test is invalid, the BD Veritor™ System Instrument will display “CONTROL INVALID” and the test or control must then be repeated. If the “CONTROL INVALID” reading recurs, contact BD.

REPORTING OF RESULTS

Positive Test – Positive for the presence of SARS-CoV-2 antigen. Posi ive results indicate he presence of viral antigens, but clinical correlation with patient history and other diagnostic information is necessary to determine infection status. Posi ive results do not rule out bacterial infection or co-infec ion with other viruses. The agent detected may not be the definite cause of disease. Laboratories within he United States and its territories are required to report all positive results to the appropriate public heal h authorities.

Negative Test – Negative results are presumptive. Nega ive test results do not preclude infection and should not be used as he sole basis for treatment or other patient management decisions, including infection control decisions, particularly in the presence of clinical signs and symptoms consistent with COVID-19, or in those who have been in contact with the virus. It is recommended that these results be confirmed by a molecular tes ing method, if necessary, for patient management.

Control Invalid – Do not report results. Repeat the test. It may be necessary to collect a fresh patient specimen, if more than one hour has passed since specimen collection, or more than 30 minutes since he specimen was placed into extraction buffer.

Batch Testing – Processing errors, including false posi ive or false negative results, may occur when inadequate time is planned between multiple specimens in batch mode. Allow adequate time for each specimen to process in the test device and for obtaining and recording Analyzer results.

Follow CDC Guidelines for changing gloves and cleaning work area between specimen handling and processing. https://www.cdc gov/coronavirus/2019-nCoV/lab/lab-biosafety-guidelines.html.

QUALITY CONTROL

Each BD Veritor™ System SARS-CoV-2 test device contains both positive and negative internal/procedural controls:

- The internal positive control line validates he immunological integrity of he device, proper reagent func ion, and assures correct test procedure.
- The membrane area surrounding test lines func ions as a background check on the assay device.

The BD Veritor™ System Instrument evaluates the posi ive and nega ive internal/procedural controls after insertion of each test device. The BD Veritor™ Plus Analyzer prompts the operator if a quality issue occurs during assay analysis. Failure of the internal/procedural controls will generate an invalid test result. NOTE: The internal controls do not assess proper sample collection technique.

EXTERNAL POSITIVE AND NEGATIVE CONTROLS

Posi ive and Negative control swabs are supplied wi h each kit. These controls provide addi ional quality control material to assess that he test reagents and he BD Veritor™ System Instrument perform as expected. Prepare kit control swabs and test using he same procedure as used for patient specimens.

BD recommends controls be run once for:

- each new kit lot,
- each new operator,
- as required by internal quality control procedures and in accordance with local, state and federal regulations or accreditation requirements.

If the kit controls do not perform as expected, do not report patient results. Contact your local BD representative.

LIMITATIONS OF THE PROCEDURE

- Clinical performance was evaluated with frozen samples, and test performance may be different with fresh samples.
- Users should test specimens as quickly as possible after specimen collec ion and always within one hour of specimen collection or 30 minutes since placement of swab into the extraction reagent.
- Posi ive test results do not rule out co-infections wi h other pa hogens.
- Results from the BD Veritor™ System for Rapid Detec ion of SARS-CoV-2 test should be correlated with the clinical history, epidemiological data, and other data available to the clinician evaluating the patient.
- A false-negative test result may occur if the level of viral antigen in a sample is below the detection limit of the test or if he sample was collected or transported improperly; therefore, a negative test result does not eliminate the possibility of SARS-CoV-2 infection.
- Based on *in vitro* testing, false positive results cannot be ruled out if patients wi h rheumatoid factor higher than 12.5 IU/mL in nasal fluid, although it is unclear if such concentra ions are clinically relevant.

- False posi ive results can occur due to contamination. Users should disinfect instrument between specimens and batch testing and follow careful disinfection procedures to limit contamination.
- Do not read test devices before 15 minutes as this could result in a false nega ive or invalid result. Do not read devices after 20 minutes as false positive, false negative or invalid results may occur.
- The amount of antigen in a sample may decrease as the duration of illness increases. Specimens collected after day 5 of illness are more likely to be nega ive compared to a RT-PCR assay.
- Failure to follow the test procedure may adversely affect test performance and/or invalidate the test result.
- The contents of his kit are to be used for he qualita ive detection of SARS-CoV-2 antigens from nasal swab specimens only.
- The BD Veritor™ System for Rapid Detec ion of SARS-Cov-2 can detect both viable and non-viable SARS-CoV-2 material. The BD Veritor™ System for Rapid Detection of SARS-CoV-2 performance depends on antigen load and may not correlate with other diagnostic methods performed on the same specimen.
- Nega ive test results are not intended to rule in other non-SARS-CoV-2 viral or bacterial infections.
- Posi ive and nega ive predictive values are highly dependent on prevalence rates. Posi ive test results are more likely to represent false positive results during periods of little/no SARS-CoV-2 activity when disease prevalence is low. False negative test results are more likely when prevalence of disease caused by SARS-CoV-2 is high.
- This device has been evaluated for use with human specimen material only.
- Monoclonal antibodies may fail to detect, or detect with less sensitivity, SARS-CoV-2 viruses that have undergone minor amino acid changes in he target epitope region.
- The performance of his test has not been evaluated for use in patients without signs and symptoms of respiratory infection and performance may differ in asymptomatic individuals.
- Sensitivity of the test after the first five days of the onset of symptoms has been demonstrated to decrease as compared to a RT-PCR SARS-CoV-2 assay.
- Nega ive results should be treated as presumptive and confirmed with an FDA authorized molecular assay, if necessary, for clinical management, including infection control. Outside the United States, a molecular assay cleared for diagnostic use in the country of use is recommended.
- Users should test specimens as quickly as possible after specimen collec ion, always within one hour after specimen collection and within 30 minutes of placing the swab into the extraction reagent.
- The validity of the BD Veritor™ System for Rapid Detection of SARS-CoV-2 test has not been proven for identifica ion/confirmation of tissue culture isolates and should not be used in his capacity.

CONDITIONS OF AUTHORIZATION FOR THE LABORATORY (APPLICABLE IN THE USA)

The BD Veritor™ System for Rapid Detec ion of SARS-CoV-2 Letter of Authoriza ion, along wi h the authorized Fact Sheet for Healthcare Providers, he authorized Fact Sheet for Patients, and authorized labeling are available on the FDA website: https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas.

However, to assist clinical laboratories using the BD Veritor™ System for Rapid Detection of SARS-CoV-2 ("your product" in the conditions below), he relevant Conditions of Authorization are listed below.

- Authorized laboratories* using your product must include with test result reports, all authorized Fact Sheets. Under exigent circumstances, o her appropriate methods for dissemina ing these Fact Sheets may be used, which may include mass media.
- Authorized laboratories using your product must use your product as outlined in the "BD Veritor™ System for Rapid Detection of SARS-CoV-2" Instruc ions for Use. Deviations from the authorized procedures, including the authorized instruments, au horized clinical specimen types, authorized control materials, authorized other ancillary reagents and authorized materials required to use your product are not permitted.
- Authorized laboratories hat receive your product must notify the relevant public health authorities of their intent to run your product prior to ini ia ing testing.
- Authorized laboratories using your product must have a process in place for reporting test results to healthcare providers and relevant public health au horities, as appropriate.
- Authorized laboratories will collect information on the performance of your product and report to DMD/OHT7-OIR/OPEQ/CDRH (via email: CDRH-EUA-Reporting@fda.hhs.gov) and to BD by contacting BD Customer Support Services at 800.638.8663 (in the U.S.) any suspected occurrence of false positive or false negative results and significant deviations from the established performance characteristics of your product of which they become aware.
- All operators using your product must be appropriately trained in performing and interpreting the results of your product, use appropriate personal protec ive equipment when handling this kit, and use your product in accordance wi h the authorized labeling.
- Becton, Dickinson and Co., authorized distributors, and au horized laboratories and patient care settings using your product must ensure hat any records associated with this EUA are maintained until otherwise notified by FDA. Such records will be made available to FDA for inspection upon request.

* The letter of authorization refers to, "Laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a, that meet the requirements to perform high, moderate, or waived complexity tests. This test is authorized for use at the Point of Care (POC), i.e., in patient care settings operating under a CLIA Certificate of Waiver, Certificate of Compliance, or Certificate of Accreditation as "authorized laboratories".

CLINICAL PERFORMANCE

The performance of he BD Veritor™ System for Rapid Detection of SARS-CoV-2 was established with 226 direct nasal swabs prospectively collected and enrolled from individual symptoma ic patients[a] (wi hin 5 days of onset) who were suspected of COVID-19. As with all antigen tests, performance may decrease as days since symptom onset increases. Samples were collected by qualified personnel in 21 geographically diverse areas across the United States.

Nasal swabs were collected following the dual nares method and handled as described in he package insert of the collec ion device. Specimens were frozen within 30 minutes of collection and stored until tested. All specimens within a pre-specified date range were selected and then sequen ially tested in a blinded fashion. The performance of the BD Veritor™ System Assay was compared to results of a nasopharyngeal or oropharyngeal swab stored in 3 mL viral transport media tested wi h an Emergency Use Au horized molecular (RT-PCR) test for detection of SARS-CoV-2.

[a]Symptoms included new loss of taste or smell, fever, shortness of breath or difficulty breathing, headache, cough, sore throat, muscle pain, chills and repeated shaking with chills.

Table 1 Summary of the Performance of the BD Veritor™ System for Rapid Detection of SARS-CoV-2 Compared to RT-PCR for Nasal Swabs

	Reference PCR Results		
BD Veritor™ Results	POS	NEG	Total
POS	26	0	26
NEG	5	195	200
Total	31	195	226

PPA: 84% (C.I. 67%–93%)
NPA: 100% (C.I. 98%–100%)
OPA: 98% (C.I. 95%–99%)
PPV: 100% (C.I. 89%, 100%)
NPV: 97.5% (C.I. 95%, 99%)

EXPLANATION OF TERMS:
C.I.: Confidence Interval
PPA: Positive Percent Agreement = True Positives / True Positives + False Negatives
NPA: Negative Percent Agreement = True Negatives / True Negatives + False Positives.
OPA: Overall Percent Agreement = True Positives + True Negatives / Total Samples
PPV: Positive Predictive Value = True Positives / True Positive + False Positive
NPV: Negative Predictive Value = True Negatives / True Negative + False Negative

The positive predicted value (PPV) point es imate was 100% with a 95% Confidence Interval of 88.6%–100%. This PPV was obtained with 13.7% observed prevalence. The PPV (percentage of positive test results that are true positives) varies with disease prevalence. As disease prevalence decreases, the percent of test result that are false positive increase. Wi h a hypothetical prevalence of 1% the PPV point estimate remains at 100% but the Confidence interval increases to 33.2%–100%.

The PPV will also decrease as he Specificity (Negative Percent Agreement or NPA) decreases. The observed NPA in this study was 100% with a 95% Confidence Interval of 98%–100%, which means that the false positive rate could be between 0–2% of all the test performed.

The local SARS-CoV-2 prevalence should be taken into considera ion when interpreting diagnostic test results.

Table 2: Hypothetical Positive and Negative Predic ive Values for the BD Veritor™ System for Rapid Detection of SARS-CoV-2 compared to RT-PCR for Varying Prevalences of COVID-19 in the Population.

	All Values Expressed as 95% Confidence Interval							
COVID-19 Prevalence	Sensitivity (PPA)	Specificity (NPA)	PPV	Theoretical False Positives Out of 100 Positive Results	Theoretical False Positives Out of 100 Results	NPV.	Theoretical False Negatives Out of 100 Negative Results	Theoretical False Negatives Out of 100 Results
0.1%	84.0% (26/31)	100.0% (195/195)	4.7%–100%	0–95	0–2	100%	0	0
1.0%			33.2%–100%	0–67	0–2	(99.7%–99.9%)	0	0
2.0%			50.1%–100%	0–50	0–2	(99.3%–99.9%)	0–1	0
5.0%			72.1%–100%	0–28	0–2	(98.3%–99.7%)	0–2	0–1
10.0%			84.5%–100%	0–17	0–2	(96.4%–99.4%)	1–4	0–2
13.7%			88.6%–100%	0–11	0–1	(94.9%–99.1%)	1–5	0–2
15.0%			89.7%–100%	0–10	0–1	(94.4%–99.0%)	1–6	0–2
20.0%			92 5%–100%	0–8	0–1	(92.2%–98.7%)	1–8	0–3
25.0%			94 2%–100%	0–6	0–1	(89.9%–98.2%)	2–10	0–4

EXPLANATION OF TERMS:
PPV: Positive Predictive Value = True Positives / True Positive + False Positive
NPV: Negative Predictive Value = True Negatives / True Negative + False Negative

The Positive Predictive Value (percentage of positive test results that are true positives) varies with disease prevalence. As disease prevalence decreases, the confidence interval of the PPV gets wider and the percent of test results that are false positive increases. Table 2 contains PPV confidence interval estimates for the BD Veritor™ assay at other prevalence levels of SARS-CoV-2 in a population. Based on the specificity at 1% prevalence, PPV could be as low as 33 2%. This means that the false positives may be

as high as 66 8%, meaning that 67 out of 100 positive results may be false positives. If you look at 100 total results, including both positive and negative results, you could see two or fewer false positive results, with the expectation of seeing a single true positive result. Similarly, in a population with 0.1% prevalence, the PPV could be as low as 4.7% meaning that approximately 95 out of 100 positive results would be false positive.

ANALYTICAL PERFORMANCE

L MIT OF DETECTION (ANALYTICAL SENSITIVITY)

The LOD for the BD Veritor™ System for Rapid Detection of SARS-CoV-2 was established using limiting dilutions of a viral sample inactivated by gamma irradiation. The material was supplied at a concentration of 2.8 x 10^5 TC D_{50}/mL. In this study, designed to estimate the LOD of the assay when using a direct nasal swab, the starting material was spiked into a volume of pooled human nasal matrix obtained from healthy donors and confirmed negative for SARS-CoV-2. An initial range finding study was performed testing devices in triplicate using a 10-fold dilution series. At each dilution, 50 µL samples were added to swabs and then tested in the BD Veritor™ assay using the procedure appropriate for patient nasal swab specimens. A concentration was chosen between the last dilution to give 3 positive results and the first to give three negative results. Using this concentration, the LOD was further refined with a 2-fold dilution series. The last dilution demonstrating 100% positivity was then tested in an additional 20 replicates tested in the same way.

Starting Material Concentration	Estimated LOD	No. Positive/Total	% Positive
2.8 x 10^5 $TCID_{50}$/mL	1.4 x 10^2 $TCID_{50}$/mL	19/20	95%

CROSS REACTIVITY (ANALYTICAL SPECIFICITY)

Cross-reactivity of the BD Veritor™ System for Rapid Detection of SARS-CoV-2 was evaluated by testing a panel of high prevalence respiratory pathogens that could poten ially cross-react with he BD Veritor™ System for Rapid Detection of SARS-CoV-2 in a negative and a 5x LOD sample. Each organism and virus was tested in triplicate. The final concentration of each organism is documented in he following table.

Potential Cross-Reactant	Concentration Tested	Cross-Reactivity (Yes/No)
Human coronavirus 229E (heat inactivated)	1.0 x 10^5 U/mL	No
Human coronavirus OC43	1.0 x 10^5 TC D_{50}/mL	No
Human coronavirus NL63	1.0 x 10^5 TC D_{50}/mL	No
Adenovirus	1.0 x 10^5 TC D_{50}/mL	No
Human Metapneumovirus	1.0 x 10^5 TC D_{50}/mL	No
Parainfluenza virus 1	1.0 x 10^5 TC D_{50}/mL	No
Parainfluenza virus 2	1.0 x 10^5 TC D_{50}/mL	No
Parainfluenza virus 3	5.2 x 10^5 TC D_{50}/mL	No
Parainfluenza virus 4	1.6 x 10^4 TC D_{50}/mL	No
Influenza A	2.5 x 10^5 TC D_{50}/mL	No
Influenza B	2.9 x 10^5 TC D_{50}/mL	No
Enterovirus	4.0 x 10^5 TC D_{50}/mL	No
Respiratory syncytial virus	4.0 x 10^5 TC D_{50}/mL	No
Rhinovirus	1.1 x 10^5 PFU/mL	No
SARS-coronavirus	4 5 x 10^5 PFU/mL	No
MERS-coronavirus	1.5 x 10^5 TC D_{50}/mL	No
Haemophilus influenza	1.4 x 10^6 CFU/mL	No
Streptococcus pneumoniae	1 0 x 10^6 CFU/mL	No
Streptococcus pyogenes	1 6 x 10^6 CFU/mL	No
Candida albicans	1 8 x 10^6 CFU/mL	No
Pooled human nasal wash	100%	No
Bordetella pertussis	1.4 x 10^6 CFU/mL	No
Mycoplasma pneumoniae	1 0 x 10^6 CFU/mL	No
Chlamydia pneumoniae	1.0 x 10^6 IFU/mL	No
Legionella pneumophila	1 0 x 10^6 CFU/mL	No

To es imate the likelihood of cross-reactivity with SARS-CoV-2 of organisms that were not available for wet testing, *In silico* analysis using the Basic Local Alignment Search Tool (BLAST) managed by he National Center for Biotechnology Information (NCBI) was used to assess he degree of protein sequence homology.

- For *P. jirovecii* one area of sequence similarity shows 45.4% homology across 9% of the sequence, making cross-reactivity in the BD Veritor sandwich immunoassay highly unlikely.
- No protein sequence homology was found between SARS-CoV-2 and *M. tuberculosis*, and thus homology-based cross-reactivity can be ruled out.
- The comparison between SARS-CoV-2 nucleocapsid protein and human coronavirus HKU1 revealed hat the only potential for homology is with he HKU1 nucleocapsid phosphoprotein. Homology is relatively low, at 36.7% across 82% of sequences, but cross-reactivity cannot be ruled out.

ENDOGENOUS INTERFERING SUBSTANCES

Various substances were evaluated with the BD Veritor™ System for Rapid Detection of SARS-CoV-2. The substances tested included whole blood 4%, mucin and various medica ions. No interference was noted with this assay for any of the substances tested.

Substance	Concentration Tested	Interference (Yes/No)
Afrin Nasal Spray (Oxymetazoline)	5% v/v	No
Flonase (Fluticasone)	5% v/v	No
Nasacort (Triamcinolone)	5% v/v	No
Neo-Synephrine (Phenylephrine hydrochloride)	5% v/v	No
Oseltamivir	2 2 µg/mL	No
Mucin protein	2.5 mg/mL	No
Rhinocort (Budesonide)	5% v/v	No
Saline nasal spray	15% v/v	No
Zanamivir	282 ng/mL	No
Zicam Cold Remedy (Galphimia glauca, Luffa operculata, Sabadilla)	5% v/v	No
Whole blood	4% v/v	No
Cepacol (Menthol/Benzocaine)	1.5 mg/mL	No
Ricola (menthol)	1.5 mg/mL	No
Tobramycin	4 µg/mL	No
Sucrets (Dyclonine/Menthol)	1.5 mg/mL	No
NeilMed Naso Gel	5% v/v	No
Zicam nasal spray (Oxymetazoline)	10% v/v	No
Alkalol nasal wash	10% v/v	No
Fisherman's Friend (menthol)	1.5 mg/mL	No
Chloraseptic (Phenol Spray)	15% v/v	No
Mupirocin	10 mg/mL	No

Additionally, the following were tested for interference in a negative and a 3x LOD sample. No interference was noted at the levels tested.

Substance	Concentration Tested	Interference (Yes/No)
Afrin Nasal Spray (Oxymetazoline)	15% v/v	No
Neo-Synephrine (Phenylephrine hydrochloride	15% v/v	No
Oseltamivir	2 2 µg/mL	No
Mucin protein	2.5 mg/mL	No
Mupirocin	10 mg/mL	No
Rheumatoid Factor	12 5 IU/mL	No

NOTE: Based on in vitro testing, false positive results may occur in patients wi h rheumatoid factor higher than 12.5 IU/ml in nasal fluid, although it is unclear if such concentrations are clinically relevant.

MICROBIAL INTERFERENCE

The BD Veritor™ System for Rapid Detec ion of SARS-CoV-2 assay was evaluated with various organisms at the concentra ions indicated below in a negative and 5x LoD sample. No interference was noted.

Potential Microbial Interferent	Concentration Tested	Interference (Yes/No)
Human coronavirus 229E	1 0 x 10^5 U/mL	No
Human coronavirus OC43	1 0 x 10^5 $TCID_{50}$/mL	No
Human coronavirus NL63	1 0 x 10^5 $TCID_{50}$/mL	No
Adenovirus	1 0 x 10^5 $TCID_{50}$/mL	No
Human Metapneumovirus	1 0 x 10^5 $TCID_{50}$/mL	No
Parainfluenza virus 1	1 0 x 10^5 $TCID_{50}$/mL	No
Parainfluenza virus 2	1 0 x 10^5 $TCID_{50}$/mL	No
Parainfluenza virus 3	5 2 x 10^5 $TCID_{50}$/mL	No
Parainfluenza virus 4a	1 5 x 10^4 $TCID_{50}$/mL	No
Influenza A	2 5 x 10^5 $TCID_{50}$/mL	No
Influenza B	2 9 x 10^5 $TCID_{50}$/mL	No
Enterovirus D68	4 0 x 10^5 $TCID_{50}$/mL	No
Respiratory syncytial virus	4 0 x 10^5 $TCID_{50}$/mL	No
Rhinovirus 3	1.1 x 10^5 PFU/mL	No
SARS-coronavirus	4 5 x 10^5 PFU/mL	No
MERS-coronavirus	1 5 x 10^5 $TCID_{50}$/mL	No
Haemophilus influenza	1.4 x 10^6 CFU/mL	No
Streptococcus pneumoniae	1 0 x 10^6 CFU/mL	No
Streptococcus pyogenes	1 6 x 10^6 CFU/mL	No
Bordetella pertussis	1.4 x 10^6 CFU/mL	No
Mycoplasma pneumoniae	1 0 x 10^6 CFU/mL	No
Chlamydia pneumoniae	1 0 x 10^6 CFU/mL	No
Legionella pneumophila	1 0 x 10^6 CFU/mL	No
Pooled human nasal wash	N/A	No
Candida albicans	1 8 x 10^6 CFU/mL	No

Additionally, the following poten ial cross-reacting organisms were tested using a negative and 3x LOD sample at the following levels. No interference was noted.

Potential Microbial Interferent	Concentration Tested	Interference (Yes/No)
Rhinovirus 3	1.1 x 10^5 PFU/mL	No
SARS-coronavirus	4 5 x 10^5 PFU/mL	No
MERS-coronavirus	1 5 x 10^5 $TCID_{50}$/mL	No
Haemophilus influenza	1.4 x 10^6 CFU/mL	No
Streptococcus pneumoniae	1 0 x 10^6 CFU/mL	No
Streptococcus pyogenes	1 6 x 10^6 CFU/mL	No
Bordetella pertussis	1.4 x 10^6 CFU/mL	No

INTRA-SITE VARIABILITY

Ano her study was designed to assess the capability of users to test seeded swab samples across the range of the assay with three (3) users, over hree (3) days, wi h three (3) lots of devices. The following table shows the performance.

Sample	Operator #1		Operator #2		Operator #3		Total	
	% Positive	95% C.I.	% Positive	95% C.I.	% Positive	95% C.I.	% Positive	95% C.I.
Negative	0% (0/27)	(0.0%,12.5%)	0% (0/27)	(0.0%,12.5%)	0% (0/27)	(0.0%,12.5%)	0% (0/81)	(0 0%,4 5%)
Low Positive (3x LOD)	100% (27/27)	(87.5%,100 0%)	100% (27/27)	(87.5%,100 0%)	100% (27/27)	(87.5%,100 0%)	100% (81/81)	(95.5%, 100 0%)
Low Positive (5x LOD)	100% (27/27)	(87.5%,100 0%)	100% (27/27)	(87.5%,100 0%)	100% (27/27)	(87.5%,100 0%)	100% (81/81)	(95.5%, 100 0%)
Moderate Positive (10x LOD)	100% (27/27)	(87.5%,100 0%)	100% (27/27)	(87.5%,100 0%)	100% (27/27)	(87.5%,100 0%)	100% (81/81)	(95.5%, 100 0%)
High Positive (40x LOD)	100% (27/27)	(87.5%,100 0%)	100% (27/27)	(87.5%,100 0%)	100% (27/27)	(87.5%,100 0%)	100% (81/81)	(95.5%, 100 0%)

HIGH DOSE HOOK EFFECT

No high dose hook effect was observed up to 2.8 x 10^5 $TCID_{50}$/mL of gamma-inactivated SARS-CoV-2 with the BD Veritor™ System for Rapid Detec ion of SARS-CoV-2 test.

TECHNICAL SUPPORT

For ques ions, or to report a problem, please call Technical Support at 1.800.638.8663 or visit bd.com. Test system problems may also be reported to the FDA using the MedWatch reporting system:
Phone: 1.800.FDA.1088; Fax: 1.800.FDA.1078 or visit http://www.fda.gov/medwatch.

Outside the United States, contact your local BD representative.

REFERENCES

1. Centers for Disease Control and Prevention. https://www cdc gov/coronavirus/2019-ncov/index.html. Accessed March 30, 2020.
2. https://www.cdc.gov/flu/symptoms/flu-vs-covid19.htm.

Change History

Revision	Date	Change Summary
03	2020-08	Added statement that kit components (other than swabs) should not make contact with the patient. Removed https://www.biorxiv.org/content/10 reference.
04	2020-11	Minor typographical corrections.
05	2021-01	Added warning not to use components from other kits. Modified Sodium Azide warning language, description of intended user, added endogenous, microbial interference data tables and reproducibility testing results.

US Customers only: For symbol glossary, refer to bd.com/symbols-glossary

SYMBOL GLOSSARY	
EC REP	Authorized Representative
LOT	Batch Code
	Biological Risk
REF	Catalogue Number
	Caution
	Consult Instructions for Use
	Contains sufficient for <n> tests
CONTROL +	Control, Positive
CONTRO –	Control, Negative
	Date of Manufacture
	Do Not Reuse
	Fragile, Handle with Care
IVD	In Vitro Diagnostic
	Manufacturer
R_x Only	Prescription Use Only
	Recyclable
SN	Serial Number
	Temperature Limitation
	This End Up
	Use By Date

BD

Quick Reference Instructions for BD Veritor™ SARS-CoV-2

REF 256082

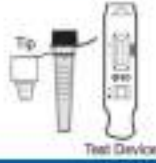
Use of BD Veritor™ System for Rapid Detection of SARS-CoV-2 with the BD Veritor™ Plus Analyzer

In the USA: For use under Emergency Use Authorization (EUA) Only

Read the complete test procedure, including recommended QC procedures before performing the test. Refer to the package insert for complete information about the test. Ensure ALL components are at room temperature (15–30 °C) when running the test.

Sample preparation

1 Gather test materials and label test device with specimen ID.



2 Remove cap from extraction reagent tube. Use only reagent tubes provided with this kit.

3 Insert patient sample swab and vigorously plunge the swab up and down for 15 seconds.

4 Remove swab while squeezing extraction reagent tube to extract liquid. Properly dispose of swab.

5 Press dispensing tip on the tube firmly. Mix the sample by flicking or swirling the bottom of the tube. Add sample to test device within 30 minutes.

Using the BD Veritor Plus Analyzer to read the assay device

ANALYZE NOW MODE

6 Add 3 drops of the processed sample to the test device sample well.

7 Allow test to develop for **15 minutes**. Do not disturb. Keep level.

CAUTION: **False positive or false negative results can occur if test device is read before 15 minutes or after 20 minutes.** Do not disturb. Keep level. Cover test device if working in a drafty environment to ensure proper sample flow.

8 When test is ready, power on instrument by pressing blue start button once. When prompted, insert test device to read.

Optional: If using the barcode scanning accessory, follow screen prompts to scan the barcodes to start the test analysis.

9 Result will appear on screen. Record result and remove test device. Properly dispose of test device. Do not re-read test devices.

OR

WALK AWAY MODE (instrument must be plugged in)

Press blue start button once to power on. When prompt appears, **double click** to enter Walk-Away mode. Three minute countdown timer displays time remaining for test device insertion.

Optional: If using the barcode scanning accessory, follow screen prompts to scan any required barcodes.

Add 3 drops of the processed sample to the test device sample well.

Confirm timer is visible and Walk Away mode is activated before inserting device. Insert device immediately to start assay timing and analysis. Delay invalidates assay result and requires a repeated test with a new test device.

Do not touch instrument during analysis. Keep level.

Result will appear on the screen after analysis is complete (15 minutes). Record result, remove test device and discard properly. Instrument returns to Analyze Now mode when test device is removed.

Quick Reference Instructions for BD Veritor™ SARS-CoV-2

REF 256082

Use of BD Veritor™ System for Rapid Detection of SARS-CoV-2 with the BD Veritor™ Plus Analyzer

In the USA: For use under Emergency Use Authorization (EUA) Only

IVD R_x Only

Display	Interpretation
CoV2: +	Positive Test for SARS-CoV-2 (antigen present)
CoV2: –	Presumptive Negative Test for SARS-CoV-2 (no antigen detected)
CONTROL INVALID	Test Invalid. Repeat the test.

INTERPRETATION OF RESULTS

Test results must **NOT** be read visually. The BD Veritor Plus System Analyzer (purchased separately) must be used for interpretation of all test results. Refer to table above.

Positive Test Results – SARS-CoV-2 antigen present; does not rule out coinfection with other pathogens.

Negative Test Results – Negative results are presumptive. Negative test results do not preclude infec ion and should not be used as the sole basis for treatment or other patient management decisions, including infection control decisions, particularly in the presence of clinical signs and symptoms consistent with COVID-19, or in those who have been in contact with the virus. It is recommended that these results be confirmed by a molecular testing method, if necessary for patient management.

Invalid Test - If the test is invalid the BD Veritor Plus System Analyzer will display a "CONTROL INVALID" result and he test or control must then be repeated.

EXTERNAL QUALITY CONTROL PROCEDURE

Swab controls are supplied with each kit. These swab controls should be used to ensure that the test reagents work properly and that the test procedure is performed correctly. For kit swab controls, insert the control swab into the extraction reagent tube and vigorously plunge the swab up and down for 15 seconds. Process according to the test procedures on the reverse side of this card beginning at step 4. BD recommends running controls for each new kit lot, each new operator, and each new shipment of test kits or at periodic intervals required by your facility. If the kit controls do not perform as expected, do not report patient results and contact BD Technical Support at 1.800.638.8663.

SPECIMEN COLLECTION AND HANDLING

Proper specimen collection and handling of nasal swabs is required to ensure accurate results (see enclosed specimen collection guide). Additional training or guidance is recommended if operators are not experienced with specimen collec ion and handling procedures.

WARNINGS AND PRECAUTIONS

1. For *in vitro* Diagnostic use only.
2. All test results must be obtained using the BD Veritor Plus Analyzer.
3. **DO NOT** read the test results visually.
4. Handle all specimens and related materials as if capable of transmitting infectious agents.
5. It is recommended to follow your institutions requirements for decontamination procedures or if spills occur. See the BD Veritor Analyzer Instructions for use for instrument cleaning.
6. Dispose of used materials as biohazardous waste in accordance with federal, state and local requirements.
7. **Ensure all components are at room temperature (15–30 °C) when running the test.**
8. Keep devices and instrument level and undisturbed for duration of the 15 minute incubation. Cover test device if working in a drafty environment to prevent sample evapora ion and incomplete sample flow which may produce an erroneous false positive result or control invalid result
9. Please refer to the package insert for detailed assay instructions, cautions, limitations and warnings.

In the USA, This product has not been FDA cleared or approved; but has been authorized by FDA under an EUA for use by authorized laboratories:

- This product has been authorized only for the detection of proteins from SARS-CoV-2, not for any other viruses or pathogens; and,
- This product is only au horized for he duration of the declaration that circumstances exist justifying he au horization of emergency use of *in vitro* diagnostics for detec ion and/or diagnosis of COVID-19 under Sec ion 564(b)(1) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or au horization is revoked sooner.

US Customers only: For symbol glossary, refer to bd.com/symbols-glossary

Technical Information: In the United States contact BD Technical Service and Support at 1.800.638.8663 or bd.com

Becton, Dickinson and Company
7 Loveton Circle
Sparks, Maryland 21152 USA

bd.com/e-labeling

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2020-12

BD Veritor™ System for Rapid Detection of SARS-CoV-2 & Flu A+B

Proper Nasal Swab Sample Collection

In the USA: For use under Emergency Use Authorization (EUA) Only

REF 256088

1

This BD Veritor™ System SARS-CoV-2 & Flu A+B Kit includes swabs for nasal specimen collection.

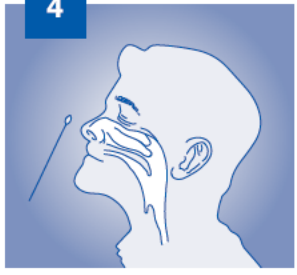
2

Carefully insert the swab into one nostril. The swab tip should be inserted up to 2.5 cm (1 inch) from the edge of the nostril. Roll the swab 5 times along the mucosa inside the nostrils to ensure that both mucus and cells are collected.

3

Using the same swab, repeat this process for the other nostril to ensure that an adequate sample is collected from both nasal cavities.

4



Withdraw the swab from the nasal cavity. The sample is now ready for processing using the BD Veritor™ System SARS-CoV-2 & Flu A+B Kit.

IVD R_x Only

Do's and Don'ts of Sample Collection

- Do collect sample as soon as possible after onset of symptoms.
- Do test sample immediately.
- Use only swabs provided with the kit.
- Refer to: Interim Guidelines for Collecting, Handling and Testing Clinical Specimens from persons for COVID-19 at https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html

In the USA, This product has not been FDA cleared or approved; but has been authorized by FDA under an EUA for use by authorized laboratories:

- This product has been authorized only for the detection of proteins from SARS-CoV-2, not for any other viruses or pathogens; and,
- This product is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostics for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization is revoked sooner.

US Customers only: For symbol glossary, refer to bd.com/symbols-glossary

Technical Information: In the United States contact BD Technical Service and Support at 1.800.638.8663 or bd.com

Becton, Dickinson and Company
7 Loveton Circle
Sparks, Maryland 21152 USA

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L012385(02)
2021-01

Analyze Now mode provides a batch testing option

BD Veritor™ System for Rapid Detection of SARS-CoV 2*

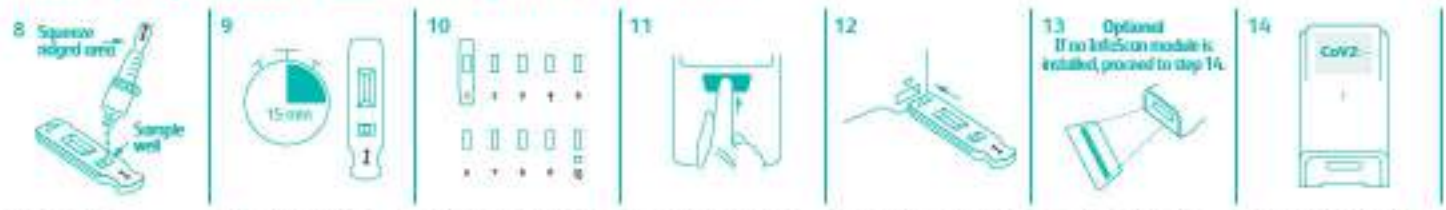
Review the complete Instructions for use for information and procedural steps; including recommended quality control procedures before performing the sample collection and analysis. Ensure all components are at room temperature (15–30 °C) when performing the test.

Example below demonstrates processing of 10 samples in 25 minutes. Using this workflow, up to 24 tests may be run in an hour (beginning after specimen collection, including steps 3-14).** These estimates are based upon a batch workflow study in which a single replicate from 12 specimens was tested by professional operators within 30 minutes. Untrained users may not be able to accurately process as many specimens in batch mode. Each institution should develop a batch testing protocol to ensure that patient specimens can be tested accurately and in accordance with the instructions for use.

Batch sample collection (10 tests)

1. **Gather 10 sets of test materials.**
   - Label each set with patient ID.
2. Label the tube tray with patient ID.
   - **Set each tube in the tray** with matching patient ID.
3. Select extraction reagent tube and **remove cap.**
4. **Insert patient sample swab** and vigorously plunge the swab up and down for 15 seconds taking care not to splash contents out of the tube.
5. **Remove swab** while squeezing to extract liquid.
   - Properly dispose of swab.
6. Press dispensing tip on the tube firmly.
   - **Mix the sample** by swirling the bottom of the tube.
7. **Place tube back in tray** with matching patient ID.
   - Repeat steps 3-7 until all remaining tubes have been prepared.
   - Specimen processed in the reagent vial must be **run within 30 minutes** on the test device.

Batch preparation and analysis (10 tests)



8. Select the extracted sample and the matching test device for each specimen.
   - **Add 3 drops of the processed sample** to the test device sample well.
   - Recommended to stagger tests by 30 seconds apart to allow time for reading individual tests.
9. Activate a 15 minute timer.
   - **Each test device must incubate for 15-20 minutes maximum*** ** before it can be analyzed.
10. Repeat steps 8-9 until **all remaining test devices have been prepared and are incubating,** each with their timers running.
11. When first test is ready, **power on the Analyzer** by pressing the blue start button once.
    - Analyzer may remain on until all testing is completed.
12. When prompted, **insert the test device to read.**
13. If using the **BD Veritor™ InfoScan module,** follow the screen prompts to scan operator ID, specimen ID and kit lot number to start the test analysis.
    - After required scans are completed, the Analyzer displays a countdown timer and test analysis begins.
14. **Result will appear on screen,** and will be stored in the Analyzer.
    - Test results are NOT maintained in the display window when the device is removed or if the Analyzer is left unattended for more than 15 minutes (60 minutes if AC power adapter is connected).
    - Record result.
    - Remove test device and properly dispose.
    - Continue with the next test device once it has incubated for 15 minutes***

False negative results can occur if specimens are read before or after the 15-20 minute reading window.

Interpretation of results

Display	Interpretation
CoV2: +	Positive Test for SARS-CoV-2 (antigen present)
CoV2: –	Presumptive Negative Test for SARS-CoV-2 (no antigen)
CONTROL INVALID	Test Invalid. Repeat the test.

*For use under Emergency Use Authorization (EUA) in the US only. IVD and Rx only.

**BD Veritor for Rapid Detection of SARS-CoV-2 Batching workflow study, September 2020

Mesich B., Faron M., Gerstbrein D., Mashock M., Buchan B., and Ledeboer N. Time of Motion Analysis for Three Point of Care Flu Assays Comparing Single and Batch Test Methods. Poster presented at American Society for Microbiology Microbe annual meeting; June 20-24, 2019; San Francisco, CA.

***CAUTION: Incorrect results may occur if development time is less than 15 minutes or more than 20 minutes. Cover test device if working in a drafty environment. Test devices used in a laminar flow hood or in areas with high air flow should be covered during test development to ensure proper sample flow. This prevents evaporation of the sample which may lead to incomplete sample flow and erroneous false positive or control invalid results.

BD

Interpretation of results

Test results must **NOT** be read visually. The BD Veritor™ Plus System Analyzer (purchased separately) must be used for interpretation of all test results. Refer to the reverse side of this card.

Positive Test Results: SARS-CoV-2 antigen present; does not rule out coinfection with other pathogens.

Negative Test Results: Negative results are presumptive. Negative test results do not preclude infection and should not be used as the sole basis for treatment or other patient management decisions, including infection control decisions, particularly in the presence of clinical signs and symptoms consistent with COVID-19, or in those who have been in contact with the virus. It is recommended that these results be confirmed by a molecular testing method, if necessary for patient management.

Invalid Test: If the test is invalid the BD Veritor™ Plus System Analyzer will display a "CONTROL INVALID" result and the test or control must then be repeated.

Warnings and precautions

1. For *in vitro* Diagnostic use only.
2. All test results must be obtained using the BD Veritor™ Plus Analyzer.
3. **DO NOT** read the test results visually.
4. Handle all specimens and related materials as if capable of transmitting infectious agents.
5. Dispose of used materials as biohazardous waste in accordance with federal, state and local requirements.
6. Ensure all components are at room temperature (15–30 °C) when running the test.
7. Please refer to the package insert for detailed assay instructions cautions, limitations and warnings.
8. Test development time is a critical parameter, test must be read between 15-20 minutes regardless of workflow choice (analyze now, walk away or batching). Reading outside this window could result in false positive or false negative results.

Specimen collection and handling

Proper specimen collection and handling is required to ensure accurate results. Additional training or guidance is recommended if operators are not experienced with specimen collection and handling procedures.

External quality control procedure

Swab controls are supplied with each kit. These swab controls should be used to ensure that the test reagents work properly and that the test procedure is performed correctly. For kit swab controls, insert the control swab into the extraction reagent tube and vigorously plunge the swab up and down for 15 seconds. Process according to the test procedures on the reverse side of this card using the same workflow as used for patient samples. BD recommends running controls for each new kit lot, each new operator, and each new shipment of test kits or at periodic intervals required by your facility. If the kit controls do not perform as expected, do not report patient results and contact BD Technical Support at 1.800.638.8663.

It is recommended to follow your institution requirements for decontamination practices or if spills occur. Follow CDC guidelines for best practices to limit contamination. See section 5.1.2 in Veritor Analyzer IFU for cleaning process.

Technical Information:
In the United States contact BD Technical Service and Support at 1.800.638.8663 or bd.com

- This product has not been FDA cleared or approved; but has been authorized by FDA under an EUA for use by authorized laboratories;
- This product has been authorized only for the detection of proteins from SARS-CoV-2, not for any other viruses or pathogens; and,
- This product is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostics for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization is revoked sooner.

BD Life Sciences
7 Loveton Circle, Sparks, MD, 21152, USA
800.638.8663

Visit BDveritor.com

Cost of Lab Devices

FOIPOP Request

List of Testing Devices from Dr. Todd Hatchett

Update: 7 June 2021

Laboratory	SARS CoV 2 Test	Technology used in test	Costs $$$	
QEII	In house assay based on BCCDC primers for RdRp on ABI 7500 fast	Nucleic acid amplification test (NAAT) specifically RT-PCR	$ 222,862	
	Hologic Panther Aptima SARS CoV 2 assay	NAAT – specifically transcription mediated amplification (TMA)	$ 246,120	
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	NAAT - specifically RT-PCR	$ 166,601	
	Roche 6800 – Cobas SARS CoV 2 assay (RT-PCR)	NAAT - specifically RT-PCR	$ -	Leased
IWK	Biofire Respiratory 2.1 panel (RT-PCR)	NAAT - specifically RT-PCR	N/A	
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV (RT-PCR)	NAAT - specifically RT-PCR	N/A	
Cape Breton Regional	Hologic Panther Aptima SARS CoV 2 assay	NAAT – specifically TMA	$ -	Existed prior to COVID-19
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV (RT-PCR)	NAAT - specifically RT-PCR	$ -	Existed prior to COVID-19
St Martha's Hospital	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV (RT-PCR)	NAAT - specifically RT-PCR	$ 61,017	
Aberdeen Hospital	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV (RT-PCR)	NAAT - specifically RT-PCR	$ -	Existed prior to COVID-19
Colchester Regional	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV (RT-PCR)	NAAT - specifically RT-PCR	$ 61,419	
Cumberland Regional Health Care Center	Biofire Respiratory 2.1 panel (RT-PCR)	NAAT - specifically RT-PCR	$ -	Supplied by National Microbiology Lab
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV (RT-PCR)	NAAT - specifically RT-PCR	$ 61,419	
Valley Regional Hospital	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV (RT-PCR)	NAAT - specifically RT-PCR	$ 61,419	
	Hologic Panther Aptima SARS CoV 2 assay	NAAT – specifically TMA	$ 179,463	
	Biofire Respiratory 2.1 panel (RT-PCR)	NAAT - specifically RT-PCR	$ -	Supplied by National Microbiology Lab
Yarmouth Regional Hospital	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV (RT-PCR)	NAAT - specifically RT-PCR	$ 61,496	

Abbott

ID NOW™

COVID-19

PRODUCT INSERT

ID NOW™
COVID-19
PRODUCT INSERT

For use with the ID NOW™ Instrument
For use with nasal, throat or nasopharyngeal specimens
For *in vitro* Use Only

INTENDED USE

ID NOW COVID-19 assay performed on the ID NOW Instrument is a rapid molecular *in vitro* diagnostic test utilizing an isothermal nucleic acid amplification technology intended for the qualitative detection of nucleic acid from the SARS-CoV-2 viral RNA in direct nasal, nasopharyngeal or throat swabs from individuals who are suspected of COVID-19 by their healthcare provider within the first seven days of the onset of symptoms.

Results are for the identification of SARS-CoV-2 RNA. The SARS-CoV-2RNA is generally detectable in respiratory samples during the acute phase of infection. Positive results are indicative of the presence of SARS-CoV-2 RNA; clinical correlation with patient history and other diagnostic information is necessary to determine patient infection status. Positive results do not rule out bacterial infection or co-infection with other viruses.

Negative results should be treated as presumptive and, if inconsistent with clinical signs and symptoms or necessary for patient management, should be tested with different authorized or cleared molecular tests. Negative results do not preclude SARS-CoV-2 infection and should not be used as the sole basis for patient management decisions. Negative results should be considered in the context of a patient's recent exposures, history and the presence of clinical signs and symptoms consistent with COVID-19.

The ID NOW COVID-19 test is intended for use by medical professionals or trained operators who are proficient in performing tests using the ID NOW Instrument in laboratory and point of care settings.

SUMMARY and EXPLANATION of the TEST

Coronaviruses are a large family of viruses which may cause illness in animals or humans. SARS-CoV-2 is an enveloped, single-stranded RNA virus of the ß genus. The virus can cause mild to severe respiratory illness and has spread globally, including the United States.

ID NOW COVID-19 is a rapid (13 minutes or less), instrument-based isothermal test for the qualitative detection and diagnosis of SARS-CoV-2 from nasal, nasopharyngeal and throat swabs. The ID NOW Instrument has a small footprint and easy to use graphical user interface for convenience within a busy hospital or near patient testing environments. The ID NOW COVID-19 kit contains all components required to carry out an assay for SARS-CoV-2 on the ID NOW Instrument.

PRINCIPLES of the PROCEDURE

ID NOW COVID-19 is an automated assay that utilizes isothermal nucleic acid amplification technology for the qualitative detection of SARS-CoV-2 viral nucleic acids. It is comprised of a Sample Receiver, containing elution/lysis buffer, a Test Base, comprising two sealed reaction tubes, each containing a lyophilized pellet, a Transfer Cartridge for transfer of the eluted sample to the Test Base, and the ID NOW Instrument.

The reaction tubes in the Test Base contain the reagents required for amplification of SARS-CoV-2, as well as an internal control. The templates (similar to primers) designed to target SARS-CoV-2 RNA amplify a unique region of the RdRp segment. Fluorescently-labeled molecular beacons are used to specifically identify each of the amplified RNA targets.

To perform the assay, the Sample Receiver and Test Base are inserted into the ID NOW Instrument. The sample is added to the Sample Receiver and transferred via the Transfer Cartridge to the Test Base, initiating target amplification. Heating, mixing and detection are provided by the instrument.

REAGENTS and MATERIALS

Materials Provided

BASE **Test Bases:** Orange plastic components containing two reaction tubes of lyophilized reagents for the targeted amplification of SARS-CoV-2 viral RNA and an internal control.

RCVR **Sample Receivers:** Blue plastic components containing 2.5 mL of elution buffer.

CARTRDG **Transfer Cartridges:** White plastic components used to transfer 2 x 100 µL of sample extract from the Sample Receiver to the Test Base.

Patient Swabs: Sterile swabs (foam) for use with the ID NOW COVID-19 Test.

Positive Control Swab: The positive control swab is coated with inactivated influenza A & B viruses. The positive control swab ensures sample elution/lysis and workflow were performed correctly but does not confirm amplification of the SARS-CoV-2 target (RdRp gene).

Package Insert

Quick Reference Instructions

Materials Required but not Provided

ID NOW Instrument

Nasopharyngeal Swabs

PRECAUTIONS

1. For *in vitro* diagnostic use.
2. To be used in conjunction with the ID NOW Instrument.
3. Treat all specimens as potentially infectious. Follow universal precautions when handling samples, this kit and its contents.
4. Proper sample collection, storage and transport are essential for correct results.
5. Leave test pieces sealed in their foil pouches until just before use.
6. Do not tamper with test pieces prior to or after use.
7. Do not use kit past its expiration date.
8. Do not mix components from different kit lots or from other ID NOW assays.
9. Solutions used to make the positive control swab are inactivated using standard methods. However, patient samples, controls, and test pieces should be handled as though they could transmit disease. Observe established precautions against microbial hazards during use and disposal.
10. Wear clean personal protection equipment and gloves when running each test. Change gloves between the handling of specimens suspected of COVID-19.
11. **If any assay components are dropped, cracked, found to be damaged or opened when received, DO NOT USE and discard. Do not use scissors or sharp objects to open foil pouches as damage to test pieces can occur.**
12. Do not open the Sample Receiver before placing in the instrument. It will prohibit the Elution Buffer from reaching temperature and may impact test performance.
13. If the Sample Receiver is spilled while opening, clean the instrument per instructions provided in the instrument User Manual and cancel test. Repeat test with a new Sample Receiver.
14. All test pieces must be removed from the instrument according to removal instructions displayed on the instrument and disposed of according to country and local requirements. **Pieces must not be separated once they are assembled**.
15. All test pieces are single use items. Do not use with multiple specimens.
16. Once reacted, the Test Base contains large amounts of amplified target (Amplicon). **Do not disassemble the Test Base and Transfer Cartridge**. In the case of a positive sample, this could lead to amplicon leakage and potential ID NOW COVID-19 false positive test results.
17. At a low frequency, clinical samples can contain inhibitors that may generate invalid results. Site to site invalid rates may vary.

18. Due to the high sensitivity of the assays run on the instrument, contamination of the work area with previous positive samples may cause false positive results. Handle samples according to standard laboratory practices. Clean instruments and surrounding surfaces according to instructions provided in the cleaning section of the instrument User Manual. Refer to Section 1.6, Maintenance & Cleaning, for further information.

STORAGE and STABILITY

Store kit at 2-30°C. The ID NOW COVID-19 kit is stable until the expiration date marked on the outer packaging and containers. Ensure all test components are at room temperature before use.

QUALITY CONTROL

ID NOW COVID-19 has built-in procedural controls. The result of the Procedural Control is displayed on the screen and is automatically stored in the instrument with each test result. This can be reviewed later by selecting Review Memory on the instrument.

Procedural Controls:

ID NOW COVID-19 contains an internal control that has been designed to control for sample inhibition and assay reagent function. In positive samples where target amplification is strong, the internal control is ignored and the target amplification serves as the 'control' to confirm that the clinical sample was not inhibitory and that assay reagent performance was robust. At a very low frequency, clinical samples can contain inhibitors that may generate invalid results.

Procedural Control Valid displayed on the instrument screen indicates that the assay reagents maintained their functional integrity and the sample did not significantly inhibit assay performance.

External Positive and Negative Controls:

Good laboratory practice suggests the use of positive and negative controls to ensure that test reagents are working and that the test is correctly performed. ID NOW COVID-19 kits contain a Positive Control Swab and Sterile Swabs that can be used as a Negative Control Swab. These swabs will monitor the entire assay. Test these swabs once with each new shipment received and once for each untrained operator. Further controls may be tested in order to conform with local, state and/or federal regulations, accrediting groups, or your lab's standard Quality Control procedures.

CONTROL SWAB PROCEDURE

Positive and Negative Controls should be tested following the Run QC Test instructions on the ID NOW Instrument. A Positive Control Swab is included in the kit. Use a sterile swab provided in the kit as the Negative Control Swab. Refer to Quality Control Swab Test Procedure or Instrument User Manual for further details.

Note: *The ID NOW Instrument reports QC results as Pass or Fail.*

If the correct control results are not obtained, do not perform patient tests or report patient results. Contact Technical Support during normal business hours before testing patient specimens.

SPECIMEN COLLECTION and HANDLING

Use freshly collected specimens for optimal test performance. Inadequate specimen collection or improper sample handling/storage/transport may yield erroneous results. Refer to the CDC Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens from Persons for Coronavirus Disease 2019 (COVID-19) https://www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html

ID NOW COVID-19 is intended for testing a swab directly without elution in viral transport media as dilution will result in decreased detection of low positive samples that are near the limit of detection of the test.

Follow Standard Precautions when handling clinical specimens, all of which may contain potentially infectious materials. Standard Precautions include hand hygiene and the use of personal protective equipment (PPE), such as laboratory coats or gowns, gloves, and eye protection.

To minimize risk of contamination of PPE and swab package during sample collection, it is recommended to widely open the package by pulling from the top down. Carefully remove the swab and perform sample collection.

Throat Swab

For optimal test performance, use the swabs provided in the test kit. Alternatively foam, polyester, HydraFlock® and nylon flocked throat swabs can be used to collect throat swab samples.

Rayon swabs are not suitable for use in this assay.

Collect patient specimen by swabbing the posterior pharynx, tonsils and other inflamed areas. Avoid touching the tongue, cheeks and teeth with the swab.[1]

Nasal Swab

For optimal test performance, use the swabs provided in the test kit. Alternatively, rayon, foam, HydraFlock® Flocked swab (standard tip), HydraFlock® Flocked swab (mini tip), Copan Mini Tip Flocked Swab, or Copan Standard Flocked swabs can be used to collect nasal swab samples.

Puritan PurFlock Standard Tip Ultra Flocked Swabs, Puritan PurFlock Mini Tip Ultra Flocked Swabs and Copan Standard Rayon Tip Swabs are not suitable for use in this assay.

To collect a nasal swab sample, carefully insert the swab into the nostril exhibiting the most visible drainage, or the nostril that is most congested if drainage is not visible. Using gentle rotation, push the swab until resistance is met at the level of the turbinates (less than one inch into the nostril). Rotate the swab several times against the nasal wall then slowly remove from the nostril. Using the same swab, repeat sample collection in the other nostril.

Nasopharyngeal Swab

Use sterile rayon, foam, polyester or flocked flexible-shaft NP swabs to collect a nasopharyngeal sample.

To collect a nasopharyngeal swab sample, carefully insert the swab into the nostril exhibiting the most visible drainage, or the nostril that is most congested if drainage is not visible. Pass the swab directly backwards without tipping the swab head up or down. The nasal passage runs parallel to the floor, not parallel to the bridge of the nose. Using gentle rotation, insert the swab into the anterior nare parallel to the palate advancing the swab into the nasopharynx, leave in place for a few seconds, and then slowly rotate the swab as it is being withdrawn.

To ensure proper collection, the swab should be passed a distance that is halfway of that from the nose to the tip of the ear. This is about half the length of the swab. **DO NOT USE FORCE** while inserting the swab. The swab should travel smoothly with minimal resistance; if resistance is encountered, withdraw the swab a little bit without taking it out of the nostril. Then elevate the back of the swab and move it forward into the nasopharynx.

SPECIMEN TRANSPORT and STORAGE

For best performance, direct nasal, throat or nasopharyngeal swabs should be tested as soon as possible after collection. If immediate testing is not possible, and to maintain best performance, it is highly recommended the nasal, throat or nasopharyngeal swab is placed in a clean, unused tube labeled with patient information, and capped tightly at room temperature (15-30°C) for up to one (1) hour prior to testing. Ensure the swab fits securely within the tube and the cap is tightly closed.

If the swab is to be returned to its package for transport, carefully return to allow the swab head to only come into contact with the lower portion of the packaging. Avoid touching the outside of the wrapper with the swab.

TEST PROCEDURE

Please refer to the ID NOW Instrument User Manual for full instructions.
Before testing with ID NOW COVID-19:

- **Put on a clean pair of gloves.**
- Allow all samples to reach room temperature.
- Allow all test pieces to reach room temperature.
- Check that a reagent pellet is visible at the bottom of the reaction tubes prior to inserting the Test Base in the ID NOW Instrument. Do not use the Test Base if a pellet is not visible at the bottom of each reaction tube.

To Perform a Test:

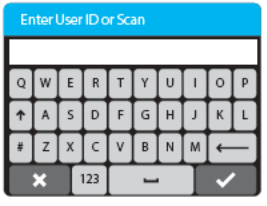
Step 1

Turn on the ID NOW Instrument - press the power button ⏻ on the side of the instrument.

Note: *If the unit is unattended for one hour, the instrument will go to a black screen power save mode. Touch the screen to return the unit to active display operation.*

Enter User ID

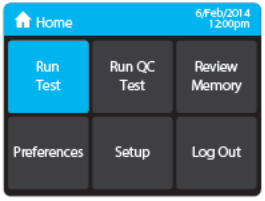
Press '✓' after entry.



To Perform a Test:

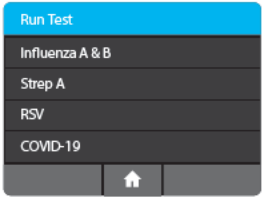
Touch 'Run Test'

This will begin the test process.



Touch 'COVID-19 Test'

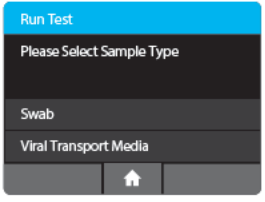
This starts a COVID-19 test.



Select Swab Sample Type (if prompted)

If the sample type has already been specified by the Admin, the instrument will automatically advance to the next step.

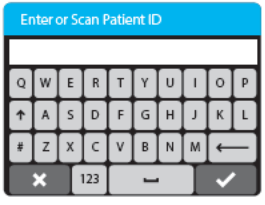
⚠ **Caution: VTM Samples are not an appropriate sample type for the ID NOW COVID-19 test.**



Enter Patient ID using on screen keyboard or barcode scanner.

Touch '✔'.

Verify that the ID was entered correctly, then touch '✔' to confirm entry.



To Perform a Test:

Step 2

Open the Lid and Insert Orange Test Base into Orange Test Base holder

⚠ **Caution: Do not apply excessive force. Excessive force could damage the instrument.**

Confirm that the correct test is displayed on the screen.

Touch 'OK' to proceed.

⚠ **Caution: Once the Test Base has been placed in the holder, the user will have 10 minutes to confirm the test. If the test is not confirmed within 10 minutes, the instrument will time out and the Test Base must be removed and discarded.**

If the incorrect Test Base has been inserted, remove and dispose of the incorrect Test Base. Close the lid. The instrument will then run a self-test before proceeding to the Home screen. Press Run Test and restart the test using the correct Test Base.

To Perform a Test:

Step 3

Insert Blue Sample Receiver into the Blue Sample Receiver holder

⚠ Caution: Do not apply excessive force. Excessive force could damage the instrument.

⚠ Caution: Once the Sample Receiver has been placed in the holder, the user will have 10 minutes to start the test (Steps 3 through 5). If the test is not started within 10 minutes, the instrument will time out and all test pieces (Test Base and Sample Receiver) must be removed and discarded. The instrument will proceed to the Home screen. Press Run Test and restart the test using a new Test Base and Sample Receiver.

Wait for the Sample Receiver to Warm Up. Do not remove the Sample Receiver from the instrument once Warm Up begins.

⚠ Caution: **DO NOT REMOVE THE FOIL SEAL UNTIL PROMPTED BY THE INSTRUMENT.**
DO NOT close the lid or insert the sample until prompted by the instrument.

To Perform a Test:

Step 4

Direct Nasal, Throat or Nasopharyngeal Swab Test Procedure

When prompted, remove the foil seal and place the patient swab to be tested into the Sample Receiver.

Mix the swab in the liquid for 10 seconds. This helps remove the sample from the swab. Lift the swab out of the liquid and press the swab head against the side of the Sample Receiver to remove excess liquid. Once the swab is removed, touch 'OK' to proceed.

Discard the swab into a biohazard waste container.

⚠ **Caution: To ensure that the Sample Receiver remains in the instrument while removing the foil seal, place two fingers along the outer edge of the Sample Receiver to hold it in place. If the Sample Receiver spills after warm up, cancel the test by pressing the Home button. Remove and discard the test pieces (Sample Receiver and Test Base) and clean the instrument. Press Run Test to start a new test using a new Test Base and Sample Receiver.**

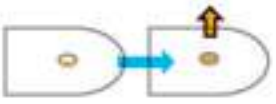
To Perform a Test:

Step 5a

Press the White Transfer Cartridge into the Blue Sample Receiver

Listen for a click.

When the Transfer Cartridge is properly attached to the Sample Receiver, the orange indicator on the Transfer Cartridge will rise. If the orange indicator does not rise, continue pushing onto the Sample Receiver until it does.

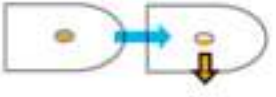


⚠ **Caution: The orange indicator should be observed closely. If the orange indicator does not fully rise, the Transfer Cartridge may not collect enough sample.**

Step 5b

Lift and then connect the Transfer Cartridge to the Test Base

When the Transfer Cartridge is properly attached to the Test Base, the orange indicator on the Transfer Cartridge will descend. If the orange indicator does not descend, continue pushing onto the Test Base until it does.



⚠ **Caution: If the orange indicator does not fully descend, not enough sample will be dispensed. This may potentially result in invalid or false test results.**

To Perform a Test:

Step 6

Close the Lid.

DO NOT OPEN THE LID until the **Test Complete** message appears on the screen.

Note: *The test will be cancelled if the lid is opened.*

⚠ **Caution: This screen will be displayed for up to 30 seconds once the Transfer Cartridge is detected. If the instrument does not detect that the lid has been closed by then, it will time out and all test pieces (Sample Receiver, Test Base, and Transfer Cartridge) must be removed and discarded. The instrument will proceed to the Home screen. Collect a new sample from the patient. Press Run Test and restart the test using a new Test Base and Sample Receiver.**

⚠ **Caution: DO NOT OPEN THE LID. The test will be cancelled and all test pieces (Sample Receiver, Test Base, and Transfer Cartridge) must be removed and discarded. A test result will not be reported or saved in the instrument memory.**

When amplification and detection is complete, the instrument will automatically save the data before advancing to the results screen.

⚠ **Caution: The test is not saved until the completed result is displayed. Do not open the lid until the results are displayed.**

The **Test Results** screen displays either a Negative or Positive result for a successfully completed test. If a test error occurs, the display will read 'Invalid'. Refer to the Result Interpretation Section for Interpretation of Results.

Press Print to print test results, press New Test to run another test, Press Home to return to the Home screen

To Perform a Test:

After printing, or if New Test or Home are selected, the instrument will prompt to open the lid and discard the used test pieces.

Remove test pieces by lifting the Transfer Cartridge attached to the Test Base, and clicking it into the Sample Receiver, by pressing into the Sample Receiver.

⚠ **Caution: Do not try to remove the Sample Receiver by any other method as there is a risk of spilling the patient sample.**

All test pieces will be connected and can now be removed from the instrument and disposed of according to federal, state and local regulations.

⚠ **Caution: DO NOT disassemble the Transfer Cartridge and the Test Base before disposal.**

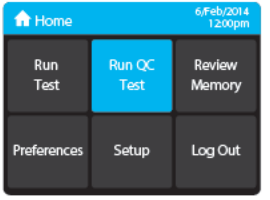
Close the lid. The instrument will then run a Self-Test before showing the Home screen or Enter Patient ID screen, depending on the previous selection.

Remove and dispose of gloves.

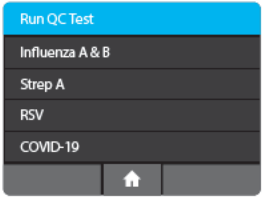
Quality Control Swab Test Procedure

For QC testing, select Run QC Test on the Home screen, and follow the displayed instructions. Refer to Running a QC Test in the ID NOW Instrument User Manual for further details.

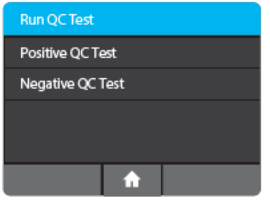
1 **Touch 'Run QC Test'**



2 **Touch 'COVID-19'**



3 **Select the QC Test to be Run**

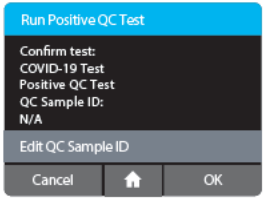


4 **Confirm Test**

Confirm the test type to match the QC sample intended for testing by touching 'OK' and following the on screen prompts to complete testing.

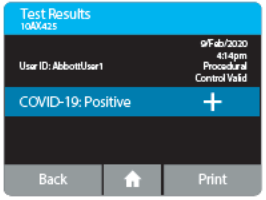
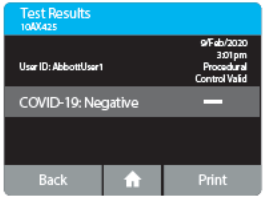
The user has the option to enter an ID for the QC Sample being run.

Note: *The QC test is run in the same manner as a Direct Nasal/Throat/Nasopharyngeal Swab Patient Test. See the* ***To Perform a Test*** *section above for step by step instructions for direct nasal/throat/nasopharyngeal swab samples.*



RESULT INTERPRETATION

When the test is complete, the results are clearly displayed on the instrument screen.

Instrument Display	Interpretation of Results and Follow-up Actions
	**COVID-19 Positive** Positive results do not rule out bacterial infection or co-infection with other viruses.
	**COVID-19 Negative** Negative results should be treated as presumptive and, if inconsistent with clinical signs and symptoms or necessary for patient management, should be tested with an alternative molecular assay. A negative result does not rule out co-infections with other pathogens.
	**The presence or absence of COVID-19 Viral RNAs cannot be determined.** Repeat testing of the sample using new test components. If repeated Invalid results are obtained, results should be confirmed by another method prior to reporting the results.

If an Invalid result is received, one additional test may be run using the same Sample Receiver. The instructions below should be followed:

- Remove the connected Test Base and Transfer Cartridge from the instrument and connect the Test Base portion to an open, UNUSED Sample Receiver. The connected Test Base and Transfer Cartridge MUST be attached to a Sample Receiver prior to disposal. The Sample Receiver from a new Transfer Cartridge package may be used for this.
- Remove the blue Sample Receiver separately and carefully from the instrument. The Sample Receiver should be retained and kept upright to avoid spilling the liquid contents.
- From the Home Screen, start a new test. Follow the screen prompts; however, when asked to insert the Sample Receiver, reuse the Sample Receiver and DO NOT re-elute the swab.

LIMITATIONS

- The performance of the ID NOW COVID-19 was evaluated using the procedures provided in this product insert only. Modifications to these procedures may alter the performance of the test.
- Negative results should be treated as presumptive and tested with an alternative authorized molecular assay, if necessary for clinical management, including infection control.
- False negative results may occur if a specimen is improperly collected, transported or handled. False negative results may also occur if amplification inhibitors are present in the specimen or if inadequate levels of viruses are present in the specimen. Negative results should be considered in the context of a patient's recent exposures, history and the presence of clinical signs and symptoms consistent with COVID-19.
- As with any molecular test, mutations within the target regions of the Abbott ID NOW COVID-19 test could affect primer and/or probe binding resulting in failure to detect the presence of the virus.
- The test cannot rule out diseases caused by other bacterial or viral pathogens.
- ID NOW COVID-19 is intended for testing a swab directly without elution in viral transport media as dilution will result in decreased detection of low positive samples that are near the limit of detection of the test.
- Swab samples eluted in VTM are not appropriate for use in this test.
- The additional recommended swab types have not been validated in the ID NOW COVID-19 test. The recommendation for use is based on data generated with other, similar ID NOW assays. For optimal test performance, use the swabs provided in the test kit.

PERFORMANCE CHARACTERISTICS

Clinical Study:

The performance of ID NOW COVID-19 was evaluated using contrived clinical nasopharyngeal (NP) swab specimens obtained from individuals with signs and symptoms of respiratory illness. The samples were prepared by spiking clinical NP swab matrix with purified viral RNA containing target sequences from the SARS-CoV-2 genome at concentrations approximately 2x LOD and 5x LOD. Negative NP swab samples were also tested in this study.

The table below presents ID NOW COVID-19 test agreement with the expected results by sample concentration.

ID NOW™ COVID-19 Test Agreement with the Expected Results by Sample Concentration

Target Concentration	Number Concordant/ Number Tested	% Agreement [95% CI]
2X LOD	20/20	100% [83.9% - 100%]
5X LOD	10/10	100% [72.3% - 100%]
Negative	30/30	100% [88.7% - 100%]

An additional study was performed to evaluate the performance of ID NOW COVID-19. Clinical performance characteristics of ID NOW COVID-19 was evaluated in an ongoing multi-site prospective study in the U.S. in which patients were sequentially enrolled and tested. A total of six (6) investigational sites throughout the U.S. participated in the study. To be enrolled in the study, patients had to be presenting at the participating study centers with suspected COVID-19.

Two nasal swabs were collected from patients and tested using ID NOW COVID-19 at all study sites. An FDA Emergency Use Authorized (EUA) real-time Polymerase Chain Reaction (RT-PCR) assay for the detection of SARS-CoV-2 was utilized as the comparator method for this study. All discrepant samples were tested on a different FDA EUA RT-PCR assay to confirm COVID-19 status.

At all sites, one nasal swab was tested directly in ID NOW COVID-19 according to product instructions and the other swab was eluted in viral transport media (VTM). Swabs were randomly assigned to testing with ID NOW or RT-PCR and were tested by minimally trained operators who were blinded to the RT-PCR test result. All sites shipped the VTM sample to a central testing laboratory for RT-PCR.

External control testing, using ID NOW COVID-19 Positive and Negative Controls, was performed prior to sample testing each day, at all study sites.

The performance of ID NOW COVID-19 was established based on an interim analysis of 852 nasal swabs collected from individual patients who were suspected of COVID-19.

ID NOW™ COVID-19 Performance against the Comparator Method

ID NOW™ COVID-19	Comparator Method		
	Positive	**Negative**	**Total**
Positive	157	12[a]	169
Negative	12[b]	671	683
Total	169	683	852
Positive Agreement: 157/169	92.9% (95% CI: 87.9% - 96.3%)		
Negative Agreement: 671/683	98.2% (95% CI: 97.0% - 99.1%)		

[a] *COVID-19 was detected in 1/12 False positive specimens using a second FDA EUA RT-PCR test*

[b] *COVID-19 was not detected in 5/12 False negative specimens and 1 sample was inconclusive using a second FDA- EUA RT-PCR test.*

ANALYTICAL STUDIES:

Analytical Sensitivity (Limit of Detection)

ID NOW COVID-19 limit of detection (LOD) in natural nasopharyngeal swab matrix was determined by evaluating different concentrations of purified viral RNA containing target sequences from the SARS-CoV-2 genome.

Presumed negative natural nasopharyngeal swab specimens were eluted in ID NOW COVID-19 elution buffer. Swab elutes were combined and mixed thoroughly to create a clinical matrix pool to be used as the diluent. Viral RNA was diluted in this natural nasopharyngeal matrix pool to generate virus dilutions for testing.

The LOD was determined as the lowest concentration that was detected ≥ 95% of the time (i.e., concentration at which at least 19 out of 20 replicates tested positive).

The confirmed LOD in natural nasopharyngeal swab matrix is presented in the table below:

Limit of Detection (LOD) Study Results

Virus	Claimed LOD (Genome Equivalents/mL)	Positive/Replicates
SARS-CoV-2 RNA	125	19/20

Analytical Reactivity (Inclusivity)

Due to the limited availability of SARS-CoV-2 isolates for inclusivity testing, an alignment was performed with the oligonucleotide primer and probe sequences of the ID NOW COVID-19 assay with all publicly available nucleic acid sequences for the 2019-nCoV in public databases (NCBI and Genbank) to demonstrate the predicted inclusivity of the ID NOW COVID-19 assay. All of the alignments show 100% identity of the ID NOW COVID-19 to the available SARS-CoV-2 sequences as of March 20, 2020.

Analytical Specificity (Cross Reactivity)

An *in silico* analysis for possible cross-reactions with all the organisms listed in the table below was conducted by mapping primers and probes of the ID NOW COVID-19 target nucleic acid sequence to the sequences download from the NCBI Genbank and GISAID databases.

The ID NOW COVID-19 assay, designed for the specific detection of SARS-CoV-2, showed no significant combined homologies with human genome, other coronaviruses, or human microflora that would predict potential ID NOW COVID-19 false results.

ID NOW™ COVID-19 Analytical Specificity Microorganisms

Microorganisms from the Same Genetic Family	High Priority Organisms
Human coronavirus 229E	Human adenovirus A
Human coronavirus OC43	Human adenovirus B
Human coronavirus HKU1	Human adenovirus B1
Human coronavirus NL63	Human adenovirus C
SARS-coronavirus	Human adenovirus D
MERS-coronavirus	Human adenovirus E
	Human adenovirus F
	Human adenovirus G
	Human adenovirus 7
	Human adenovirus 8
	Human metapneumovirus (hMPV)
	Human parainfluenza virus 1 - 4
	Influenza A
	Influenza B
	Enterovirus A-L
	Human respiratory syncytial virus
	Rhinovirus A - C
	Chlamydia pneumoniae
	Haemophilus influenzae

Microorganisms from the Same Genetic Family	High Priority Organisms
	Legionella pneumophila
	Mycobacterium tuberculosis
	Streptococcus pneumoniae
	Streptococcus pyogenes
	Bordetella pertussis
	Mycoplasma pneumoniae
	Pneumocystis jiroveci (PJP)
	Candida albicans
	Pseudomonas aeruginosa
	Staphylococcus epidermis
	Staphylococcus salivarius (Rhodotorula mucilaginosa)
	Streptococcus salivarius

SYMBOLS

 Fragile, handle with care	BASE Test Base	CARTRDG Transfer Cartridge
RCVR Sample Receiver	 Caution, consult accompanying documents.	CE Mark
IVD *In Vitro* Diagnostics	EUA For Use Under an Emergency Use Authorization Only (Applies to US only)	

ORDERING and CONTACT INFORMATION

Reorder numbers:

191-000: ID NOW COVID-19 Test Kit

190-080: ID NOW COVID-19 External Control Kit

US +1 877 441 7440
OUS +1 321 441 7200

Technical Support Advice Line
Further information can be obtained by contacting Technical Support on:

US
+1 855 731 2288 ts.scr@abbott.com

Africa, Russia, CIS
+44 161 483 9032 EMEproductsupport@abbott.com

Asia Pacific
+61 7 3363 7711 APproductsupport@abbott.com

Canada
+1 800 818 8335 CANproductsupport@abbott.com

Europe & Middle East
+44 161 483 9032 EMEproductsupport@abbott.com

Latin America
+57 (1) 4824033 LAproductsupport@abbott.com

REFERENCES

1. Manual of Clinical Microbiology, 11th Edition, Vol. 1, ASM. (2015) pg. 279.
2. https://www.iata.org/en/programs/cargo/dgr

Abbott

Abbott Diagnostics Scarborough, Inc.
10 Southgate Road
Scarborough, Maine 04074 USA
www.globalpointofcare.abbott

CE IVD

IN191000CAN Rev.1 2020/09

Abbott
ID NOW
COVID-19

PI - CAN

Size:
Flat size: 8.375″ x 10.75″
Finished: 8.375″ x 5.375″

Printed Colors

CMYK

Incoming Inspection Colors
(For Reference Only)
Colors below are not used for printing

PMS 2995 U
Primary Blue

PMS 224 U
Magenta-Pink

PMS 303 U
Dark Blue

PN: IN191000CAN
Rev: 1

Date of Last Revision:
1.3 2020/09/29

Abbott

REF 41FK11

CE

Panbio™

COVID-19 Ag Rapid Test Device

(NASAL)

In vitro **diagnostic rapid test for qualitative detection of SARS-CoV-2 antigen (Ag)**

In-vitro **diagnostischer Schnelltest zum qualitativen Nachweis von SARS-CoV-2 Antigen (Ag)**

Prueba rápida de diagnóstico *In vitro* para la detección cualitativa del antígeno (Ag) del SARS-CoV-2

Test rapide de diagnostic *in vitro* pour la détection qualitative de l'antigène SARS-CoV-2 (Ag)

Test diagnostico rapido *in vitro* per la ricerca qualitativa dell'antigene SARS-CoV-2 (Ag)

Teste rápido de diagnóstico *in vitro* para detecção qualitativa do antígeno SARS-CoV-2 (Ag)

Экспресс-тест *in vitro* для качественного определения антигена SARS-CoV-2 (Ag)

About the Test

EN

Introduction

The Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. The SARS-CoV-2 is a β-coronavirus, which is an enveloped non-segmented positive-sense RNA virus[2]. It is spread by human-to-human transmission via droplets or direct contact, and infection has been estimated to have a mean incubation period of 6.4 days and a basic reproduction number of 2.24-3.58. Among patients with pneumonia caused by SARS-CoV-2, fever was the most common symptom, followed by cough[3]. The main IVD assays used for COVID-19 employ real-time reverse transcriptase-polymerase chain reaction (RT-PCR) that takes a few hours[4]. The availability of a cost-effective, rapid point-of-care diagnostic test is critical to enable healthcare professionals to aid in the diagnosis of patients and prevent further spread of the virus[5]. Antigen tests will play a critical role in the fight against COVID-19[6].

Test Principle

Panbio™ COVID-19 Ag Rapid Test Device contains a membrane strip, which is pre-coated with immobilized anti-SARS-CoV-2 antibody on the test line and mouse monoclonal anti-chicken IgY on the control line. Two types of conjugates (human IgG specific to SARS-CoV-2 Ag gold conjugate (binds to the nucleocapsid protein) and chicken IgY gold conjugate) move upward on the membrane chromatographically and react with anti-SARS-CoV-2 antibody and pre-coated mouse monoclonal anti-chicken IgY respectively. For a positive result, human IgG specific to SARS-CoV-2 Ag gold conjugate and anti-SARS-CoV-2 antibody will form a test line in the result window. Neither the test line nor the control line are visible in the result window prior to applying the patient specimen. A visible control line is required to indicate a test result is valid.

Intended Use

Panbio™ COVID-19 Ag Rapid Test Device is an *in vitro* diagnostic rapid test for the qualitative detection of SARS-CoV-2 antigen (Ag) in human nasal swab specimens from individuals who meet COVID-19 clinical and / or epidemiological criteria. Panbio™ COVID-19 Ag Rapid Test Device is for professional use only and is intended to be used as an aid in the diagnosis of SARS-CoV-2 infection. The product may be used in any laboratory and non-laboratory environment that meets the requirements specified in the Instructions for Use and local regulation. The test provides preliminary test results. Negative results don't preclude SARS-CoV-2 infection and they cannot be used as the sole basis for treatment or other management decisions. Negative results must be combined with clinical observations, patient history, and epidemiological information. The test is not intended to be used as a donor screening test for SARS-CoV-2.

Materials Provided

- 25 Test devices with desiccant in individual foil pouch
- Buffer (1 x 9 ml/bottle)
- 25 Extraction tubes
- 25 Extraction tube caps
- 1 Positive control swab
- 1 Negative control swab
- 25 Sterilized nasal swabs for sample collection
- 1 Tube rack
- 1 Quick Reference Guide
- 1 Instructions for use

Materials Required but not Provided

- Personal Protective Equipment per local recommendations (i.e. gown/ lab coat, face mask, face shield/eye goggles and gloves), Timer, Biohazard container

Active Ingredients of Main Components

- **1 Test device** Gold conjugate: Human IgG specific to SARS-CoV-2 Ag gold colloid and Chicken IgY - gold colloid, Test line: Mouse monoclonal anti-SARS-CoV-2, Control line: Mouse monoclonal anti-Chicken IgY
- **Buffer** Tricine, Sodium Chloride, Tween 20, Sodium Azide (<0.1%), Proclin 300

Storage and Stability

1. The test kit should be stored at a temperature between 2-30 °C. Do not freeze the kit or its components.
   Note: When stored in a refrigerator, all kit components must be brought to room temperature (15-30 °C) for a minimum of 30 minutes prior to performing the test. Do not open the pouch while components come to room temperature.
2. The Buffer bottle may be opened and resealed for each assay. The Buffer cap should be firmly sealed between each use. The Buffer is stable until expiration date if kept at 2-30 °C.
3. Perform the test immediately after removing the test device from the foil pouch.
4. Do not use the test kit beyond its expiration date.
5. The shelf life of the kit is as indicated on the outer package.
6. Do not use the test kit if the pouch is damaged or the seal is broken.
7. Direct swab specimens should be tested immediately after collection. If immediate testing is not possible, the swab specimen can be kept in an extraction tube filled with extraction buffer (300 µl) at room temperature (15-30 °C) for up to two hours prior to testing.

Warnings

1. For *in vitro* diagnostic use only. Do not reuse the test device and kit components.
2. These instructions must be strictly followed by a trained healthcare professional to achieve accurate results. All users have to read the instruction prior to performing a test.
3. Do not eat or smoke while handling specimens.
4. Wear protective gloves while handling specimens and wash hands thoroughly afterwards.
5. Avoid splashing or aerosol formation of specimen and buffer.
6. Clean up spills thoroughly using an appropriate disinfectant.
7. Decontaminate and dispose of all specimens, reaction kits and potentially contaminated materials (i.e. swab, extraction tube, test device) in a biohazard container as if they were infectious waste and dispose according to applicable local regulations.
8. Do not mix or interchange different specimens.
9. Do not mix reagent of different lots or those for other products.
10. Do not store the test kit in direct sunlight.
11. To avoid contamination, do not touch the head of provided swab when opening the swab pouch.
12. The sterilized swabs should be used only for nasal specimen collection.
13. To avoid cross-contamination, do not reuse the sterilized swabs for specimen collection.
14. Do not dilute the collected swab with any solution except for the provided extraction buffer.
15. The buffer contains <0.1% sodium azide as a preservative which may be toxic if ingested. When disposed of through a sink, flush with a large volume of water.[7]
16. Do not use the positive or negative control swab for specimen collection.

Test Procedure (Refer to Figure)

Nasal swab Specimens

Note: Healthcare professionals should comply with personal safety guidelines including the use of personal protective equipment.

Test Preparation

1. Allow all kit components to reach a temperature between 15-30 °C prior to testing for 30 minutes.
2. Remove the test device from the foil pouch prior to use. Place on a flat, horizontal and clean surface.
3. Hold the buffer bottle vertically and fill the extraction tube with buffer fluid until it flows up to the Fill-line of the extraction tube (300 µl).
   ⚠ **Caution:** If the amount of buffer is excessive or insufficient, an improper test result may occur.

4. Place the extraction tube in the tube rack.

Specimen Collection & Extraction

1. Tilt the patient's head back 70 degrees. While gently rotating the swab, insert swab less than one inch (about 2 cm) into nostril (until resistance is met at the turbinates).
2. Rotate the swab five times against the nasal wall then slowly remove from the nostril.
3. Using the same swab repeat the collection procedure with the second nostril.
   ⚠ **Caution:** If the swab stick breaks during specimen collection, repeat specimen collection with a new swab.
4. Swirl the swab tip in the buffer fluid inside the extraction tube, pushing into the wall of the extraction tube at least five times and then squeeze out the swab by squeezing the extraction tube with your fingers.
5. Break the swab at the breakpoint and close the cap of extraction tube.

Reaction with Test Device

1. Open the dropping nozzle cap at the bottom of the extraction tube.
2. Dispense 5 drops of extracted specimens vertically into the specimen well (S) on the device. Do not handle or move the test device until the test is complete and ready for reading.
   ⚠ **Caution:** Bubbles that occur in the extraction tube can lead to inaccurate results. If you are unable to create sufficient drops, this may be caused by clogging in the dispensing nozzle. Shake the tube gently to release the blockage until you observe free drop formation.
3. Close the nozzle and dispose of the extraction tube containing the used swab according to your local regulations and biohazard waste disposal protocol.
4. Start timer. Read result at 15 minutes. Do not read results after 20 minutes.
5. Dispose of the used device according to your local regulations and biohazard waste disposal protocol.

Positive / Negative Control Swab

⚠ **Caution:** Control use only. Do not use the positive or negative control swab for specimen collection.

Note: Please refer to the External Quality Control section of this Instructions for use for the frequency of testing external quality control swabs.

1. Hold the buffer bottle vertically and fill the extraction tube with buffer fluid until it flows up to the Fill-line of the extraction tube (300 µl).
   ⚠ **Caution:** If the amount of buffer is excessive or insufficient, an improper test result may occur.
2. Place the extraction tube in the tube rack.
3. Insert the positive or negative control swab in the buffer fluid inside of the extraction tube and soak the swab for 1 minute. Swirl the control swab tip

in the buffer fluid inside of the extraction tube, pushing into the wall of the extraction tube at least five times and then squeeze out the swab by squeezing the extraction tube with your fingers.

4. Dispose of the used control swab in accordance with your biohazard waste disposal protocol.
5. Close the cap of the extraction tube.
6. Follow the above test procedure [Reaction with Test Device].

Test Interpretation (Refer to Figure)

1. **Negative result:** The presence of only the control line (C) and no test line (T) within the result window indicates a negative result.
2. **Positive result:** The presence of the test line (T) and the control line (C) within the result window, regardless of which line appears first, indicates a positive result.

   ⚠ **Caution:** The presence of any test line (T), no matter how faint, indicates a positive result.
3. **Invalid result:** If the control line (C) is not visible within the result window after performing the test, the result is considered invalid.

Test Limitations

1. The contents of this kit are to be used for the professional and qualitative detection of SARS-CoV-2 antigen from nasal swab. Other specimen types may lead to incorrect results and must not be used.
2. Failure to follow the instructions for test procedure and interpretation of test results may adversely affect test performance and/or produce invalid results.
3. A negative test result may occur if the specimen was collected, extracted or transported improperly. A negative test result does not eliminate the possibility of SARS-CoV-2 infection and should be confirmed by viral culture or a molecular assay.
4. Positive test results do not rule out co-infections with other pathogens.
5. Test results must be evaluated in conjunction with other clinical data available to the physician.
6. Reading the test results earlier than 15 minutes or later than 20 minutes may give incorrect results.
7. Panbio™ COVID-19 Ag Rapid Test Device is not intended to detect from defective (non-infectious) virus during the later stages of viral shedding that might be detected by PCR molecular tests.[8]
8. Positive results may occur in cases of infection with SARS-CoV.

Quality Control

1. **Internal Quality Control:**
   The test device has a test line (T) and a control line (C) on the surface of the test device. Neither the test line nor the control line are visible in the result window before applying a specimen. The control line is used for procedural control and should always appear if the test procedure is performed properly and the test reagents of the control line are working.
2. **External Quality Control:**
   The controls are specifically formulated and manufactured to ensure performance of the Panbio™ COVID-19 Ag Rapid Test Device and are used to verify the user's ability to properly perform the test and interpret the results. The Positive Control will produce a positive test result and has been manufactured to produce a visible test line (T). The Negative Control will produce a negative test result.
   Good laboratory practice suggests the use of positive and negative controls to ensure that:

- Test reagents are working, and
- The test is correctly performed.

The external controls can be run under any of the following circumstances:

- By a new operator prior to performing testing on patient specimens,
- When receiving a new test shipment,
- At periodic intervals as dictated by local requirements, and/or by the user's Quality Control procedures.

Performance Characteristics

1. **External evaluation of Panbio™ COVID-19 Ag Rapid Test Device**
   Clinical performance of Panbio™ COVID-19 Ag Rapid Test Device was determined by testing 104 positive nasal swab specimens and 404 negative specimens for SARS-CoV-2 antigen (Ag) to have a sensitivity of 98.1% (95% CI: 93.2-99.8%) and a specificity of 99.8% (95% CI: 98.6-100.0%). Clinical specimens were determined to be positive or negative using an FDA EUA RT-PCR reference method.

Panbio™ COVID-19 Ag Rapid Test Device Results

		Nasal PCR Test Result		
		Positive	**Negative**	**Total**
Panbio™ COVID-19 Ag Rapid Test Device Result (nasal swab specimens)	**Positive**	102	1	103
	Negative	2	403	405
	Total	104	404	508
		Sensitivity	Specificity	Overall Percent Agreement
		98.1% [93.2%;99.8%]	**99.8%** [98.6%;100.0%]	**99.4%** [98.3%;99.9%]

- Performance data was calculated from a study of individuals suspected of exposure to COVID-19 or who have presented with symptoms in the last 7 days.
- Stratification of the positive specimens post onset of symptoms or suspected exposure between 0-3 days has a sensitivity of 100.0% (n=46) and 4-7 days has a sensitivity of 96.6% (n=58).
- Positive agreement of the Panbio™ COVID-19 Ag Rapid Test Device is higher with samples of Ct values ≤33 with a sensitivity of 99.0%. As indicated in References 8 and 9, patients with Ct value >33 are no longer contagious.[8, 9]
- The clinical performance data was also calculated vs nasopharyngeal swab specimens using an FDA EUA RT-PCR reference and has a sensitivity of 91.1% (95% CI: 84.2-95.6%) and specificity of 99.7% (95% CI: 98.6-100.0%).

2. Detection Limit

Panbio™ COVID-19 Ag Rapid Test Device was confirmed to detect $2.5X10^{1.8}$ $TCID_{50}$/ml of SARS-CoV-2 which was isolated from a COVID-19 confirmed patient in Korea.

3. Hook Effect

There is no hook effect at $1.0x10^{5.8}$ $TCID_{50}$/ml of SARS-CoV-2 which was isolated from a COVID-19 confirmed patient in Korea.

4. Cross Reactivity

Cross-reactivity of Panbio™ COVID-19 Ag Rapid Test Device was evaluated by testing 28 viruses and 13 other microorganisms. The final test concentrations of viruses and other microorganisms are documented in the Table below. The following viruses and other microorganisms except the Human SARS-coronavirus Nucleoprotein have no effect on the test results of Panbio™ COVID-19 Ag Rapid Test Device.

Panbio™ COVID-19 Ag Rapid Test Device has cross-reactivity with Human-SARS-coronavirus Nucleoprotein at a concentration of 25 ng/ml or more because SARS-CoV has high homology (79.6%) to the SARS-CoV-2.

No.	Types of Specimen	Cross Reaction Substance	Final Test Concentration	Test Result
1	Virus	Adenovirus Type 1	2.2×10^7 $TCID_{50}$/ml	No cross reaction
2		Adenovirus Type 5	5.71×10^8 $TCID_{50}$/ml	No cross reaction
3		Adenovirus Type 7	2.86×10^9 $TCID_{50}$/ml	No cross reaction
4		Enterovirus (EV68)	2.81×10^7 $TCID_{50}$/ml	No cross reaction
5		Echovirus2	$1.0 \times 10^{6.5}$ $TCID_{50}$/ml	No cross reaction
6		Echovirus11	$5.0 \times 10^{6.25}$ $TCID_{50}$/ml	No cross reaction
7		Enterovirus D68	2.81×10^7 $TCID_{50}$/ml	No cross reaction
8		Human herpesvirus (HSV) 1	$5.0 \times 10^{7.5}$ $TCID_{50}$/ml	No cross reaction
9		Human herpesvirus (HSV) 2	$5.0 \times 10^{5.75}$ $TCID_{50}$/ml	No cross reaction
10		Mumps Virus Ag	1.58×10^5 $TCID_{50}$/ml	No cross reaction
11		Influenza virus A (H1N1) Strain (A/Virginia/ATCC1/2009)	3.71×10^5 PFU/ml	No cross reaction
12		Influenza virus A (H1N1) Strain (A/WS/33)	$5.0 \times 10^{7.25}$ $TCID_{50}$/ml	No cross reaction
13		Influenza virus A(H1N1) Strain (A/California/08/2009/pdm09)	1.6×10^8 $TCID_{50}$/ml	No cross reaction
14		Influenza virus B Strain (B/Lee/40)	$5.0 \times 10^{6.25}$ $TCID_{50}$/ml	No cross reaction
15		Parainfluenza Type 1	3.06×10^8 $TCID_{50}$/ml	No cross reaction
16		Parainfluenza Type 2	5.0×10^5 $TCID_{50}$/ml	No cross reaction
17		Parainfluenza Type 3	6.6×10^7 $TCID_{50}$/ml	No cross reaction
18		Parainfluenza Type 4A	2.81×10^7 $TCID_{50}$/ml	No cross reaction

No.	Types of Specimen	Cross Reaction Substance	Final Test Concentration	Test Result
19	Virus	Respiratory syncytial virus (RSV) type A	4.22×10^5 $TCID_{50}$/ml	No cross reaction
20		Respiratory syncytial virus (RSV) type B	5.62×10^5 $TCID_{50}$/ml	No cross reaction
21		Rhinovirus A16	1.26×10^6 $TCID_{50}$/ml	No cross reaction
22		HCoV-HKU1	1.5mg/ml	No cross reaction
23		HCoV-NL63	1.7×10^5 $TCID_{50}$/ml	No cross reaction
24		HCoV-OC43	8.9×10^5 $TCID_{50}$/ml	No cross reaction
25		HCoV-229E	1.51×10^6 $TCID_{50}$/ml	No cross reaction
26		Human SARS-coronavirus Nucleoprotein	25ng/ml	Cross reaction
27		MERS-CoV Nucleoprotein	0.25mg/ml	No cross reaction
28		Human Metapneumovirus (hMPV) 16 Type A1	1.51×10^6 $TCID_{50}$/ml	No cross reaction

No.	Types of Specimen	Cross Reaction Substance	Final Test Concentration	Test Result
1	Other Microorganism	*Staphylococcus saprophyticus*	1.9 X 10^7 CFU/ml	No cross reaction
2		*Neisseria sp.(Neisseria lactamica)*	1.7 X 10^8 CFU/ml	No cross reaction
3		*Staphylococcus haemolyticus*	3.5 X 10^9 CFU/ml	No cross reaction
4		*Streptococcus salivarius*	1.96 X 10^7 CFU/ml	No cross reaction
5		*Hemophilus parahaemolyticus*	2.2 X 10^8 CFU/ml	No cross reaction
6		*Proteus vulgaris*	7.2 X 10^6 CFU/ml	No cross reaction
7		*Moraxella catarrhalis*	4.7 X 10^7 CFU/ml	No cross reaction
8		*Klebsiella pneumoniae*	5.0 X 10^6 CFU/ml	No cross reaction
9		*Fusobacterium necrophorum*	1.75 X 10^8 CFU/ml	No cross reaction
10		*Mycobacterum tuberculosis*	10mg/ml	No cross reaction
11		Pooled human nasal wash	N/A*	No cross reaction
12		*Streptococcus pyogenes*	3.6 X 10^7 CFU/ml	No cross reaction
13		*Mycoplasma pneumoniae*	4 X 10^8 CFU/ml	No cross reaction

** No concentration provided by supplier. Undiluted stock solution was tested.*

5. Interfering Substances

The following 43 potentially interfering substances have no impact on Panbio™ COVID-19 Ag Rapid Test Device. The final test concentrations of the interfering substances are documented in the Table below.

No.	Types of Specimen	Interfering Substances	Final Test Concentration	Test Result
1	Endogenous Substance	Mucin	0.5%	No Interference
2		Hemoglobin	100 mg/L	No Interference
3		Triglycerides	1.5 mg/L	No Interference
4		Icteric (Bilirubin)	40 mg/dL	No Interference
5		Rheumatoid factor	200 IU/ml	No Interference
6		Anti-nuclear antibody	>1:40	No Interference
7		Pregnant	10-fold dilution	No Interference
8	Exogenous Substance	Guaiacol glyceryl ether	1 µg/ml	No Interference
9		Albuterol	0.005 mg/dL	No Interference
10		Ephedrine	0.1 mg/ml	No Interference
11		Chlorpheniramine	0.08 mg/dL	No Interference
12		Diphenhydramine	0.08 mg/dL	No Interference
13		Ribavirin	26.7 µg /ml	No Interference
14		Oseltamivir	0.04 mg/dL	No Interference
15		Zanamivir	17.3 µg /ml	No Interference
16		Phenylephrine hydrochloride	15% v/v	No Interference
17		Oxymetazolin hydrochloride	15% v/v	No Interference
18		Amoxicillin	5.4 mg/dL	No Interference
19		Acetylsalicylic acid	3 mg/dL	No Interference
20		Ibuprofen	21.9 mg/dL	No Interference
21		Chlorothiazide	2.7 mg/dL	No Interference
22		Indapamide	140 ng/ml	No Interference
23		Glimepiride (Sulfonylureas)	0.164 mg/dL	No Interference
24		Acarbose	0.03 mg/dL	No Interference
25		Ivermectin	4.4 mg/L	No Interference
26		Lopinavir	16.4 µg/L	No Interference
27		Ritonavir	16.4 µg/L	No Interference
28		Chloroquine phosphate	0.99 mg/L	No Interference

No.	Types of Specimen	Interfering Substances	Final Test Concentration	Test Result
29	Exogenous Substance	Sodium chloride with preservatives	4.44 mg/ml	No Interference
30		Beclomethasone	4.79 ng/ml	No Interference
31		Dexamethasone	0.6 µg/ml	No Interference
32		Flunisolide	0.61 µg/ml	No Interference
33		Triamcinolone	1.18 ng/ml	No Interference
34		Budesonide	2.76 ng/ml	No Interference
35		Mometasone	1.28 ng/ml	No Interference
36		Fluticasone	2.31 ng/ml	No Interference
37		Sulfur	9.23 µg/ml	No Interference
38		Benzocaine	0.13 mg/ml	No Interference
39		Menthol	0.15 mg/ml	No Interference
40		Mupirocin	10 µg/ml	No Interference
41		Tobramycin	24.03 µg/ml	No Interference
42		Biotin	1.2 µg/ml	No Interference
43		HAMA	63.0 ng/ml	No Interference

6. Repeatability & Reproducibility

Repeatability & Reproducibility of Panbio™ COVID-19 Ag Rapid Test Device was established using in-house reference panels containing negative specimens and a range of positive specimens. There were no differences observed within-run, between-run, between-lots, between-sites, and between-days.

PREPARATION

1 Allow all kit components to reach a temperature between 15-30°C prior to testing for 30 minutes.
Note: Healthcare professionals should comply with personal safety guidelines including the use of personal protective equipment.

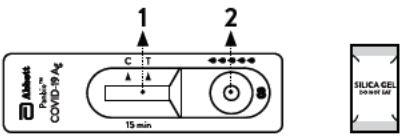
2 **Open the package and look for the following:**
1. Test device with desiccant in individual foil pouch
2. Buffer
3. Extraction tube
4. Extraction tube cap
5. Positive control swab
6. Negative control swab
7. Sterilized nasal swabs for sample collection
8. Tube rack
9. Quick reference guide
10. Instructions for use

3 Carefully read these instructions prior to using Panbio™ COVID-19 Ag Rapid Test Device kit.

4 Look at the expiration date of the kit box. If the expiration date has passed, use another kit.

5 **Open the foil pouch and look for the following:**
1. Result window
2. Specimen well

Then, label the device with the patient identifier.



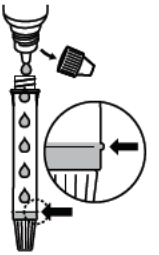
●●●●● : 5 drops of the extracted specimen

ENGLISH

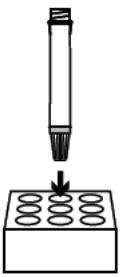
TEST PROCEDURE

1 Hold the buffer bottle vertically and fill the extraction tube with buffer fluid until it flows up to the Fill-line of the extraction tube (300µl).

⚠ **Caution:** If the amount of buffer is excessive or insufficient, an improper test result may occur.

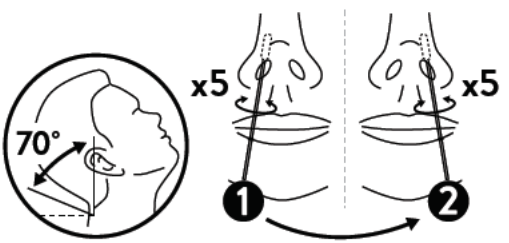


2 Place the extraction tube in the tube rack.



3 Tilt the patient's head back 70 degrees. While gently rotating the swab, insert swab less than one inch (about 2 cm) into nostril (until resistance is met at the turbinates). Rotate the swab five times against the nasal wall. Using the same swab repeat the collection procedure with the second nostril. Slowly remove swab from the nostril.

⚠ **Caution:** If the swab stick breaks during specimen collection, repeat specimen collection with a new swab.



ENGLISH

TEST PROCEDURE

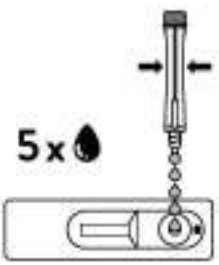
4 Insert the swab specimen in the extraction tube. Swirl the swab tip in the buffer fluid inside the extraction tube, pushing into the wall of the extraction tube at least five times and then squeeze out the swab by squeezing the extraction tube with your fingers.

5 Break the swab at the breakpoint and close the cap of extraction tube.

6 Open the dropping nozzle cap at the bottom of the extraction tube.

7 Dispense 5 drops of extracted specimens vertically into the specimen well (S) on the device. Do not handle or move the test device until the test is complete and ready for reading.

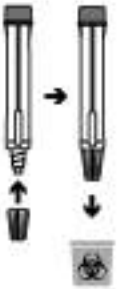
⚠ **Caution:** Bubbles that occur in the extraction tube can lead to inaccurate results. If you are unable to create sufficient drops, this may be caused by clogging in the dispensing nozzle. Shake the tube gently to release the blockage until you observe free drop formation.



ENGLISH

TEST PROCEDURE

8 Close the nozzle and dispose of the extraction tube containing the used swab according to your local regulations and biohazard waste disposal protocol.



9 Start timer. Read result at 15 minutes. Do not read results after 20 minutes.

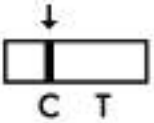
10 Dispose of the used device according to your local regulations and biohazard waste disposal protocol.

ENGLISH

TEST INTERPRETATION

NEGATIVE

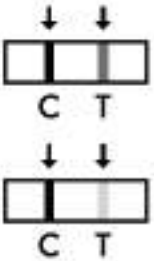
The presence of only the control line (C) and no test line (T) within the result window indicates a negative result.



POSITIVE

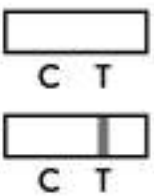
The presence of the test line (T) and the control line (C) within the result window, regardless of which line appears first, indicates a positive result.

⚠ **Caution**: The presence of any test line (T), no matter how faint, indicates a positive result.



INVALID

If the control line (C) is not visible within the result window after performing the test, the result is considered invalid. Instructions may not have been followed correctly. It is recommended to read the IFU again before re-testing the specimen with a new test device.



ENGLISH

Über den Test

DE

Übersicht

Die Coronavirus Krankheit (Covid-19) ist eine Infektionskrankheit. Sie wird verursacht durch das neuartige Coronavirus, das schwere akute respiratorische Syndrom Coronavirus 2 (SARS-CoV-2)[1]. SARS-CoV-2 gehört der Gattung β an, bei dem es sich um ein umhülltes, nicht segmentiertes RNA-Virus mit positiver Polarität handelt[2]. Es wird über Tröpfchen oder direkten Kontakt von Mensch zu Mensch übertragen. Für die Infektion wurde eine Inkubationszeit von 6,4 Tagen ermittelt und die geschätzte Reproduktionszahl liegt bei 2,24-3,58. Bei Patienten mit einer durch SARS-CoV-2 verursachten Lungenentzündung war Fieber das häufigste Symptom, gefolgt von Husten[3]. Der am häufigsten für COVID-19 verwendete IVD-Assay ist die Reverse Transkriptase-Polymerase-Kettenreaktion (RT-PCR) in Echtzeit, die nur wenige Stunden dauert[4]. Die Verfügbarkeit eines kostengünstigen, schnellen diagnostischen Point-of-Care-Diagnosetests ist von entscheidender Bedeutung für die Unterstützung des medizinischen Fachpersonals bei der Diagnose von Patienten und somit für die Verhinderung einer weiteren Verbreitung des Virus[5]. Antigentests werden im Kampf gegen COVID-19 eine entscheidende Rolle spielen[6].

Testprinzip

Panbio™ COVID-19 Ag Rapid Test Device beinhaltet einen Membranstreifen, der auf der Testlinie mit immobilisiertem Anti-SARS-CoV-2-Antikörpern und auf der Kontrolllinie mit monoklonalem Anti-Huhn-IgY der Maus vorbeschichtet ist. Zwei Arten von Konjugaten (humanes IgG, spezifisch für SARS-CoV-2 Ag Goldkonjugat (bindet an das Nucleocapsidprotein) und Hühner-IgY-Goldkonjugat) bewegen sich chromatographisch auf der Membran nach oben und reagieren mit dem Anti-SARS-CoV-2-Antikörper bzw. dem vorbeschichteten monoklonalen Anti-Hühner-IgY der Maus. Bei einem positiven Ergebnis bildet humanes IgG, das spezifisch für das Goldkonjugat SARS-CoV-2 Ag ist mit dem Anti-SARS-CoV-2-Antikörper eine Testlinie im Testergebnislesefenster. Weder die Testlinie noch die Kontrolllinie sind vor dem Auftragen der Patientenprobe im Testergebnislesefenster sichtbar. Eine sichtbare Kontrolllinie weist nach, dass das Testergebnis valide ist.

In-vitro diagnostischer Gebrauch

Der Panbio™ COVID-19 Ag Rapid Test Device ist ein *in-vitro* diagnostischer Schnelltest zum qualitativen Nachweis von SARS-CoV-2 Antigen (Ag) in menschlichen nasalen Abstrichproben von Personen, die die klinischen und / oder epidemiologischen Kriterien von COVID-19 erfüllen. Der Panbio™ COVID-19 Ag Rapid Test Device ist nur für den professionellen Gebrauch bestimmt und dient als Hilfsmittel zur Diagnose einer SARS-CoV-2 Infektion. Das Produkt kann in jeder Laborumgebung sowie Umgebungen außerhalb des Labors eingesetzt werden, die den Anforderungen aus der Gebrauchsanweisung und den vor Ort geltenden, regulatorischen Anforderungen entsprechen. Der Test liefert vorläufige Testergebnisse. Negative Testergebnisse schließen eine SARS CoV-2 Infektion nicht aus und dürfen nicht als alleinige Grundlage

für eine weitere Behandlung oder andere Managemententscheidungen herangezogen werden.
Negative Ergebnisse müssen mit klinischen Beobachtungen, Patientenanamnesen und epidemiologischen Informationen abgeglichen werden. Der Test ist nicht für das SARS-CoV-2 Screening von Blutspendern vorgesehen.

Bereitgestellte Materialien

- 25 Testkassetten verpackt in Folienbeutel mit Trockenmittel
- Puffer (1x 9 ml/Fläschchen)
- 25 Extraktionsröhrchen
- 25 Deckel für Extraktionsröhrchen
- 1 Positivkontrolltupfer
- 1 Negativkontrolltupfer
- 25 Sterilisierte nasale Tupfer zur Probennahme
- 1 Ständer für Röhrchen
- 1 Kurzanleitung
- 1 Gebrauchsanweisung

Zusätzlich benötigte Materialien

- Persönliche Schutzausrüstung gemäß den örtlichen Empfehlungen (d.h. Laborkittel, Gesichtsmaske, Gesichtsschutz / Schutzbrille und Handschuhe), Uhr, Biohazard-Abfallbehälter

Aktive Bestandteile der Hauptkomponenten

- **Testkassette** Goldkonjugat: Human-IgG spezifisch für SARS-CoV-2 Ag Goldkolloid und Hühner-IgY - Goldkolloid, Testlinie: Maus-monoklonales anti-SARS-CoV-2, Kontrolllinie: Maus-monoklonales Anti-Huhn IgY
- **Puffer** Tricin, Natriumchlorid, Tween 20, Natriumazid (<0,1%), Proclin 300

Lagerung und Stabilität

1. Das Test-Kit ist bei einer Temperatur von 2-30 °C zu lagern. Die Testkassette und die Komponenten des Test-Kits dürfen nicht eingefroren werden.
   Hinweis: Bei Lagerung im Kühlschrank müssen alle Komponenten mindestens 30 Minuten vor der Testdurchführung auf Raumtemperatur (15-30 °C) gebracht werden. Öffnen Sie die Verpackung nicht, während die Komponenten auf Raumtemperatur gebracht werden.
2. Die Pufferflasche kann für jeden Test geöffnet und wieder verschlossen werden. Die Kappe der Pufferflasche ist nach jedem Gebrauch fest zu verschließen. Der Puffer ist bis zum Verfallsdatum anwendbar und stabil bei einer Aufbewahrung bei 2-30 °C.
3. Führen Sie den Test umgehend nach Entnahme der Testkassette aus der Verpackung durch.

4. Verwenden Sie den Test nicht nach Ablauf des Verfallsdatums.
5. Das Verfallsdatum des Kits ist sichtbar gedruckt auf der äußeren Verpackung.
6. Verwenden Sie den Test nicht, wenn die Verpackung oder Verpackungssiegel beschädigt sind.
7. Direkte Abstrichproben sollten unmittelbar nach der Entnahme getestet werden. Wenn ein sofortiger Test nicht möglich ist, kann die Abstrichprobe in einem mit Extraktionspuffer (300 µl) gefüllten Extraktionsröhrchen bei Raumtemperatur (15-30 °C) bis zu zwei Stunden vor dem Test aufbewahrt werden.

Warnhinweise

1. Nur für den Einsatz in der *In-vitro* Diagnostik. Die Testkassette und die Komponenten des Kits dürfen nicht wiederverwendet werden.
2. Diese Gebrauchsanweisung ist von einer ausgebildeten, medizinischen Fachkraft strikt zu befolgen, um genaue Ergebnisse zu erzielen. Alle Anwender müssen die Anleitung vor der Test-Durchführung sorgfältig lesen.
3. Essen und Trinken Sie nicht beim Umgang mit Proben.
4. Tragen Sie bei der Handhabung der Proben Schutzhandschuhe und waschen Sie anschließend die Hände gründlich.
5. Vermeiden Sie Spritzer oder Aerosolbildung von Proben und Puffer.
6. Reinigen Sie verschüttete Flüssigkeiten gründlich mit geeigneten Desinfektionsmitteln.
7. Dekontaminieren und entsorgen Sie alle Proben, Reaktionskits und potenziell kontaminierten Materialien (d. h. Tupfer, Extraktionsröhrchen, Testkassette) in einem Behälter für biologische Gefahrenstoffe, als ob sie infektiöser Abfall wären, und entsorgen Sie sie gemäß den geltenden örtlichen Vorschriften.
8. Proben dürfen nicht gemischt werden. Stellen Sie sicher, dass Proben nicht vertauscht werden.
9. Reagenzien von verschiedenen Chargen dürfen nicht gemischt werden. Mischen Sie diese auch nicht mit anderen Produkten.
10. Test-Kits dürfen nicht unter direkter Sonneneinstrahlung gelagert werden.
11. Um Kontaminationen zu vermeiden, berühren Sie nicht beim Öffnen des Tupferbeutels die Spitze des Tupfers.
12. Die sterilen Tupfer sind nur für die Entnahme von nasalen Abstrichen zu verwenden.
13. Um eine Kreuzkontamination zu vermeiden, dürfen die sterilen Tupfer nicht zur wiederholten Probenentnahme verwendet werden.
14. Verdünnen Sie den Tupfer nicht mit einer anderen Lösung als dem mitgelieferten Extraktionspuffer.
15. Der Puffer enthält <0,1% Natriumazid als Konservierungsmittel, das bei Verschlucken giftig sein kann. Bei einer Entsorgung über das Waschbecken, ist das Mittel mit einer großen Wassermenge weg zu spülen.[7]
16. Verwenden Sie die positiven oder negativen Kontrolltupfer nicht für die Probenentnahme.

Testablauf (siehe Abbildung)

Nasaltupfer-Proben

Hinweis: Persönliche Sicherheitsrichtlinien einschließlich der Verwendung persönlicher Schutzausrüstung sind durch das Fachpersonal einzuhalten.

Testvorbereitung

1. Lassen Sie alle Komponenten des Test-Kits 30 Minuten vor Beginn des Testens eine Temperatur von 15-30°C erreichen.
2. Entfernen Sie die Testkassette aus der Verpackung. Platzieren Sie die Testkassette auf einer flachen und sauberen Oberfläche.
3. Halten Sie das Pufferfläschchen vertikal und füllen Sie das Extraktionsröhrchen mit Pufferflüssigkeit, bis die Fülllinie des Extraktionsröhrchens erreicht ist (300 µl).
   ⚠ **Achtung:** Bei einer zu hohen oder geringen Puffermenge sind falsche Testergebnisse möglich.
4. Stellen Sie das Extraktionsröhrchen in den Röhrchenständer.

Probensammlung und -Extraktion

1. Neigen Sie den Kopf des Patienten um 70 Grad nach hinten. Führen Sie den Tupfer unter sanftem Drehen ca. 2 cm tief in das Nasenloch ein (bis Widerstand an den Nasenmuscheln spürbar ist).
2. Drehen Sie den Tupfer fünfmal gegen die Nasenwand und entfernen Sie ihn dann langsam aus dem Nasenloch.
3. Wiederholen Sie mit demselben Tupfer die Probennahme im zweiten Nasenloch.
   ⚠ **Achtung:** Sollte der Stab des Tupfers während der Probennahme brechen, wiederholen Sie die Probennahme mit einem neuen Tupfer.
4. Schwenken Sie die Tupferspitze in der Pufferflüssigkeit im Inneren des Extraktionsröhrchens. Drücken Sie dabei mindestens fünfmal gegen die Wand des Extraktionsröhrchens und drücken Sie anschließend denn Tupfer aus, indem Sie mit den Fingern das Extraktionsröhrchen zusammendrücken.
5. Brechen Sie den Tupferstiel an der Bruchstelle ab und schließen Sie die Kappe des Extraktionsröhrchens.

Reaktion mit der Test-Kassette

1. Öffnen Sie die Kappe der Dosieröffnung am Boden des Extraktionsröhrchens.
2. Geben Sie 5 Tropfen der extrahierten Probe senkrecht in die Probenvertiefung (S) der Testkassette. Bewegen Sie die Testkassette nicht, bis der Test abgeschlossen und zum Ablesen bereit ist.
   ⚠ **Achtung:** Blasen, die im Extraktionsröhrchen auftreten, können zu ungenauen Ergebnissen führen. Wenn es nicht möglich ist, genügend Tropfen zu erzeugen, kann dies an einer Verstopfung der Dosieröffnung liegen. Schütteln Sie das Röhrchen leicht, um die Verstopfung zu lösen, bis Sie eine freie Tropfenbildung beobachten können.

3. Schließen Sie die Dosieröffnung und entsorgen Sie das Extraktionsröhrchen mit dem gebrauchten Tupfer gemäß den örtlichen Vorschriften und dem Entsorgungsprotokoll für biologisch gefährliche Abfälle.
4. Starten Sie die Uhr und lesen Sie das Ergebnis nach 15 Minuten ab. Lesen Sie das Ergebnis nicht mehr nach 20 Minuten ab.
5. Entsorgen Sie die gebrauchte Testkassette gemäß den örtlichen Vorschriften und dem Entsorgungsprotokoll für biologisch gefährlichen Abfall.

Positive/ Negative Kontrolltupfer

⚠ **Achtung:** nur für Kontrollzwecke. Verwenden Sie positive oder negative Kontrolltupfer nicht für die Probennahme.

Hinweis: Informationen zur Häufigkeit der Prüfung externer Qualitätskontrolltupfer finden Sie im Abschnitt Externe Qualitätskontrolle dieser Gebrauchsanweisung.

1. Halten Sie das Pufferfläschchen vertikal und füllen Sie das Extraktionsröhrchen mit Pufferflüssigkeit, bis die Fülllinie des Extraktionsröhrchens erreicht ist (300 µl).
   ⚠ **Achtung:** Bei einer zu hohen oder geringen Puffermenge sind falsche Testergebnisse möglich.
2. Stellen Sie das Extraktionsröhrchen in den Röhrchenständer.
3. Führen Sie den Positiv- oder Negativkontrolltupfer in die Pufferflüssigkeit des Extraktionsröhrchens ein und weichen Sie den Tupfer 1 Minute lang ein. Schwenken Sie die Spitze des Kontrolltupfers in der Pufferflüssigkeit im Inneren des Extraktionsröhrchens. Drücken Sie dabei den Tupfer mindestens fünfmal gegen die Wand des Extraktionsröhrchens und drücken Sie anschließend den Tupfer aus, indem Sie mit den Fingern das Extraktionsröhrchen zusammendrücken.
4. Entsorgen Sie den gebrauchten Kontrolltupfer gemäß dem Entsorgungsprotokoll für biologisch gefährliche Abfälle.
5. Schließen Sie den Deckel des Extraktionsröhrchens.
6. Befolgen Sie anschließend das obige Testverfahren [siehe Reaktion mit der Testkassette].

Testinterpretation (siehe Abbildung)

1. **Negatives Ergebnis:** Erscheinen eine Kontrolllinie (C) und keine Testlinie (T) innerhalb des Testergebnislesefensters, ist das Ergebnis negativ.
2. **Positives Ergebnis:** Erscheinen eine Kontrolllinie (C) und eine Testlinie (T) innerhalb des Testergebnislesefensters, unabhängig davon, welche Linie zuerst erscheint, ist das Ergebnis positiv.
   ⚠ **Achtung:** Jede Testlinie (T), unabhängig davon, wie schwach diese Linie ist, ist als positives Testergebnis zu bewerten.
3. **Ungültiges Ergebnis:** Ist die Kontrolllinie (C) nach der Testdurchführung innerhalb des Testergebnislesefensters nicht sichtbar, ist das Ergebnis ungültig.

Einschränkungen

1. Der Inhalt dieses Test-Kits ist für den professionellen und qualitativen Nachweis von SARS-CoV-2 Antigen aus nasalen Abstrichproben zu verwenden. Andere Probentypen können zu falschen Ergebnissen führen und dürfen nicht verwendet werden.
2. Die Nichtbeachtung der Anweisungen zum Testverfahren und zur Interpretation der Testergebnisse kann die Testleistung beeinträchtigen und/oder zu ungültigen Ergebnissen führen.
3. Ein negatives Testergebnis kann auftreten, wenn die Probe nicht ordnungsgemäß entnommen, extrahiert oder transportiert wurde. Ein negatives Testergebnis schließt die Möglichkeit einer SARS-CoV-2-Infektion nicht aus und sollte durch eine Viruskultur oder einen molekularen Assay bestätigt werden.
4. Ein positives Testergebnis schließt eine Co-Infektion mit anderen Erregern nicht aus.
5. Die Testergebnisse müssen in Verbindung mit anderen klinischen Daten bewertet werden, die dem Arzt zur Verfügung stehen.
6. Das Ablesen der Testergebnisse früher als 15 Minuten oder später als 20 Minuten kann zu falschen Ergebnissen führen.
7. Panbio™ COVID-19 Ag Rapid Test Device ist nicht zum Nachweis von defekten (nicht infektiösen) Viren in den späteren Stadien der Virusabgabe bestimmt, die durch PCR-Molekulartests nachgewiesen werden könnten. [8]
8. Eine Infektion mit SARS-CoV kann zu positiven Ergebnissen führen.

Qualitätskontrolle

1. Interne Qualitätskontrolle:

Die Testkassette besitzt eine Testlinie (T) und eine Kontrolllinie (C) auf der Oberfläche der Testvorrichtung. Die Testlinie und die Kontrolllinie sind vor dem Aufbringen einer Probe im Testergebnislesefensters nicht sichtbar. Die Kontrolllinie dient zur Verfahrenskontrolle und sollte immer dann erscheinen, wenn der Test ordnungsgemäß durchgeführt wird und die Testreagenzien der Kontrolllinie funktionieren.

2. Externe Qualitätskontrolle:

Die Kontrollen sind speziell formuliert und hergestellt, um die Leistung des Panbio™ COVID-19 Ag Rapid Tests zu gewährleisten, und dienen dazu, die Fähigkeit des Anwenders zu überprüfen, Tests korrekt durchzuführen und deren Ergebnisse richtig zu interpretieren. Die Positivkontrolle liefert ein positives Testergebnis und wurde hergestellt, um eine sichtbare Testlinie (T) zu erzeugen. Die Negativkontrolle liefert ein negatives Testergebnis.

Gute Laborpraxis empfiehlt die Verwendung von Positiv- und Negativkontrollen, um sicher zu stellen, dass:

- Testreagenzien funktionieren, und
- der Test korrekt durchgeführt wird.

Die externen Kontrollen können unter den folgenden Umständen durchgeführt werden:

- Von einem neuen Anwender vor der Durchführung von Tests an Patientenproben,
- Wenn Sie eine neue Sendung an Tests erhalten,
- In regelmäßigen Abständen gemäß den lokalen Vorschriften und / oder den Qualitätskontrollverfahren des Anwenders.

Leistungsmerkmale

1. Externe Bewertung des Panbio™ COVID-19 Ag Rapid Test Device

Die klinische Leistung von Panbio™ COVID-19 Ag Rapid Test Device wurde durch das Testen von 104 SARS-CoV-2 Antigen (Ag)-positiven und 404 -negativen Proben aus Nasenabstrichen mit einer Sensitivität von 98,1% (95% CI: 93,2-99,8%) und einer Spezifität von 99,8% (95% CI: 98,6-100,0%) bestimmt, Positivität und Negativität von Proben wurden mit einer FDA-EUA RT-PCR Referenzmethode ermittelt.

Ergebnis für Panbio™ COVID-19 Ag Rapid Test Device

		PCR Testergebnis (nasal)		
		Positiv	**Negativ**	**Gesamt**
Ergebnis für Panbio™ COVID-19 Ag Rapid Test Device (Nasaltupfer-Proben)	**Positiv**	102	1	103
	Negativ	2	403	405
	Gesamt	104	404	508
		Sensitivität	Spezifität	Kombinierte prozentale Übereinstimmung
		98,1% [93,2%;99,8%]	**99,8%** [98,6%;100,0%]	**99,4%** [98,3%;99,9%]

- Die Leistungsdaten wurden aus einer Studie mit Personen berechnet, bei denen der Verdacht auf Exposition mit COVID-19 bestand oder die in den letzten 7 Tagen Symptome zeigten.
- Die Stratifizierung der positiven Proben nach dem Auftreten von Symptomen oder einer vermuteten Exposition zwischen 0-3 Tagen ergibt eine Sensitivität von 100,0% (n=46) und zwischen 4-7 Tagen eine Sensitivität von 96,6% (n=58).
- Die positive Übereinstimmung des Panbio™ COVID-19 Ag Rapid Test Device ist mit einer Sensitivität von 99,0% höher für Proben mit Ct Werten ≤33. Referenzen 8 und 9 legen nahe, dass Patienten mit Ct Werten >33 nicht mehr ansteckend sind.[8,9]
- Die klinischen Leistungsdaten wurden auch mit Proben aus nasopharyngealen Abstrichen unter Verwendung einer FDA-EUA RT-PCR Referenzmethode verglichen und zeigen eine Sensitivität von 91,1% (95% CI: 84,2-95,6%) und eine Spezifizität von 99,7% (95% CI: 98,6-100,0%).

2. Nachweisgrenze

Es wurde bestätigt, dass Panbio™ COVID-19 Ag Rapid Test Device in der Lage

ist 2,5X10^{1,8} TCID$_{50}$/ml SARS-CoV-2 nachzuweisen, das aus einem COVID-19 bestätigten Patienten in Korea isoliert wurde.

3. Hook Effekt Hook Effect

Es gibt keinen Hook Effekt bei 1,0x10^{5,8} TCID$_{50}$/ml of SARS- CoV-2, das aus einem COVID-19 bestätigten Patienten in Korea isoliert wurde.

4. Kreuzreaktionen

Die Kreuzreaktivität des Panbio™ COVID-19 Ag Rapid Test Device wurde anhand von Tests mit 28 Viren und 13 anderen Mikroorganismen bewertet. Die finalen Testkonzentrationen von Viren und anderen Mikroorganismen sind in der folgenden Tabelle dokumentiert. Die folgenden Viren und andere Mikroorganismen mit Ausnahme des humanen SARS-Coronavirus-Nukleoproteins haben keinen Einfluss auf die Testergebnisse des Panbio™ COVID-19 Ag Rapid Test Device. Panbio™ COVID-19 Ag Rapid Test Device zeigt Kreuzreaktivität mit dem humanen SARS-Coronavirus-Nukleoprotein bei einer Konzentration von 25 ng/ml oder mehr, da SARS-CoV eine hohe Homologie (79,6%) zu SARS-CoV-2 aufweist.

Nr,	Art der Probe	Kreuzreaktion Substanz	Finale Testkonzentration	Testergebnis
1	Virus	Adenovirus Typ 1	2,2 X 10^{7} TCID$_{50}$/ml	Keine Kreuzreaktion
2		Adenovirus Typ 5	5,71 X 10^{8} TCID$_{50}$/ml	Keine Kreuzreaktion
3		Adenovirus Typ 7	2,86 X 10^{9} TCID$_{50}$/ml	Keine Kreuzreaktion
4		Enterovirus (EV68)	2,81 X 10^{7} TCID$_{50}$/ml	Keine Kreuzreaktion
5		Echovirus2	1,0 X 10^{6,5} TCID$_{50}$/ml	Keine Kreuzreaktion
6		Echovirus11	5,0 X10^{6,25} TCID$_{50}$/ml	Keine Kreuzreaktion
7		Enterovirus D68	2,81 X 10^{7} TCID$_{50}$/ml	Keine Kreuzreaktion
8		Human herpesvirus (HSV) 1	5,0 X 10^{7,5} TCID$_{50}$/ml	Keine Kreuzreaktion
9		Human herpesvirus (HSV) 2	5,0 X 10^{5,75} TCID$_{50}$/ml	Keine Kreuzreaktion
10		Mumps Virus Ag	1,58 X 10^{5} TCID$_{50}$/ml	Keine Kreuzreaktion
11		Influenza-Virus A (H1N1) Stamm (A/Virginia/ ATCC1/2009)	3,71 X 10^{5} PFU/ml	Keine Kreuzreaktion
12		Influenza-Virus A (H1N1) Stamm (A/WS/33)	5,0 X 10^{7,25} TCID$_{50}$/ml	Keine Kreuzreaktion

Nr,	Art der Probe	Kreuzreaktion Substanz	Finale Testkonzentration	Testergebnis
13		Influenzavirus A (H1N1) Stamm (A/ California/08/2009/ pdm09)	1,6 X 10^8 $TCID_{50}$/ml	Keine Kreuzreaktion
14	Virus	Influenza-Virus B Stamm (B/Lee/40)	5,0 X $10^{6,25}$ $TCID_{50}$/ ml	Keine Kreuzreaktion
15		Parainfluenza Typ 1	3,06 X 10^8 $TCID_{50}$/ ml	Keine Kreuzreaktion
16		Parainfluenza Typ 2	5,0 X 10^5 $TCID_{50}$/ml	Keine Kreuzreaktion
17		Parainfluenza Typ 3	6,6 X 10^7 $TCID_{50}$/ml	Keine Kreuzreaktion
18		Parainfluenza Typ 4A	2,81 X 10^7 $TCID_{50}$/ml	Keine Kreuzreaktion
19		Respiratory syncytial virus (RSV) Typ A	4,22 X 10^5 $TCID_{50}$/ml	Keine Kreuzreaktion
20		Respiratory syncytial virus (RSV) Typ B	5,62 X 10^5 $TCID_{50}$/ml	Keine Kreuzreaktion
21		Rhinovirus A16	1,26 X 10^6 $TCID_{50}$/ml	Keine Kreuzreaktion
22		HCoV-HKU1	1,5mg/ml	Keine Kreuzreaktion
23		HCoV-NL63	1,7 X 10^5 $TCID_{50}$/ml	Keine Kreuzreaktion
24		HCoV-OC43	8,9 X 10^5 $TCID_{50}$/ml	Keine Kreuzreaktion
25		HCoV-229E	1,51 X 10^6 $TCID_{50}$/ml	Keine Kreuzreaktion
26		Human SARS-coronavirus Nucleoprotein	25ng/ml	Kreuzreaktion
27		MERS-CoV Nucleoprotein	0,25mg/ml	Keine Kreuzreaktion
28		Human Metapneumovirus (hMPV) 16 Typ A1	1,51 X 10^6 $TCID_{50}$/ml	Keine Kreuzreaktion

Nr.	Art der Probe	Kreuzreaktion Substanz	Finale Testkonzentration	Testergebnis
1	Andere Mikroorganismen	*Staphylococcus saprophyticus*	1,9 X 10^7 CFU/ml	Keine Kreuzreaktion
2		*Neisseria sp,(Neisseria lactamica)*	1,7 X 10^8 CFU/ml	Keine Kreuzreaktion
3		*Staphylococcus haemolyticus*	3,5 X 10^9 CFU/ml	Keine Kreuzreaktion
4		*Streptococcus salivarius*	1,96 X 10^7 CFU/ml	Keine Kreuzreaktion
5		*Hemophilus parahaemolyticus*	2,2 X 10^8 CFU/ml	Keine Kreuzreaktion
6		*Proteus vulgaris*	7,2 X 10^6 CFU/ml	Keine Kreuzreaktion
7		*Moraxella catarrhalis*	4,7 X 10^7 CFU/ml	Keine Kreuzreaktion
8		*Klebsiella pneumoniae*	5,0 X 10^6 CFU/ml	Keine Kreuzreaktion
9		*Fusobacterium necrophorum*	1,75 X 10^8 CFU/ml	Keine Kreuzreaktion
10		*Mycobacterum tuberculosis*	10mg/ml	Keine Kreuzreaktion
11		Humane Nasalspülung (gepoolt)	N/A*	Keine Kreuzreaktion
12		*Streptococcus pyogenes*	3,6 X 10^7 CFU/ml	Keine Kreuzreaktion
13		*Mycoplasma pneumoniae*	4 X 10^8 CFU/ml	Keine Kreuzreaktion

** Keine Konzentrationsangabe durch den Lieferanten. Unverdünnte Stammlösung wurde getestet.*

5. Interferierende Substanzen

Die folgenden 43 potenziell interferierenden Substanzen haben keinen Einfluss auf Panbio™ COVID-19 Ag Rapid Test Device. Die endgültigen Testkonzentrationen der Störsubstanzen sind in der folgenden Tabelle dokumentiert.

Nr,	Art der Probe	Interferierende Substanzen	Finale Testkonzentration	Testergebnis
1	Endogene Substanz	Mucin	0,5%	Keine Interferenz
2		Hämoglobin	100 mg/L	Keine Interferenz
3		Triglyceride	1,5 mg/L	Keine Interferenz
4		Icteric (Bilirubin)	40 mg/dL	Keine Interferenz
5		Rheuma-Faktor	200 IU/ml	Keine Interferenz
6		Anti-nuklearer Antikörper	>1:40	Keine Interferenz
7		Schwanger	10-fach verdünnt	Keine Interferenz
8	Exogene Substanz	Guajakol-Glyceryl-Ether	1 µg/ml	Keine Interferenz
9		Albuterol	0,005 mg/dL	Keine Interferenz
10		Ephedrin	0,1 mg/ml	Keine Interferenz
11		Chlorpheniramin	0,08 mg/dL	Keine Interferenz
12		Diphenhydramin	0,08 mg/dL	Keine Interferenz
13		Ribavirin	26,7 µg /ml	Keine Interferenz
14		Oseltamivir	0,04 mg/dL	Keine Interferenz
15		Zanamivir	17,3 µg /ml	Keine Interferenz
16		Phenylephrin-Hydrochlorid	15% v/v	Keine Interferenz
17		Oxymetazolin-Hydrochlorid	15% v/v	Keine Interferenz
18		Amoxicillin	5,4 mg/dL	Keine Interferenz
19		Acetylsalicylsäure	3 mg/dL	Keine Interferenz
20		Ibuprofen	21,9 mg/dL	Keine Interferenz
21		Chlorothiazid	2,7 mg/dL	Keine Interferenz
22		Indapamid	140 ng/ml	Keine Interferenz
23		Glimepirid (Sulfonylharnstoffe)	0,164 mg/dL	Keine Interferenz
24		Acarbose	0,03 mg/dL	Keine Interferenz
25		Ivermectin	4,4 mg/L	Keine Interferenz
26		Lopinavir	16,4 µg/L	Keine Interferenz
27		Ritonavir	16,4 µg/L	Keine Interferenz
28		Chloroquinphosphat	0,99 mg/L	Keine Interferenz

Nr,	Art der Probe	Interferierende Substanzen	Finale Testkonzentration	Testergebnis
29	Exogene Substanz	Natriumchlorid mit Konservierungsstoffen	4,44 mg/ml	Keine Interferenz
30		Beclomethason	4,79 ng/ml	Keine Interferenz
31		Dexamethason	0,6 µg/ml	Keine Interferenz
32		Flunisolid	0,61 µg/ml	Keine Interferenz
33		Triamcinolon	1,18 ng/ml	Keine Interferenz
34		Budesonid	2,76 ng/ml	Keine Interferenz
35		Mometason	1,28 ng/ml	Keine Interferenz
36		Fluticason	2,31 ng/ml	Keine Interferenz
37		Sulfur	9,23 µg/ml	Keine Interferenz
38		Benzocain	0,13 mg/ml	Keine Interferenz
39		Menthol	0,15 mg/ml	Keine Interferenz
40		Mupirocin	10 µg/ml	Keine Interferenz
41		Tobramycin	24,03 µg/ml	Keine Interferenz
42		Biotin	1,2 µg/ml	Keine Interferenz
43		HAMA	63,0 ng/ml	Keine Interferenz

6. Wiederholbarkeit & Reproduzierbarkeit

Die Wiederholbarkeit und Reproduzierbarkeit von Panbio™ COVID-19 Ag Rapid Test Device wurde unter Verwendung eines internen Referenzpanels mit negativen Proben und einer Reihe positiver Proben festgestellt. Es wurden keine Unterschiede innerhalb der Testreihe, zwischen den Testreihen, zwischen den Chargen, zwischen den Standorten und zwischen den Tagen festgestellt.

VORBEREITUNG

1 Lassen Sie alle Komponenten des Test-Kits 30 Minuten vor Beginn des Testens eine Temperatur von 15-30°C erreichen.
Hinweis: Das medizinische Personal sollte die persönlichen Sicherheitsrichtlinien einschließlich der Verwendung persönlicher Schutzausrüstung einhalten.

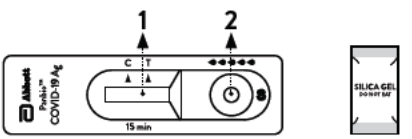
2 **Öffnen Sie die Verpackung und Entnehmen Sie Folgendes:**
1. Testkassetten verpackt in Folienbeutel mit Trockenmittel
2. Puffer
3. Extraktionsröhrchen
4. Deckel für Extraktionsröhrchen
5. Positivkontrolltupfer
6. Negativkontrolltupfer
7. Sterilisierte nasale Tupfer zur Probennahme
8. Ständer für Röhrchen
9. Kurzanleitung
10. Gebrauchsanweisung

3 Lesen Sie diese Anleitung vor Verwendung des Panbio™ COVID-19 Ag Rapid Test Device sorgfältig durch.

4 Beachten Sie das Verfallsdatum der Kit-Box. Wenn das Verfallsdatum abgelaufen ist, verwenden Sie einen anderen Kit.

5 **Öffnen Sie den Folienbeutel und schauen Sie nach Folgendem:**
1. Testergebnislesefenster
2. Probenvertiefung

Beschriften Sie die Testkassette mit der Patient-ID.



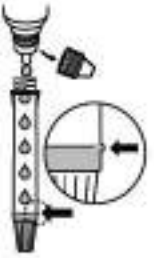
●●●●●: 5 Tropfen der extrahierten Probe

DEUTSCH

TESTVERFAHREN

1 Halten Sie das Pufferfläschchen vertikal und füllen Sie das Extraktionsröhrchen mit Pufferflüssigkeit, bis die Füllinie des Extraktionsröhrchens erreicht ist (300 µl).

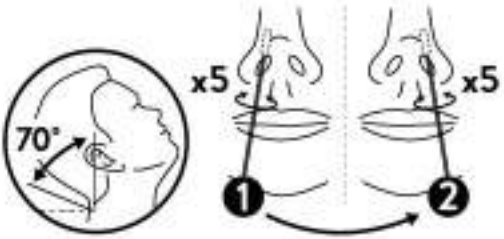
⚠ **Achtung:** Bei einer zu hohen oder geringen Puffermenge sind falsche Testergebnisse möglich.



2 Stellen Sie das Extraktionsröhrchen in den Röhrchenständer.

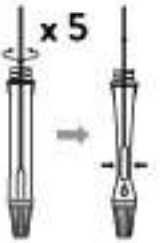
3 Neigen Sie den Kopf des Patienten um 70 Grad nach hinten. Führen Sie den Tupfer unter sanftem Drehen ca. 2 cm tief in das Nasenloch ein (bis Widerstand an den Nasenmuscheln spürbar ist). Drehen Sie den Tupfer fünfmal gegen die Nasenwand und entfernen Sie ihn dann langsam aus dem Nasenloch. Wiederholen Sie mit demselben Tupfer die Probennahme im zweiten Nasenloch.

⚠ **Achtung:** Sollte der Stab des Tupfers während der Probennahme brechen, wiederholen Sie die Probennahme mit einem neuen Tupfer.



TESTVERFAHREN

4 Führen Sie die Abstrichprobe in das Extraktionsröhrchen ein. Schwenken Sie die Tupferspitze in der Pufferflüssigkeit des Extraktionsröhrchens. Drücken Sie dabei den Tupfer mindestens fünfmal an die Wand des Extraktionsröhrchens und drücken Sie anschließend denn Tupfer aus, indem Sie mit den Fingern das Extraktionsröhrchen zusammendrücken.

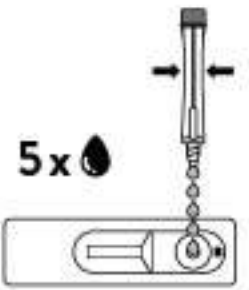


5 Brechen Sie den Tupfer an der Bruchstelle ab und schließen Sie den Deckel des Extraktionssröhrchens.

6 Öffnen Sie die Kappe der Dosieröffnung am Boden des Extraktionsröhrchens.

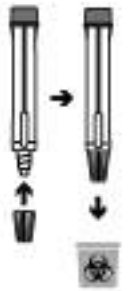
7 Geben Sie 5 Tropfen der extrahierten Proben senkrecht in die Probenvertiefung (S) der Testkassette. Bewegen Sie die Testkassette nicht, bis der Test abgeschlossen und zum Ablesen bereit ist.

⚠ **Achtung:** Blasen, die im Extraktionsröhrchen auftreten, können zu ungenauen Ergebnissen führen. Wenn Sie nicht in der Lage sind, genügend Tropfen zu erzeugen, kann dies an einer Verstopfung der Dosieröffnung liegen. Schütteln Sie das Röhrchen leicht, um die Verstopfung zu lösen, bis Sie eine freie Tropfenbildung beobachten können.



TESTVERFAHREN

8 Schließen Sie die Dosieröffnung und entsorgen Sie das Extraktionsröhrchen mit dem gebrauchten Tupfer gemäß den örtlichen Vorschriften und dem Entsorgungsprotokoll für biologisch gefährliche Abfälle.



9 Starten Sie die Uhr und lesen Sie das Ergebnis nach 15 Minuten ab. Lesen Sie das Ergebnis nicht mehr nach 20 Minuten ab.

10 Entsorgen Sie die gebrauchte Testkassette gemäß den örtlichen Vorschriften und dem Entsorgungsprotokoll für biologisch gefährlichen Abfall.

TEST INTERPRETATION

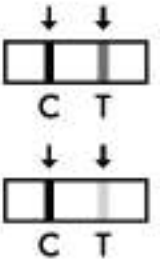
NEGATIV

Erscheinen eine Kontrolllinie (C) und keine Testlinie (T) innerhalb des Testergebnislesefensters, ist das Ergebnis negativ.

POSITIV

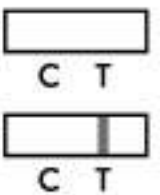
Erscheinen eine Kontrolllinie (C) und eine Testlinie (T) innerhalb des Testergebnislesefensters, unabhängig davon, welche Linie zuerst erscheint, ist das Ergebnis positiv.

⚠ **Achtung:** Jede Testlinie (T), unabhängig davon, wie schwach diese Linie ist, ist als positives Testergebnis zu bewerten.



UNGÜLTIG

Ist die Kontrolllinie (C) nach der Testdurchführung innerhalb des Testergebnislesefensters nicht sichtbar, ist das Ergebnis ungültig.
Die Anweisungen wurden möglicherweise nicht korrekt befolgt. Es wird empfohlen, die IFU erneut zu lesen, bevor die Probe mit einer neuen Testkassette erneut getestet wird.



Acerca de la prueba

ES

Introducción

La enfermedad por coronavirus (COVID-19) es una enfermedad infecciosa causada por un coronavirus recién descubierto, el síndrome respiratorio agudo severo coronavirus 2 (SARS-CoV-2) [1]. El SARS-CoV-2 es un β-coronavirus, que es un virus de ARN de sentido positivo no segmentado con envoltura[2]. Se transmite de persona a persona a través de gotitas o contacto directo, y se ha estimado que la infección tiene un período de incubación medio de 6,4 días y un número de reproducción básico de 2,24 a 3,58. Entre los pacientes con neumonía causada por SARS-CoV-2, la fiebre fue el síntoma más común, seguido de la tos[3]. Las principales pruebas de DIV utilizadas para COVID-19 emplean la reacción en cadena de la polimerasa con transcriptasa inversa en tiempo real (RT-PCR) que tarda unas pocas horas[4]. La disponibilidad de una prueba de diagnóstico rápida y costo efectiva en el lugar de atención es fundamental para que los profesionales de la salud puedan ayudar en el diagnóstico de los pacientes y prevenir una mayor propagación del virus[5]. Las pruebas de antígeno jugarán un papel fundamental en la lucha contra COVID-19[6].

Principio de la prueba

Panbio™ COVID-19 Ag Rapid Test Device contiene una tira de membrana, que está pre-revestida con anticuerpo anti-SARS-CoV-2 inmovilizado en la línea de prueba e IgY anti-pollo monoclonal de ratón en la línea de control. Dos tipos de conjugados (IgG humana específica para el conjugado de oro de SARS-CoV-2 Ag (se une a la proteína de la nucleocápside) y el conjugado de oro de IgY de pollo) se desplazan hacia arriba en la membrana cromatográficamente y reaccionan con el anticuerpo anti-SARS-CoV-2 y el anticuerpo monoclonal de ratón anti-IgY de pollo pre-revestido respectivamente. Para obtener un resultado positivo, la IgG humana específica para el conjugado de oro SARS-CoV-2 Ag y el anticuerpo anti-SARS-CoV-2 formarán una línea de prueba en la ventana de resultados. Ni la línea de prueba, ni la línea de control son visibles en la ventana de resultados antes de aplicar la muestra del paciente. Se requiere una línea de control visible para indicar que el resultado de una prueba es válido.

Uso Indicado

Panbio™ COVID-19 Ag Rapid Test Device es una prueba rápida de diagnóstico *in vitro* para la detección cualitativa del antígeno (Ag) del SARS-CoV-2 en muestras de hisopado nasal humanos de individuos que cumplen con los criterios clínicos y / o epidemiológicos de COVID-19. Panbio™ COVID-19 Ag Rapid Test Device es solo para uso profesional y está destinado a ser utilizado como ayuda en el diagnóstico de la infección por SARS-CoV-2. El producto se puede utilizar en cualquier entorno de laboratorio y no laboratorio que cumpla con los requisitos especificados en las Instrucciones de uso y la normativa local.

La prueba proporciona resultados preliminares de la prueba. Los resultados negativos no excluyen la infección por SARS-CoV-2 y no pueden usarse como la única base para el tratamiento u otras decisiones de manejo. Los resultados negativos deben combinarse con observaciones clínicas, historial del paciente e información epidemiológica. La prueba no está destinada a utilizarse como prueba de detección de donantes para el SARS-CoV-2.

Materiales Suministrados

- 25 dispositivos de prueba con desecante en bolsa de aluminio individual
- Solución tampón (1 x 9 mL / frasco)
- 25 tubos de extracción
- 25 tapas de tubos de extracción
- 1 hisopo control positivo
- 1 hisopo control negativo
- 25 hisopos nasales esterilizados para la recolección de muestras
- 1 gradilla para tubos
- 1 guía de referencia rápida
- 1 Instrucciones de uso

Materiales Requeridos pero NO suministrados

- Elementos de protección personal según las recomendaciones locales (es decir, bata/bata de laboratorio, mascarilla, careta/gafas y guantes), temporizador, contenedor de riesgo biológico

Ingredientes Activos de los componentes principales

- **1 Dispositivo de prueba** Conjugado de oro: IgG humana específica para el coloide de oro SARS-CoV-2 Ag y coloide de oro IgY de pollo, línea de prueba: anti-SARS-CoV-2 monoclonal de ratón, línea control: IgY anti-pollo monoclonal de ratón
- **Tampón** Tricina, Cloruro de sodio, Tween 20, Azida de sodio (<0,1%), Proclin 300

Almacenamiento y estabilidad

1. El kit de prueba debe almacenarse a una temperatura entre 2 y 30 ° C. No congele el kit ni sus componentes.
   Nota: Cuando se almacena en un refrigerador, todos los componentes del kit deben llevarse a temperatura ambiente (15-30 °C) durante un mínimo de 30 minutos antes de realizar la prueba. No abra la bolsa mientras los componentes alcancen la temperatura ambiente.
2. El frasco de tampón se puede abrir y volver a sellar para cada prueba. La tapa del tampón debe sellarse firmemente entre cada uso. El tampón es estable

hasta la fecha de caducidad si se mantiene a 2-30 °C.

3. Realice la prueba inmediatamente después de extraer el dispositivo de prueba de la bolsa de aluminio.
4. No use el kit de prueba después de su fecha de vencimiento.
5. La vida útil del kit es la indicada en el empaque exterior.
6. No utilice el kit de prueba si la bolsa está dañada o el sello está roto.
7. Las muestras de hisopo directo deben analizarse inmediatamente después de la recolección. Si la prueba inmediata no es posible, la muestra de hisopo se puede mantener en un tubo de extracción lleno de tampón de extracción (300 µL) a temperatura ambiente (15-30 °C) hasta dos horas antes de la prueba.

Advertencias

1. Solo para uso diagnóstico *in vitro*. No reutilice el dispositivo de prueba ni los componentes del kit.
2. Estas instrucciones deben seguirse estrictamente por profesionales de la salud entrenados para lograr resultados precisos. Todos los usuarios deben leer las instrucciones antes de realizar una prueba.
3. No coma ni fume mientras manipula las muestras.
4. Utilice guantes protectores al manipular las muestras y lávese bien las manos después.
5. Evite las salpicaduras o la formación de aerosoles en la muestra y el tampón.
6. Limpie los derrames a fondo con un desinfectante adecuado.
7. Descontamine y deseche todas las muestras, kits de reacción y materiales potencialmente contaminados (es decir, hisopo, tubo de extracción, dispositivo de prueba) en un contenedor de riesgo biológico como si fueran desechos infecciosos y elimínelos de acuerdo con las regulaciones locales aplicables.
8. No mezcle ni intercambie muestras diferentes.
9. No mezcle reactivos de diferentes lotes o de otros productos.
10. No almacene el kit de prueba a la luz solar directa.
11. Para evitar la contaminación, no toque la cabeza del hisopo suministrado al abrir la bolsa del hisopo.
12. Los hisopos esterilizados deben usarse solo para la recolección de muestras nasales.
13. Para evitar la contaminación cruzada, no reutilice los hisopos esterilizados para la recolección de muestras.
14. No diluya el hisopo recogido con ninguna solución excepto el tampón de extracción proporcionado.
15. El tampón contiene azida sódica <0,1% como conservante que puede ser tóxico si se ingiere. Cuando se deseche a través de un fregadero, enjuague con una gran cantidad de agua.[7]

16. No utilice el hisopo de control positivo o negativo para la recolección de muestras.

Procedimiento de prueba (consulte la figura)

Muestras de hisopado nasal

Note: El profesional de la salud debe cumplir con las pautas de seguridad personal, incluido el uso de equipo de protección personal.

Preparación de la prueba

1. Permita que todos los componentes del kit alcancen una temperatura entre 15 y 30 °C durante 30 minutos antes de realizar la prueba.
2. Extraiga el dispositivo de prueba de la bolsa de aluminio antes de usarlo. Colocar sobre una superficie plana, horizontal y limpia.
3. Sostenga el frasco de tampón verticalmente y llene el tubo de extracción con solución tampón hasta que fluya hasta la línea de llenado del tubo de extracción (300 µL).
   ⚠ **Precaución:** Si la cantidad de tampón es excesiva o insuficiente, puede producirse un resultado de prueba incorrecto.
4. Coloque el tubo de extracción en la gradilla de tubos.

Recolección y extracción de la muestra

1. Incline la cabeza del paciente hacia atrás 70 grados. Mientras gira suavemente el hisopo, inserte el hisopo menos de una pulgada (aproximadamente 2 cm) en la fosa nasal (hasta que encuentre resistencia en los cornetes).
2. Gire el hisopo cinco veces contra la pared nasal y luego retírelo lentamente de la fosa nasal.
3. Con el mismo hisopo, repita el procedimiento de recolección con la segunda fosa nasal.
   ⚠ **Precaución:** Si el hisopo se quiebra durante la recolección de la muestra, repita la recolección de la muestra con un hisopo nuevo.
4. Gire la punta del hisopo en la solución tampón dentro del tubo de extracción, empujando hacia la pared del tubo de extracción al menos cinco veces y luego exprima el hisopo apretando el tubo de extracción con los dedos.
5. Quiebre el hisopo en el punto de ruptura y cierre la tapa del tubo de extracción.

Reacción con dispositivo de prueba

1. Abra la tapa de la boquilla de goteo en la parte inferior del tubo de extracción.
2. Dispense 5 gotas de la muestra extraída de manera vertical en el pocillo de muestra (S) del dispositivo. No manipule ni mueva el dispositivo de prueba hasta que la prueba esté completa y lista para leer.
   ⚠ **Precaución:** Las burbujas que se forman en el tubo de extracción pueden dar lugar a resultados inexactos. Si no puede crear suficientes gotas, esto puede

deberse a una obstrucción en la boquilla dispensadora. Agite el tubo suavemente para liberar el bloqueo hasta que observe la formación de gotas libres.
3. Cierre la boquilla y deseche el tubo de extracción que contiene el hisopo usado de acuerdo con las regulaciones locales y el protocolo de eliminación de desechos de riesgo biológico.
4. De inicio al temporizador. Lea el resultado a los 15 minutos. No lea los resultados después de 20 minutos.
5. Deseche el dispositivo usado de acuerdo con las regulaciones locales y el protocolo de eliminación de desechos de riesgo biológico.

Hisopo de control positivo / negativo

⚠ **Precaución:** Solo para uso como control. No utilice el hisopo de control positivo o negativo para la recolección de muestras.

Nota: Consulte la sección Control de calidad externo de estas Instrucciones de uso para conocer la frecuencia de las pruebas con hisopos de control de calidad externos.

1. Sostenga el frasco de tampón verticalmente y llene el tubo de extracción con solución tampón hasta que fluya hasta la línea de llenado del tubo de extracción (300 µL).

   ⚠ **Precaución:** Si la cantidad de tampón es excesiva o insuficiente, puede producirse un resultado de prueba incorrecto.
2. Coloque el tubo de extracción en la gradilla de tubos.
3. Inserte el hisopo de control positivo o negativo en el líquido tampón dentro del tubo de extracción y humedezca el hisopo durante 1 minuto. Gire la punta del hisopo de control en la solución tampón dentro del tubo de extracción, empuje hacia la pared del tubo de extracción al menos cinco veces y luego exprima el hisopo apretando el tubo de extracción con los dedos.
4. Deseche el hisopo de control usado de acuerdo con su protocolo de eliminación de desechos de riesgo biológico.
5. Cierre la tapa del tubo de extracción.
6. Siga el procedimiento de prueba anterior [Reacción con dispositivo de prueba].

Interpretación de la prueba (consulte la figura)

1. **Resultado negativo:** La presencia de solo la línea de control (C) y ninguna línea de prueba (T) dentro de la ventana de resultados indica un resultado negativo.
2. **Resultado positivo:** La presencia de la línea de prueba (T) y la línea de control (C) dentro de la ventana de resultados, independientemente de la línea que aparezca primero, indica un resultado positivo.

   ⚠ **Precaución:** La presencia de cualquier línea de prueba (T), no importa cuán débil sea, indica un resultado positivo.

3. **Resultado no válido:** si la línea de control (C) no es visible dentro de la ventana de resultados después de realizar la prueba, el resultado se considera no válido.

Limitaciones de la prueba

1. El contenido de este kit está indicado para uso profesional y para la detección cualitativa del antígeno del SARS-CoV-2 a partir de un hisopado nasal. Otros tipos de muestras pueden dar lugar a resultados incorrectos y no deben utilizarse.
2. No seguir las instrucciones para el procedimiento de prueba y la interpretación de los resultados de la prueba puede afectar adversamente el desempeño de la prueba y/o producir resultados no válidos.
3. Puede producirse un resultado negativo de la prueba si la muestra se recolectó, extrajo o transportó incorrectamente. Un resultado negativo de la prueba no elimina la posibilidad de infección por SARS-CoV-2 y debería ser confirmado mediante cultivo viral o un ensayo molecular.
4. Los resultados positivos de las pruebas no descartan coinfecciones con otros patógenos.
5. Los resultados de la prueba deben evaluarse junto con otros datos clínicos disponibles para el médico.
6. La lectura de resultados de la prueba antes de 15 minutos o después de 20 minutos puede dar resultados incorrectos.
7. Panbio™ COVID-19 Ag Rapid Test Device no está destinado para detectar virus defectuosos (no infecciosos) en etapas tardías de la diseminación viral que podrían detectarse mediante pruebas moleculares de PCR.[8]
8. Pueden producirse resultados positivos en casos de infección por SARS-CoV.

Control de calidad

1. **Control de calidad interno:**
   El dispositivo de prueba tiene una línea de prueba (T) y una línea de control (C) en la superficie del dispositivo de prueba. Ni la línea de prueba, ni la línea de control son visibles en la ventana de resultados antes de aplicar una muestra. La línea de control se utiliza para el control del procedimiento y siempre debe aparecer si el procedimiento de prueba se realiza correctamente y los reactivos de prueba de la línea de control están funcionando.
2. **Control de calidad externo:**
   Los controles están específicamente formulados y fabricados para garantizar el rendimiento de Panbio™ COVID-19 Ag Rapid Test Device y se utilizan para verificar la capacidad del usuario para realizar correctamente la prueba e interpretar los resultados. El control positivo producirá un resultado de prueba positivo y ha sido fabricado para producir una línea de prueba visible

(T). El control negativo producirá un resultado de prueba negativo.
Las buenas prácticas de laboratorio sugieren el uso de controles positivos y negativos para asegurarse de que:

- Los reactivos de prueba están funcionando y
- La prueba se realiza correctamente.

Los controles externos se pueden ejecutar en cualquiera de las siguientes circunstancias:

- Por un nuevo operador antes de realizar pruebas en muestras de pacientes,
- Al recibir un nuevo envío de prueba,
- A intervalos periódicos según lo dicten los requisitos locales, y/o los procedimientos de control de calidad del usuario.

Características de desempeño

1. **Evaluación externa de Panbio™ COVID-19 Ag Rapid Test Device**
   El desempeño clínico de Panbio™ COVID-19 Ag Rapid Test Device se determinó analizando 104 muestras positivas obtenidas por hisopado nasal y 404 negativas para el antígeno (Ag) del SARS-CoV-2 para tener una sensibilidad de 98,1% (95% IC: 93,2-99,8%) y una especificidad de 99,8% (95% IC: 98,6-100,0%). Se determinó que las muestras clínicas eran positivas o negativas utilizando un método de referencia FDA EUA RT-PCR.

Resultados de Panbio™ COVID-19 Ag Rapid Test Device

		Resultado de prueba PCR nasal		
		Positiva	**Negativa**	**Total**
Resultados de Panbio™ COVID-19 Ag Rapid Test Device (muestra de hisopado nasal)	**Positiva**	102	1	103
	Negativa	2	403	405
	Total	104	404	508
		Sensibilidad	Especificidad	Porcentaje de concordancia total
		98,1% [93,2%;99,8%]	**99,8%** [98,6%;100,0%]	**99,4%** [98,3%;99,9%]

- Los datos de desempeño se calcularon a partir de un estudio de individuos sospechosos de exposición a COVID-19 o que presentaron síntomas en los últimos 7 días.
- La estratificación de las muestras positivas después de la aparición de los síntomas o la presunta exposición entre 0-3 días tiene una sensibilidad de 100,0% (n=46) y 4-7 días tiene una sensibilidad de 96,6% (n=58).

- La concordancia positiva de Panbio™ COVID-19 Ag Rapid Test Device es mayor con valores de Ct ≤33 con una sensibilidad del 99,0%. Como se sugiere en las referencias 8 y 9, los pacientes con un valor de Ct >33 ya no son contagiosos.[8, 9]
- Los datos de rendimiento clínico también se calcularon frente a las muestras de hisopado nasofaríngeo utilizando una referencia de RT-PCR EUA de la FDA teniendo una sensibilidad del 91,1% (IC del 95%: 84,2-95,6%) y una especificidad del 99,7% (IC del 95%: 98,6-100,0 %).

2. Límite de detección

Panbio™ COVID-19 Ag Rapid Test Device confirmó detectar 2,5X10^{1,8} $TCID_{50}$/mL de SARS-CoV-2 el cual fue aislado de un paciente confirmado por COVID-19 en Corea.

3. Efecto gancho

No hay efecto de gancho a 1,0x10^{5,8} $TCID_{50}$/mL de SARS-CoV-2 que se aisló de un paciente confirmado por COVID-19 en Corea.

4. Reactividad cruzada

La reactividad cruzada de Panbio™ COVID-19 Ag Rapid Test Device se evaluó analizando 28 virus y otros 13 microorganismos. Las concentraciones finales de prueba de virus y otros microorganismos se documentan en la siguiente tabla. Los siguientes virus y otros microorganismos, excepto la nucleoproteína del coronavirus del SARS humano, no tienen ningún efecto sobre los resultados de la prueba con Panbio™ COVID-19 Ag Rapid Test Device. Panbio™ COVID-19 Ag Rapid Test Device tiene reactividad cruzada con la nucleoproteína de coronavirus SARS humano a una concentración de 25 ng/mL o más porque el SARS-CoV tiene una alta homología (79,6%) con el SARS-CoV-2.

No,	Tipo de muestra	Sustancia de reacción cruzada	Concentración final de la prueba	Resultado de la prueba
1	Virus	Adenovirus Tipo 1	2,2 X 10^{7} $TCID_{50}$/mL	Sin reacción cruzada
2		Adenovirus Tipo 5	5,71 X 10^{8} $TCID_{50}$/mL	Sin reacción cruzada
3		Adenovirus Tipo 7	2,86 X 10^{9} $TCID_{50}$/mL	Sin reacción cruzada
4		Enterovirus (EV68)	2,81 X 10^{7} $TCID_{50}$/mL	Sin reacción cruzada
5		Echovirus2	1,0 X $10^{6,5}$ $TCID_{50}$/mL	Sin reacción cruzada
6		Echovirus11	5,0 X$10^{6,25}$ $TCID_{50}$/mL	Sin reacción cruzada

No,	Tipo de muestra	Sustancia de reacción cruzada	Concentración final de la prueba	Resultado de la prueba
7	Virus	Enterovirus (D68)	$2{,}81 \times 10^{7}$ $TCID_{50}$/mL	Sin reacción cruzada
8		Virus del herpes humano (HSV) 1	$5{,}0 \times 10^{7{,}5}$ $TCID_{50}$/mL	Sin reacción cruzada
9		Virus del herpes humano (HSV) 2	$5{,}0 \times 10^{5{,}75}$ $TCID_{50}$/mL	Sin reacción cruzada
10		Ag Virus Paperas	$1{,}58 \times 10^{5}$ $TCID_{50}$/mL	Sin reacción cruzada
11		Virus de la Influenza A (H1N1) cepa (A/Virginia/ ATCC1/2009)	$3{,}71 \times 10^{5}$ PFU/ mL	Sin reacción cruzada
12		Virus de la Influenza A (H1N1) cepa (A/WS/33)	$5{,}0 \times 10^{7{,}25}$ $TCID_{50}$/mL	Sin reacción cruzada
13		Virus de la Influenza A (H1N1) cepa (A/ California/08/2009/ pdm09	$1{,}6 \times 10^{8}$ $TCID_{50}$/mL	Sin reacción cruzada
14		Virus de la Influenza B cepa (B/Lee/40)	$5{,}0 \times 10^{6{,}25}$ $TCID_{50}$/mL	Sin reacción cruzada
15		Parainfluenza Tipo 1	$3{,}06 \times 10^{8}$ $TCID_{50}$/mL	Sin reacción cruzada
16		Parainfluenza Tipo 2	$5{,}0 \times 10^{5}$ $TCID_{50}$/mL	Sin reacción cruzada
17		Parainfluenza Tipo 3	$6{,}6 \times 10^{7}$ $TCID_{50}$/mL	Sin reacción cruzada
18		Parainfluenza Tipo 4A	$2{,}81 \times 10^{7}$ $TCID_{50}$/mL	Sin reacción cruzada
19		Virus sincitial respiratorio (RSV) tipo A	$4{,}22 \times 10^{5}$ $TCID_{50}$/mL	Sin reacción cruzada
20		Virus sincitial respiratorio (RSV) tipo B	$5{,}62 \times 10^{5}$ $TCID_{50}$/mL	Sin reacción cruzada
21		Rinovirus A16	$1{,}26 \times 10^{6}$ $TCID_{50}$/mL	Sin reacción cruzada
22		HCoV-HKU1	1,5mg/mL	Sin reacción cruzada
23		HCoV-NL63	$1{,}7 \times 10^{5}$ $TCID_{50}$/mL	Sin reacción cruzada

No,	Tipo de muestra	Sustancia de reacción cruzada	Concentración final de la prueba	Resultado de la prueba
24	Virus	HCoV-OC43	8,9 X 10^5 $TCID_{50}$/mL	Sin reacción cruzada
25		HCoV-229E	1,51 X 10^6 $TCID_{50}$/mL	Sin reacción cruzada
26		Nucleoproteína del coronavirus del SARS humano	25ng/mL	Reacción cruzada
27		Nucleoproteina del MERS-CoV	0,25mg/mL	Sin reacción cruzada
28		Metaneumovirus humano (hMPV) 16 tipo A1	1,51 X 10^6 $TCID_{50}$/mL	Sin reacción cruzada

No,	Tipo de muestra	Sustancia de reacción cruzada	Concentración final de la prueba	Resultado de la prueba
1	Otros Microorganismos	*Staphylococcus saprophyticus*	1,9 X 10^7 CFU/mL	Sin reacción cruzada
2		*Neisseria sp,(Neisseria lactamica)*	1,7 X 10^8 CFU/mL	Sin reacción cruzada
3		*Staphylococcus haemolyticus*	3,5 X 10^9 CFU/mL	Sin reacción cruzada
4		*Streptococcus salivarius*	1,96 X 10^7 CFU/mL	Sin reacción cruzada
5		*Hemophilus parahaemolyticus*	2,2 X 10^8 CFU/mL	Sin reacción cruzada
6		*Proteus vulgaris*	7,2 X 10^6 CFU/mL	Sin reacción cruzada
7		*Moraxella catarrhalis*	4,7 X 10^7 CFU/mL	Sin reacción cruzada
8		*Klebsiella pneumoniae*	5,0 X 10^6 CFU/mL	Sin reacción cruzada
9		*Fusobacterium necrophorum*	1,75 X 10^8 CFU/mL	Sin reacción cruzada
10		*Tuberculosis micobacteriana*	10mg/mL	Sin reacción cruzada

No,	Tipo de muestra	Sustancia de reacción cruzada	Concentración final de la prueba	Resultado de la prueba
11	Otros Microorganismos	Lavado nasal humano agrupado	N/A*	Sin reacción cruzada
12		*Streptococcus pyogenes*	3,6 X 10^7 CFU/mL	Sin reacción cruzada
13		*Mycoplasma pneumoniae*	4 X 10^8 CFU/mL	Sin reacción cruzada

** Sin concentración proporcionada por el proveedor. Se evaluó la solución madre sin diluir.*

5. Sustancias interferentes

Las siguientes 43 sustancias potencialmente interferentes no tienen ningún impacto en Panbio™ COVID-19 Ag Rapid Test Device. Las concentraciones de prueba finales de las sustancias interferentes se documentan en la siguiente tabla.

No,	Tipo de muestra	Sustancias Interferentes	Concentración final de la prueba	Resultado de la prueba
1	Sustancia Endógena	Mucina	0,5%	Sin interferencia
2		Hemoglobina	100 mg/L	Sin interferencia
3		Triglicéridos	1,5 mg/L	Sin interferencia
4		Icterico (Bilirrubina)	40 mg/dL	Sin interferencia
5		Factor reumatoide	200 IU/mL	Sin interferencia
6		Anticuerpo antinuclear	>1:40	Sin interferencia
7		Embarazo	Dilución de 10 veces	Sin interferencia
8	Sustancia Exógena	Éter de glicerilo guayacol	1 µg/mL	Sin interferencia
9		Albuterol	0,005 mg/dL	Sin interferencia
10		Efedrina	0,1 mg/mL	Sin interferencia
11		Clorfeniramina	0,08 mg/dL	Sin interferencia
12		Difenhidramina	0,08 mg/dL	Sin interferencia
13		Ribavirina	26,7 µg /mL	Sin interferencia
14		Oseltamivir	0,04 mg/dL	Sin interferencia
15		Zanamivir	17,3 µg /mL	Sin interferencia
16		Clorhidrato de fenilefrina	15% v/v	Sin interferencia
17		Clorhidrato de oximetazolina	15% v/v	Sin interferencia
18		Amoxicilina	5,4 mg/dL	Sin interferencia

No,	Tipo de muestra	Sustancias Interferentes	Concentración final de la prueba	Resultado de la prueba
19		Ácido acetilsalicílico	3 mg/dL	Sin interferencia
20		Ibuprofeno	21,9 mg/dL	Sin interferencia
21		Clorotiazida	2,7 mg/dL	Sin interferencia
22		Indapamida	140 ng/mL	Sin interferencia
23		Glimepirida (sulfonilureas)	0,164 mg/dL	Sin interferencia
24		Acarbose	0,03 mg/dL	Sin interferencia
25		Ivermectina	4,4 mg/L	Sin interferencia
26		Lopinavir	16,4 µg/L	Sin interferencia
27		Ritonavir	16,4 µg/L	Sin interferencia
28		Fosfato de cloroquina	0,99 mg/L	Sin interferencia
29		Cloruro de sodio con conservantes	4,44 mg/mL	Sin interferencia
30	Sustancia	Beclometasona	4,79 ng/mL	Sin interferencia
31	Exógena	Dexametasona	0,6 µg/mL	Sin interferencia
32		Flunisolida	0,61 µg/mL	Sin interferencia
33		Triamcinolona	1,18 ng/mL	Sin interferencia
34		Budesonida	2,76 ng/mL	Sin interferencia
35		Mometasona	1,28 ng/mL	Sin interferencia
36		Fluticasona	2,31 ng/mL	Sin interferencia
37		Azufre	9,23 µg/mL	Sin interferencia
38		Benzocaína	0,13 mg/mL	Sin interferencia
39		Mentol	0,15 mg/mL	Sin interferencia
40		Mupirocina	10 µg/mL	Sin interferencia
41		Tobramicina	24,03 µg/mL	Sin interferencia
42		Biotina	1,2 µg/mL	Sin interferencia
43		HAMA	63,0 ng/mL	Sin interferencia

6. Repetibilidad y reproducibilidad

La repetibilidad y reproducibilidad de Panbio™ COVID-19 Ag Rapid Test Device se estableció utilizando paneles de referencia internos que contienen muestras negativas y una variedad de muestras positivas. No se observaron diferencias dentro de las evaluaciones, entre evaluaciones, entre lotes, entre sitios y entre días.

PREPARACIÓN

1 Permita que todos los componentes del kit alcancen una temperatura entre 15 y 30 °C durante 30 minutos antes de realizar la prueba.
Nota: Los profesionales de la salud deben cumplir con las pautas de seguridad personal, incluido el uso de equipo de protección personal.

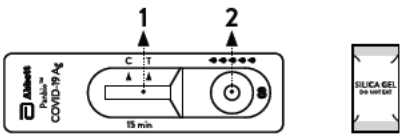
2 **Abra el paquete y revise los siguientes componentes:**
1. Dispositivo de prueba con desecante en bolsa de aluminio individual
2. Solución tampón
3. Tubo de extracción
4. Tapa de tubos de extracción
5. Hisopo control positivo
6. Hisopo control negativo
7. Hisopos nasales esterilizados para recolección de muestras
8. Gradilla para tubos
9. Guía de referencia rápida
10. Instrucciones de uso

3 Lea cuidadosamente estas instrucciones de uso antes de usar Panbio™ COVID-19 Ag Rapid Test Device kit.

4 Revise la fecha de vencimiento de la caja del kit. Si la fecha de vencimiento ha pasado, use otro kit.

5 **Abra la bolsa de aluminio y revise lo siguiente:**
1. Ventana de resultados
2. Pocillo de muestra

Luego, rotule el dispositivo con el identificador del paciente.

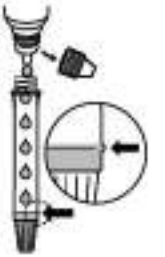


●●●●●: 5 gotas de la muestra extraída

PROCEDIMIENTO DE LA PRUEBA

1 Sostenga el frasco de tampón verticalmente y llene el tubo de extracción con solución tampón hasta que fluya hasta la línea de llenado del tubo de extracción (300µL).

⚠ **Precaución:** Si la cantidad de tampón es excesiva o insuficiente, puede producirse un resultado de prueba incorrecto.



2 Coloque el tubo de extracción en la gradilla para tubos.

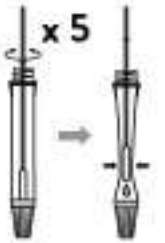
3 Incline la cabeza del paciente hacia atrás 70 grados. Mientras gira suavemente el hisopo, inserte el hisopo menos de una pulgada (aproximadamente 2 cm) en la fosa nasal (hasta que encuentre resistencia en los cornetes).
Gire el hisopo cinco veces contra la pared nasal. Usando el mismo hisopo, repita el procedimiento de recolección con la segunda fosa nasal. Retire lentamente el hisopo de la fosa nasal.

⚠ **Precaución:** Si el hisopo se quiebra durante la recolección de la muestra, repita la recolección de la muestra con un hisopo nuevo.

ESPAÑOL

PROCEDIMIENTO DE LA PRUEBA

4 Inserte la muestra de hisopado en el tubo de extracción. Gire la punta del hisopo en la solución tampón dentro del tubo de extracción, empujando hacia la pared del tubo de extracción al menos cinco veces y luego exprima el hisopo apretando el tubo de extracción con los dedos.

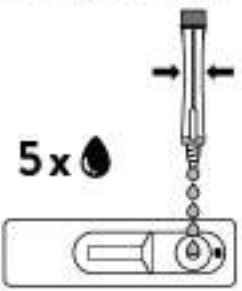


5 Quiebre el hisopo en el punto de ruptura y cierre la tapa del tubo de extracción.

6 Abra la tapa de la boquilla de goteo en la parte inferior del tubo de extracción.

7 Dispense 5 gotas de las muestras extraídas verticalmente en el pocillo de la muestra (S) en el dispositivo. No manipule ni mueva el dispositivo de prueba hasta que la prueba esté completa y lista para leer.

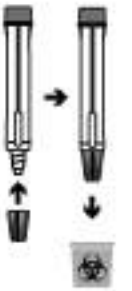
⚠ **Precaución:** Las burbujas que se forman en el tubo de extracción pueden dar lugar a resultados incorrectos. Si no puede crear suficientes gotas, esto puede deberse a una obstrucción en la boquilla dispensadora. Agite el tubo suavemente para liberar el bloqueo hasta que observe la formación de gotas libres.



ESPAÑOL

PROCEDIMIENTO DE LA PRUEBA

8 Cierre la boquilla y deseche el tubo de extracción que contiene el hisopo usado de acuerdo con las regulaciones locales y el protocolo de eliminación de desechos de riesgo biológico.



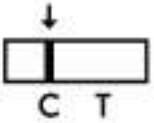
9 De inicio al temporizador. Leer resultado a los 15 minutos. No lea los resultados después de 20 minutos.

10 Deseche el dispositivo usado de acuerdo con las regulaciones locales y el protocolo de eliminación de desechos de riesgo biológico.

INTERPRETACIÓN DE LA PRUEBA

NEGATIVA

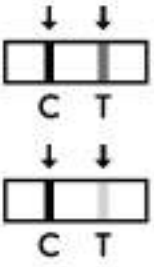
La presencia de solo la línea de control (C) y ninguna línea de prueba (T) dentro de la ventana de resultados indica un resultado negativo.



POSITIVA

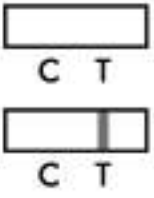
La presencia de la línea de prueba (T) y la línea de control (C) dentro de la ventana de resultados, independientemente de la línea que aparezca primero, indica un resultado positivo.

⚠ **Precaución:** La presencia de cualquier línea de prueba (T), no importa cuán débil sea, indica un resultado positivo.



NO VÁLIDA

Si la línea de control (C) no está visible dentro de la ventana de resultados después de realizar la prueba, el resultado se considera inválido. Es posible que las instrucciones no se hayan seguido correctamente. Se recomienda volver a leer las instrucciones de uso antes de volver a analizar la muestra con un nuevo dispositivo de prueba.



ESPAÑOL

A propos du Test

FR

Introduction

La maladie à coronavirus (COVID-19) est une maladie infectieuse causée par un coronavirus nouvellement découvert, le coronavirus du syndrome respiratoire aigu sévère 2 (SARS-CoV-2)[1]. Le SARS-CoV-2 est un β-coronavirus, qui est un virus à ARN sens positif non segmenté enveloppé[2]. Il se propage par transmission interhumaine via des gouttelettes ou par contact direct, et l'infection a été estimée avoir une période d'incubation moyenne de 6,4 jours et un nombre de reproduction de base de 2,24 à 3,58. Parmi les patients atteints de pneumonie causée par le SARS-CoV-2, la fièvre était le symptôme le plus courant, suivie de la toux [3]. Les principaux dosages IVD utilisés pour le COVID-19 utilisent une réaction en chaîne transcriptase-polymérase inverse en temps réel (RT-PCR) qui prend quelques heures[4]. La disponibilité d'un test efficient de diagnostic rapide en biologie délocalisée est primordial pour les professionnels de santé. Pour leur permettre d'aider au diagnostic des patients et d'empêcher la propagation du virus [5]. Les tests d'antigènes joueront un rôle essentiel dans la lutte contre le COVID-19 [6].

Principe du Test

Panbio™ COVID-19 Ag Rapid Test Device contient une bande de membrane pré-enduite d'anticorps anti-SARS-CoV-2 immobilisés sur la ligne de test et un anticorps IgY monoclonal de souris anti-poulet sur la ligne de contrôle. Deux types de conjugués (IgG humaine spécifique au SARS-CoV-2 Ag conjugué d'Or (liés aux protéines de la nucléocapside) et IgY Poulet conjugué d'Or) se déplacent vers le haut sur la membrane par chromatographie et réagissent respectivement avec l'anticorps anti-SARS-CoV-2 et l'IgY monoclonal de souris anti-poulet pré-enduit. Pour un résultat positif, l'IgG humaine spécifique au conjugué SARS-CoV-2 Ag et l'anticorps anti-SARS-CoV-2 formeront une ligne de test dans la fenêtre de résultat. Ni la ligne de test ni la ligne de contrôle ne sont visibles dans la fenêtre de résultat avant l'application de l'échantillon du patient. Une ligne de contrôle visible est requise pour indiquer qu'un résultat de test est valide.

FRENCH

Utilisation prévue

Panbio™ COVID-19 Ag Rapid Test Device est un test de diagnostic rapide *in vitro* pour la détection qualitative de l'antigène SARS-CoV-2 (Ag) dans des échantillons sur écouvillons nasaux humains provenant de personnes répondant aux critères cliniques et / ou épidémiologiques du COVID-19. Panbio™ COVID-19 Ag Rapid Test Device est destiné à un usage professionnel uniquement et est destiné à être utilisé comme une aide au diagnostic de l'infection par le SARS-CoV-2. Le produit peut être utilisé dans tout environnement de laboratoire et hors laboratoire qui répond aux exigences spécifiées dans le mode d'emploi et selon la réglementation

locale. Le test fournit des résultats de test préliminaires. Les résultats négatifs n'empêchent pas l'infection par le SARS-CoV-2 et ils ne peuvent pas être utilisés comme seule base de traitement ou d'autres décisions de prise en charge. Les résultats négatifs doivent être associés aux observations cliniques, aux antécédents du patient et aux informations épidémiologiques. Le test n'est pas destiné à être utilisé comme test de dépistage des donneurs pour le SARS-CoV-2.

Matériel fourni

- 25 appareils de test avec dessiccateur dans une pochette individuelle en aluminium
- Solution tampon (1 x 9 ml / flacon)
- 25 tubes d'extraction
- 25 bouchons pour les tubes d'extraction
- 1 écouvillon de contrôle positif
- 1 écouvillon de contrôle négatif
- 25 écouvillons nasaux stérilisés pour le prélèvement d'échantillons
- 1 porte tubes
- 1 guide de référence rapide
- 1 Notice d'utilisation

Matériel requis mais non fourni

- Équipement de protection individuelle selon les recommandations locales (ex : blouse de laboratoire, masque facial, écran facial / lunettes et gants), minuterie, conteneur à déchets

Ingrédients actifs des principaux composants

- **1 test** Conjugué or : IgG humaines spécifiques au colloïde d'or SARS-CoV-2 Ag et IgY de poulet - colloïde d'or, Ligne de test : anti-SARS-CoV-2 monoclonale de souris, Ligne de contrôle : IgY monoclonale de souris anti-poulet
- **Tampon** Tricine, chlorure de sodium, Tween 20 , azide de sodium (<0,1%), Proclin 300

Stockage et stabilité

1. Le kit de test doit être conservé à une température comprise entre 2 et 30 ° C. Ne pas congeler le kit ou ses composants.
   Remarque : Lorsqu'ils sont conservés au réfrigérateur, tous les composants du kit doivent être portés à température ambiante (15-30° C) pendant au moins 30 minutes avant d'effectuer le test. Ne pas ouvrir la pochette tant que les composants ne sont pas à température ambiante.

2. Le flacon de tampon peut être ouvert et refermé pour chaque test. Le bouchon du tampon doit être fermement scellé entre chaque utilisation. Le tampon est stable jusqu'à la date d'expiration s'il est conservé entre 2 et 30 ° C.
3. Effectuer le test immédiatement après avoir retiré le dispositif de test de la pochette en aluminium.
4. Ne pas utiliser le kit de test au-delà de sa date d'expiration.
5. La durée de conservation du kit est celle indiquée sur l'emballage extérieur.
6. Ne pas utiliser le kit de test si la pochette est endommagée ou si le sceau est brisé.
7. Les échantillons directs sur écouvillon doivent être testés immédiatement après le prélèvement. Si un test immédiat n'est pas possible, l'échantillon sur écouvillon peut être conservé dans un tube d'extraction rempli de tampon d'extraction (300 µl) à température ambiante (15-30° C) jusqu'à deux heures avant le test.

Précautions d'usage

1. Pour usage de diagnostic *in vitro* uniquement. Ne pas réutiliser le dispositif de test et les composants du kit.
2. Ces instructions doivent être strictement suivies par un professionnel de santé qualifié pour obtenir des résultats précis. Tous les utilisateurs doivent lire les instructions avant d'effectuer un test.
3. Ne pas manger ni fumer pendant la manipulation des échantillons.
4. Porter des gants de protection lors de la manipulation des échantillons et laver-vous soigneusement les mains par la suite.
5. Eviter les éclaboussures ou la formation d'aérosols sur l'échantillon et le tampon.
6. Nettoyer soigneusement les déversements en utilisant un désinfectant approprié.
7. Décontaminer et éliminer tous les échantillons, kits de réaction et matériaux potentiellement contaminés (c'est-à-dire écouvillon, tube d'extraction, dispositif de test) dans un récipient contenant des risques biologiques comme s'il s'agissait de déchets infectieux et éliminer conformément aux réglementations locales applicables.
8. Ne pas mélanger ni échanger différents échantillons.
9. Ne pas mélanger les réactifs de lots différents ou ceux d'autres produits.
10. Ne pas stocker le kit de test à la lumière directe du soleil.
11. Pour éviter toute contamination, ne pas toucher la tête de l'écouvillon fourni lors de l'ouverture de la poche de l'écouvillon.
12. Les écouvillons stérilisés ne doivent être utilisés que pour le prélèvement d'échantillons nasaux.
13. Pour éviter toute contamination croisée, ne réutiliser pas les écouvillons

stérilisés pour le prélèvement d'échantillons.
14. Ne pas diluer l'écouvillon collecté avec une solution à l'exception du tampon d'extraction fourni.
15. Le tampon contient < 0,1% d'azide de sodium comme agent de conservation qui peut être toxique en cas d'ingestion. Lorsqu'il est éliminé dans un évier, rincer avec un grand volume d'eau[7].
16. Ne pas utiliser l'écouvillon de contrôle positif ou négatif pour le prélèvement d'échantillons.

Procédure de test (reportez-vous au schéma)

Ecouvillons pour prélèvement nasal

Remarque : le professionnel de santé doit se conformer aux directives de sécurité personnelle, y compris l'utilisation d'équipements de protection individuelle.

Préparation du test

1. Laisser tous les composants du kit atteindre une température comprise entre 15 et 30 ° C avant le test pendant 30 minutes.
2. Retirer le dispositif de test de la pochette en aluminium avant de l'utiliser. Le placer sur une surface plane, horizontale et propre.
3. Tenir le flacon de tampon verticalement et remplisser le tube d'extraction de fluide tampon jusqu'à ce qu'il s'écoule jusqu'à la ligne de remplissage du tube d'extraction (300 µl).
   ⚠ **Attention :** Si la quantité de tampon est excessive ou insuffisante, un résultat de test incorrect peut se produire.
4. Placer le tube d'extraction dans le support de tubes.

Prélèvement et extraction des échantillons

1. Incliner la tête du patient de 70 degrés en arrière. Tout en tournant doucement l'écouvillon, insérer l'écouvillon environ 2 cm dans la narine (jusqu'à ce que la résistance soit rencontrée au niveau des cornets).
2. Faire tourner l'écouvillon cinq fois contre la paroi nasale, puis le retirer lentement de la narine.
3. En utilisant le même écouvillon, répéter la procédure de prélèvement dans la deuxième narine.
   ⚠ **Attention:** si le bâtonnet de l'écouvillon se brise pendant le prélèvement de l'échantillon, répéter le prélèvement de l'échantillon avec un nouvel écouvillon.
4. Faire tourbillonner la pointe de l'écouvillon dans le fluide tampon à l'intérieur du tube d'extraction, en poussant dans la paroi du tube d'extraction au moins cinq fois, puis Faire sortir l'écouvillon en pressant le tube d'extraction avec vos doigts.
5. Casser l'écouvillon au point de rupture et fermer le capuchon du tube d'extraction.

Réaction avec le dispositif de test

1. Ouvrir le capuchon de la buse de descente au bas du tube d'extraction.
2. Distribuer verticalement 5 gouttes d'échantillons extraits dans le puits d'échantillon (S) de l'appareil. Ne pas manipuler ni déplacer le dispositif de test tant que le test n'est pas terminé et prêt pour la lecture.
   ⚠ **Attention :** les bulles qui se produisent dans le tube d'extraction peuvent conduire à des résultats inexacts. Si vous ne parvenez pas à créer suffisamment de gouttes, cela peut être dû à un colmatage de la buse de distribution. Secouer doucement le tube pour libérer le blocage jusqu'à ce que vous observiez la formation de gouttes libres.
3. Fermer la buse et jeter le tube d'extraction contenant l'écouvillon usagé conformément à vos réglementations locales et au protocole d'élimination des déchets biologiques
4. Démarrer le minuteur, lire le résultat à 15 minutes. Ne pas lire les résultats après 20 minutes.
5. Eliminer l'appareil usagé conformément aux réglementations locales et au protocole d'élimination des déchets biologiques.

Ecouvillons de contrôle Positif et Négatif

⚠ **Attention:** utilisation pour contrôle uniquement. Ne pas utiliser l'écouvillon de contrôle positif ou négatif pour le prélèvement d'échantillons.

Remarque: veuillez consulter la section Contrôle de qualité externe de ce mode d'emploi pour la fréquence de test des écouvillons de contrôle de qualité externe.

1. Tenir le flacon de tampon verticalement et remplir le tube d'extraction de liquide tampon jusqu'à la ligne de remplissage du tube d'extraction (300 µl).
   ⚠ **Attention :** Si la quantité de tampon est excessive ou insuffisante, un résultat de test incorrect peut se produire.
2. Placer le tube d'extraction dans le support de tubes.
3. Insérer l'écouvillon de contrôle positif ou négatif dans le liquide tampon à l'intérieur du tube d'extraction et faire tremper l'écouvillon pendant 1 minute. Faire tourbillonner la pointe de l'écouvillon de contrôle dans le liquide tampon à l'intérieur du tube d'extraction, en poussant dans la paroi du tube d'extraction au moins cinq fois, puis faire sortir l'écouvillon en pressant le tube d'extraction avec vos doigts.
4. Eliminer l'écouvillon de contrôle utilisé conformément à votre protocole d'élimination des déchets biologiques dangereux.
5. Fermer le bouchon du tube d'extraction.
6. Suivre la procédure de test ci-dessus [Réaction avec le dispositif de test].

Interprétation du test (voir la figure)

1. **Résultat négatif :** La présence de seulement la ligne de contrôle (C) et aucune ligne de test (T) dans la fenêtre de résultat indique un résultat négatif.
2. **Résultat positif :** la présence de la ligne de test (T) et de la ligne de contrôle (C) dans la fenêtre de résultat, quelle que soit la ligne qui apparaît en premier, indique un résultat positif.
   ⚠ **Attention :** la présence d'une ligne de test (T), aussi faible soit-elle, indique un résultat positif.
3. **Résultat invalide :** si la ligne de contrôle (C) n'est pas visible dans la fenêtre de résultats après avoir effectué le test, le résultat est considéré comme invalide.

Limitations du test

1. Le contenu de ce kit doit être utilisé pour la détection professionnelle et qualitative de l'antigène SARS-CoV-2 à partir d'un écouvillon nasal. D'autres types d'échantillons peuvent conduire à des résultats incorrects et ne doivent pas être utilisés.
2. Le non-respect des instructions relatives à la procédure de test et à l'interprétation des résultats du test peut affecter les performances du test et / ou produire des résultats invalides.
3. Un résultat de test négatif peut survenir si l'échantillon a été collecté, extrait ou transporté de manière incorrecte. Un résultat de test négatif n'élimine pas la possibilité d'une infection par le SARS-CoV-2 et doit être confirmé par une culture virale ou un test moléculaire.
4. Des résultats de test positifs n'excluent pas la possibilité de co-infections avec d'autres agents pathogènes.
5. Les résultats des tests doivent être évalués conjointement avec d'autres données cliniques disponibles pour le médecin.
6. La lecture des résultats du test avant 15 minutes ou après 20 minutes peut donner des résultats incorrects.
7. Panbio™ COVID-19 Ag Rapid Test n'est pas destiné à détecter les virus défectueux (non infectieux) au cours des dernières étapes de l'excrétion virale qui pourraient être détectés par des tests moléculaires PCR.[8]
8. Des résultats positifs peuvent survenir en cas d'infection par le SARS-CoV.

Contrôle de qualité

1. **Contrôle de qualité interne :**
   Le dispositif de test a une ligne de test (T) et une ligne de contrôle (C) sur la surface du dispositif de test. Ni la ligne de test ni la ligne de contrôle ne sont visibles dans la fenêtre de résultat avant l'application d'un échantillon. La ligne de contrôle est utilisée pour le contrôle de la procédure et doit toujours apparaître si la procédure de test est effectuée correctement et que les réactifs de test de la ligne de contrôle fonctionnent.
2. **Contrôle de qualité externe :**
   Les contrôles sont spécifiquement formulés et fabriqués pour garantir les performances du Panbio™ COVID-19 Ag Rapid Test Device et sont utilisés pour vérifier la capacité de l'utilisateur à effectuer correctement le test et à interpréter les résultats. Le contrôle positif produira un résultat de test positif et a été fabriqué pour produire une ligne de test visible (T). Le contrôle négatif produira un résultat de test négatif.
   Les bonnes pratiques de laboratoire suggèrent l'utilisation de contrôles positifs et négatifs pour veiller à ce que :

- Les réactifs de test fonctionnent et
- Que le test soit correctement effectué.

Des contrôles externes peuvent être réalisés dans l'une des circonstances suivantes :

- Par un nouvel opérateur avant d'effectuer des tests sur des échantillons de patients,
- Lors de la réception d'un nouvel envoi de tests,
- À intervalles réguliers, selon les exigences locales et / ou selon les procédures de contrôle qualité de l'utilisateur.

Caractéristiques de performance

1. **Évaluation externe du Panbio™ COVID-19 Ag Rapid Test Device**
   Les performances cliniques du Panbio™ COVID-19 Ag Rapid Test Device ont été déterminées en testant des échantillons 104 prélèvements nasaux positifs et 404 négatifs pour l'antigène SARS-CoV-2 (Ag) pour avoir une sensibilité de 98,1% (95% CI: 93,2-99,8%) et une spécificité de 99,8% (95% CI: 98,6-100,0%). Les échantillons cliniques ont été jugés positifs ou négatifs en utilisant une méthode de référence FDA EUA RT-PCR.

Panbio™ COVID-19 Ag Rapid Test Device Resultats

		Résultats PCR par prélèvement nasal		
		Positif	**Negatif**	**Total**
Panbio™ COVID-19 Ag Rapid Test Device Resultats (prélèvement nasal)	**Positif**	102	1	103
	Negatif	2	403	405
	Total	104	404	508
		Sensibilité	Spécificité	Pourcentage de concordance Global
		98,1% [93,2%;99,8%]	**99,8%** [98,6%;100,0%]	**99,4%** [98,3%;99,9%]

- Les données de performance ont été calculées à partir d'une étude sur des personnes soupçonnées d'avoir été exposées au COVID-19 ou qui ont présenté des symptômes au cours des 7 derniers jours.
- La stratification des échantillons positifs après l'apparition des symptômes ou une exposition suspectée entre 0-3 jours a une sensibilité de 100,0% (n=46) et 4-7 jours a une sensibilité de 96,6% (n=58).
- La concordance positive du Panbio™ COVID-19 Ag Rapid Test Device est plus élevée avec des échantillons ayant des valeurs de Ct ≤ 33 avec une sensibilité de 99,0%. Comme suggéré dans les références 8 et 9, les patients avec une valeur de Ct > 33 ne sont plus contagieux.[8, 9]
- Les données de performance clinique ont également été calculées par rapport aux échantillons sur écouvillons nasopharyngés en utilisant une RT-PCR référencée FDA et EUA, et ont une sensibilité de 91,1 % (IC 95 %: 84,2-95,6 %) et une spécificité de 99,7 % (IC 95 %: 98,6-100,0 %).

2. Limite de détection

Il a été confirmé que le Panbio™ COVID-19 Ag Rapid Test Device détecte 2,5 x $10^{1,8}$ $TCID_{50}$ / ml de SARS-CoV-2 qui a été isolé à partir d'un patient confirmé COVID-19 en Corée.

3. Effet de crochet

Il n'y a pas d'effet crochet à 1,0x$10^{5,8}$ $TCID_{50}$ / ml de SARS-CoV-2 qui a été isolé d'un patient confirmé COVID-19 en Corée.

4. Réactivité croisée

La réactivité croisée du Panbio™ COVID-19 Ag Rapid Test Device a été évaluée en testant 28 virus et 13 autres micro-organismes. Les concentrations d'essai finales de virus et d'autres micro-organismes sont documentées dans le tableau ci-dessous. Les virus et autres micro-organismes suivants, à l'exception de la nucléoprotéine du coronavirus

humain SARS, n'ont aucun effet sur les résultats des tests du Panbio™ COVID-19 Ag Rapid Test Device. Le test rapide Panbio™ COVID-19 Ag Rapid Test Device a une réactivité croisée avec la nucléoprotéine du SARS-coronavirus humain à une concentration de 25 ng / ml ou plus car le SARS-CoV a une forte homologie (79,6%) avec le SARS-CoV-2.

No,	Types d' échantillons	Substance de réaction croisée	Concentration finale du test	Résultat du Test
1	Virus	Adenovirus Type 1	$2,2 \times 10^{7}$ $TCID_{50}$/ml	Pas de réaction croisée
2		Adenovirus Type 5	$5,71 \times 10^{8}$ $TCID_{50}$/ml	Pas de réaction croisée
3		Adenovirus Type 7	$2,86 \times 10^{9}$ $TCID_{50}$/ml	Pas de réaction croisée
4		Enterovirus (EV68)	$2,81 \times 10^{7}$ $TCID_{50}$/ml	Pas de réaction croisée
5		Echovirus2	$1,0 \times 10^{6,5}$ $TCID_{50}$/ml	Pas de réaction croisée
6		Echovirus11	$5,0 \times 10^{6,25}$ $TCID_{50}$/ml	Pas de réaction croisée
7		Enterovirus D68	$2,81 \times 10^{7}$ $TCID_{50}$/ml	Pas de réaction croisée
8		Virus Herpès simplex humain (VHS) 1	$5,0 \times 10^{7,5}$ $TCID_{50}$/ml	Pas de réaction croisée
9		Virus Herpès simplex humain (VHS) 2	$5,0 \times 10^{5,75}$ $TCID_{50}$/ml	Pas de réaction croisée
10		Virus Measles Ag	$1,58 \times 10^{5}$ $TCID_{50}$/ml	Pas de réaction croisée
11		Influenza virus A (H1N1) Strain (A/Virginia/ ATCC1/2009)	$3,71 \times 10^{5}$ PFU/ml	Pas de réaction croisée
12		Influenza virus A (H1N1) Strain (A/WS/33)	$5,0 \times 10^{7,25}$ $TCID_{50}$/ml	Pas de réaction croisée
13		Influenza virus A(H1N1) Strain (A/ California/08/2009/ pdm09)	$1,6 \times 10^{8}$ $TCID_{50}$/ml	Pas de réaction croisée
14		Influenza virus B Strain (B/ Lee/40)	$5,0 \times 10^{6,25}$ $TCID_{50}$/ml	Pas de réaction croisée
15		Parainfluenza Type 1	$3,06 \times 10^{8}$ $TCID_{50}$/ml	Pas de réaction croisée

No,	Types d' échantillons	Substance de réaction croisée	Concentration finale du test	Résultat du Test
16	Virus	Parainfluenza Type 2	5,0 X 10^5 $TCID_{50}$/ml	Pas de réaction croisée
17		Parainfluenza Type 3	6,6 X 10^7 $TCID_{50}$/ml	Pas de réaction croisée
18		Parainfluenza Type 4A	2,81 X 10^7 $TCID_{50}$/ml	Pas de réaction croisée
19		Virus Respiratoire Syncitial (VRS) type A	4,22 X 10^5 $TCID_{50}$/ml	Pas de réaction croisée
20		Virus Respiratoire Syncitial (RSV) type B	5,62 X 10^5 $TCID_{50}$/ml	Pas de réaction croisée
21		HCoV-HKU1	1,26 X 10^6 $TCID_{50}$/ml	Pas de réaction croisée
22		Rhinovirus A16	1,5mg/ml	Pas de réaction croisée
23		HCoV-NL63	1,7 X 10^5 $TCID_{50}$/ml	Pas de réaction croisée
24		HCoV-OC43	8,9 X 10^5 $TCID_{50}$/ml	Pas de réaction croisée
25		HCoV-229E	1,51 X 10^6 $TCID_{50}$/ml	Pas de réaction croisée
26		Nucléoprotéine du SARS-coronavirus humain	25ng/ml	Réaction croisée
27		Nucleoproteine du MERS-CoV	0,25mg/ml	Pas de réaction croisée
28		Metapneumovirus humain (hMPV) 16 Type A1	1,51 X 10^6 $TCID_{50}$/ml	Pas de réaction croisée

No,	Types d' échantillons	Substance de réaction croisée	Concentration finale du test	Résultat du Test
1	Autre Microorganisme	*Staphylococcus saprophyticus*	1,9 X 10^7 CFU/ml	Pas de réaction croisée
2		*Neisseria sp.(Neisseria lactamica)*	1,7 X 10^8 CFU/ml	Pas de réaction croisée
3		*Staphylococcus haemolyticus*	3,5 X 10^9 CFU/ml	Pas de réaction croisée
4		*Streptococcus salivarius*	1,96 X 10^7 CFU/ml	Pas de réaction croisée

No,	Types d' échantillons	Substance de réaction croisée	Concentration finale du test	Résultat du Test
5	Autre Microorganisme	*Hemophilus parahaemolyticus*	2,2 X 10^8 CFU/ml	Pas de réaction croisée
6		*Proteus vulgaris*	7,2 X 10^6 CFU/ml	Pas de réaction croisée
7		*Moraxella catarrhalis*	4,7 X 10^7 CFU/ml	Pas de réaction croisée
8		*Klebsiella pneumoniae*	5,0 X 10^6 CFU/ml	Pas de réaction croisée
9		*Fusobacterium necrophorum*	1,75 X 10^8 CFU/ml	Pas de réaction croisée
10		*Mycobacterium tuberculosis*	10mg/ml	Pas de réaction croisée
11		Pool de lavages nasaux humains	N/A*	Pas de réaction croisée
12		*Streptococcus pyogenes*	3,6 X 10^7 CFU/ml	Pas de réaction croisée
13		*Mycoplasma pneumoniae*	4 X 10^8 CFU/ml	Pas de réaction croisée

** Aucune concentration fournie par le fournisseur. La solution mère non diluée a été testée.*

5. Substances interférentes

Les 43 substances potentiellement interférentes suivantes n'ont aucun impact sur le Panbio™ COVID-19 Ag Rapid Test Device. Les concentrations d'essai finales des substances interférentes sont documentées dans le tableau ci-dessous.

No,	Types d' échantillons	Substances interférentes	Concentration finale du test	Résultat du Test
1	Substance Endogène	Mucine	0,5%	Pas d'interférence
2		Hémoglobine	100 mg/L	Pas d'interférence
3		Triglycérides	1,5 mg/L	Pas d'interférence
4		Ictère (Bilirubine)	40 mg/dL	Pas d'interférence
5		Facteur Rhumatoïde	200 IU/ml	Pas d'interférence
6		Anticorps anti-nucléaire	>1:40	Pas d'interférence
7		Enceinte	Dilution au dixième	Pas d'interférence

No,	Types d' échantillons	Substances interférentes	Concentration finale du test	Résultat du Test
8		Éther glycérylique de guaiacol	1 µg/ml	Pas d'interférence
9		Albuterol	0,005 mg/dL	Pas d'interférence
10		Ephedrine	0,1 mg/ml	Pas d'interférence
11		Chlorpheniramine	0,08 mg/dL	Pas d'interférence
12		Diphenhydramine	0,08 mg/dL	Pas d'interférence
13		Ribavirin	26,7 µg /ml	Pas d'interférence
14		Oseltamivir	0,04 mg/dL	Pas d'interférence
15		Zanamivir	17,3 µg /ml	Pas d'interférence
16		Chlorhydrate de phényléphrine	15% v/v	Pas d'interférence
17		Chlorhydrate d'oxymétazoline	15% v/v	Pas d'interférence
18		Amoxicilline	5,4 mg/dL	Pas d'interférence
19		Acide acétylsalicylique	3 mg/dL	Pas d'interférence
20		Ibuprofène	21,9 mg/dL	Pas d'interférence
21		Chlorothiazide	2,7 mg/dL	Pas d'interférence
22	Substance Exogène	Indapamide	140 ng/ml	Pas d'interférence
23		Glimépiride (sulfonylurées)	0,164 mg/dL	Pas d'interférence
24		Acarbose	0,03 mg/dL	Pas d'interférence
25		Ivermectine	4,4 mg/L	Pas d'interférence
26		Lopinavir	16,4 µg/L	Pas d'interférence
27		Ritonavir	16,4 µg/L	Pas d'interférence
28		Phosphate de chloroquine	0,99 mg/L	Pas d'interférence
29		Chlorure de sodium chloride avec conservateurs	4,44 mg/ml	Pas d'interférence
30		Beclomethasone	4,79 ng/ml	Pas d'interférence
31		Dexamethasone	0,6 µg/ml	Pas d'interférence
32		Flunisolide	0,61 µg/ml	Pas d'interférence
33		Triamcinolone	1,18 ng/ml	Pas d'interférence
34		Budesonide	2,76 ng/ml	Pas d'interférence
35		Mometasone	1,28 ng/ml	Pas d'interférence
36		Fluticasone	2,31 ng/ml	Pas d'interférence

No,	Types d' échantillons	Substances interférentes	Concentration finale du test	Résultat du Test
37	Substance Exogène	Sulfure	9,23 µg/ml	Pas d'interférence
38		Benzocaine	0,13 mg/ml	Pas d'interférence
39		Menthol	0,15 mg/ml	Pas d'interférence
40		Mupirocine	10 µg/ml	Pas d'interférence
41		Tobramycine	24,03 µg/ml	Pas d'interférence
42		Biotine	1,2 µg/ml	Pas d'interférence
43		HAMA	63,0 ng/ml	Pas d'interférence

6. Répétabilité et reproductibilité

La répétabilité et la reproductibilité du Panbio™ COVID-19 Ag Rapid Test Device ont été établies à l'aide de panels de référence internes contenant des échantillons négatifs et une gamme d'échantillons positifs.. Aucune différence n'a été observée à l'intérieur des séries, entre les séries, entre les lots, entre les sites et entre les jours.

PREPARATION

1 Laisser tous les composants du kit atteindre une température comprise entre 15 et 30 ° C avant de procéder au test pendant 30 minutes.
Remarque: le professionnel de santé doit se conformer aux directives de sécurité personnelle, y compris l'utilisation d'équipements de protection individuelle.

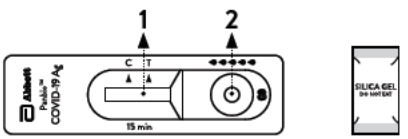
2 **Ouvrir la boite et rechercher les éléments suivants**
1. Test avec dessiccateur dans une pochette individuelle en aluminium
2. Solution tampon
3. Tube d'extraction
4. Bouchon pour les tubes d'extraction
5. Écouvillon de contrôle positif
6. Écouvillon de contrôle négatif
7. Écouvillons stérilisés pour le prélèvement nasal
8. Porte tubes
9. Guide de référence rapide
10. Notice d'utilisation

3 Lire attentivement ces instructions avant d'utiliser le kit de Panbio™ COVID-19 Ag Rapid Test Device.

4 Regarder la date d'expiration de la boîte du kit. Si la date d'expiration est dépassée, utiliser un autre kit.

5 **Ouvrir la pochette en aluminium et rechercher les éléments suivants:**
1. Fenêtre de résultats
2. Échantillon bien

Ensuite, étiqueter l'appareil avec l'identifiant du patient.



●●●●●: 5 gouttes de l'échantillon extrait

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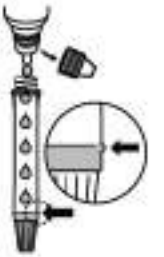
PROCEDURE

1 Tenir le flacon de tampon verticalement et remplir le tube d'extraction avec du liquide tampon jusqu'à ce qu'il s'écoule jusqu'à la ligne de remplissage du tube d'extraction (300 µl).



⚠ **Attention:** Si la quantité de tampon est excessive ou insuffisante, un résultat de test incorrect peut se produire.

2 Placer le tube d'extraction dans le support de tubes.

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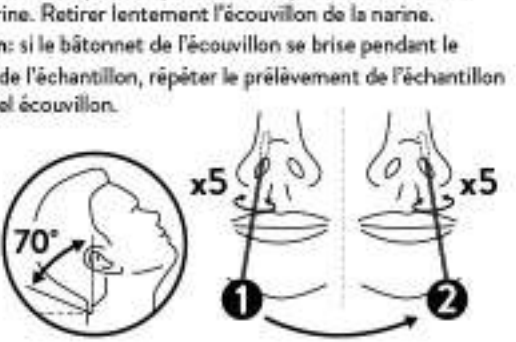
3 Incliner la tête du patient de 70 degrés en arrière. Tout en tournant doucement l'écouvillon, insérer l'écouvillon d'environ 2 cm dans la narine (jusqu'à ce que la résistance soit rencontrée au niveau des cornets).

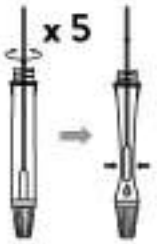
Faire tourner l'écouvillon cinq fois contre la paroi nasale. En utilisant le même écouvillon, répéter la procédure de prélèvement dans la deuxième narine. Retirer lentement l'écouvillon de la narine.

⚠ **Attention:** si le bâtonnet de l'écouvillon se brise pendant le prélèvement de l'échantillon, répéter le prélèvement de l'échantillon avec un nouvel écouvillon.



PROCEDURE

4 Insérer l'échantillon sur écouvillon dans le tube d'extraction. Faire tourbillonner la pointe de l'écouvillon dans le fluide tampon à l'intérieur du tube d'extraction, en poussant dans la paroi du tube d'extraction au moins cinq fois, puis faire sortir l'écouvillon en pressant le tube d'extraction avec vos doigts.

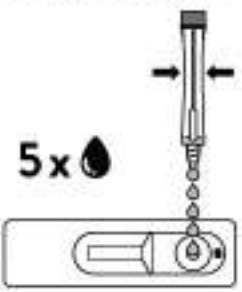


5 Casser l'écouvillon au point de rupture et fermer le capuchon du tube d'extraction.

6 Ouvrir le capuchon de la buse à goutte au bas du tube d'extraction.

7 Distribuer verticalement 5 gouttes d'échantillons extraits dans le puits d'échantillon (S) de l'appareil. Ne pas manipuler ni déplacer le dispositif de test tant que le test n'est pas terminé et prêt pour la lecture.

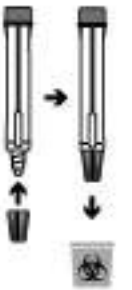
⚠ **Attention:** les bulles qui se produisent dans le tube d'extraction peuvent conduire à des résultats inexacts. Si vous ne parvenez pas à créer suffisamment de gouttes, cela peut être dû à un colmatage de la buse de distribution. Secouer doucement le tube pour libérer le blocage jusqu'à ce que vous observiez la formation de gouttes libres.



FRENCH

PROCEDURE

8 Fermer la buse et jeter le tube d'extraction avec l'écouvillon usagé conformément à vos réglementations locales et au protocole d'élimination des déchets biologiques.



9 Démarrer le minuteur, lire le résultat à 15 minutes. Ne pas lire le résultat après 20 minutes.

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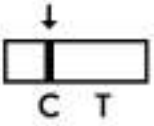
10 L'Elimination des appareils usagés se fait conformément à la réglementation locale en vigueur et selon le protocole d'élimination des déchets dangereux.

INTERPRETATION DU TEST

NEGATIF

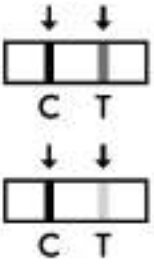
La présence seule de la ligne de contrôle (C) et aucune ligne de test (T) dans la fenêtre de résultat indique un résultat négatif.



POSITIF

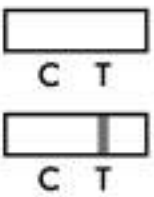
La présence de la ligne de test (T) et de la ligne de contrôle (C) dans la fenêtre de résultat, quelle que soit la ligne qui apparaît en premier, indique un résultat positif.

⚠ **Attention:** la présence d'une ligne de test (T), aussi faible soit-elle, indique un résultat positif.



INVALIDE

Si la ligne de contrôle (C) n'est pas visible dans la fenêtre de résultat après l'exécution du test, le résultat est considéré comme invalide. Les instructions peuvent ne pas avoir été suivies correctement. Il est recommandé de relire la notice d'utilisation avant de tester à nouveau l'échantillon avec un nouveau dispositif de test.



FRENCH

A proposito del test

IT

Introduzione

La patologia provocata da Coronavirus (COVID-19) è una malattia infettiva causata da un coronavirus appena scoperto, la sindrome respiratoria acuta grave coronavirus 2 (SARS-CoV-2)[1]. Il SARS-CoV-2 è un β-coronavirus, che è un virus a RNA a filamento positivo, incapsulato e non segmentato[2]. Si diffonde per trasmissione da uomo a uomo tramite goccioline o contatto diretto, ed è stato stimato che l'infezione ha un periodo medio di incubazione di 6,4 giorni e un numero di riproduzione di base di 2,24-3,58. Tra i pazienti con polmonite causata dalla SARS-CoV-2, la febbre era il sintomo più comune, seguita dalla tosse[3]. I principali test IVD utilizzati per COVID-19 utilizzano la real-time reverse transcriptase-polymerase chain reaction (RT-PCR) che richiede alcune ore[4]. La disponibilità di un test diagnostico point-of-care rapido ed economico è fondamentale per supportare gli operatori sanitari nella diagnosi dei pazienti e prevenire un'ulteriore diffusione del virus[5]. I test antigenici avranno un ruolo fondamentale nella lotta contro il COVID-19[6].

Principio del test

Il dispositivo Panbio™ COVID-19 Ag Rapid Test Device contiene una striscia di membrana che è pre-rivestita con anticorpo anti-SARS-CoV-2 immobilizzato sulla linea di test e un anticorpo monoclonale di topo anti-IgY di pollo sulla linea di controllo. Due tipi di coniugati (IgG umane specifiche per SARS-CoV-2 Ag coniugate con oro (si lega alla proteina nucleocapside) e IgY di pollo coniugate con oro) migrano cromatograficamente verso l'alto sulla membrana e reagiscono rispettivamente con l'anticorpo anti-SARS-CoV-2 e con l'anticorpo monoclonale di topo anti-IgY di pollo pre-rivestito. Per un risultato positivo, le IgG umane specifiche per SARS-CoV-2 Ag coniugate con oro e l'anticorpo anti-SARS-CoV-2 formeranno una linea di test nella finestra dei risultati. Né la linea del test né la linea di controllo sono visibili nella finestra dei risultati prima dell'applicazione del campione del paziente. Una linea di controllo visibile è necessaria per indicare che il risultato del test è valido.

Uso previsto

Panbio™ COVID-19 Ag Rapid Test Device è un test rapido diagnostico *in vitro* per la ricerca qualitativa dell'antigene SARS-CoV-2 (Ag) in campioni umani da tampone nasale provenienti da individui che soddisfano criteri clinici e/o epidemiologici COVID-19. Il dispositivo Panbio™ COVID-19 Ag Rapid Test Device è solo per uso professionale ed è destinato ad essere utilizzato come ausilio nella diagnosi dell'infezione da SARS-CoV-2. Il prodotto può essere utilizzato in qualsiasi ambiente, di laboratorio e non, che soddisfi i requisiti specificati nelle Istruzioni per l'uso e nella normativa locale.

Il test fornisce risultati preliminari. I risultati negativi non precludono l'infezione

da SARS-CoV-2 e non possono essere utilizzati come unica base per il trattamento o per altre decisioni di gestione. I risultati negativi devono essere combinati con le osservazioni cliniche, l'anamnesi del paziente e le informazioni epidemiologiche. Il test non è destinato ad essere utilizzato come test di screening per SARS-CoV-2 sui donatori.

Materiali forniti

- 25 Dispositivi di test confezionati singolarmente in buste di alluminio con essiccante
- Buffer (1 x 9 ml/flacone)
- 25 Provette di estrazione
- 25 Tappi per provette di estrazione
- 1 Tampone di controllo positivo
- 1 Tampone di controllo negativo
- 25 Tamponi nasali sterilizzati per la raccolta del campione
- 1 Rack portaprovette
- 1 Guida rapida di riferimento
- 1 Istruzioni per l'uso

Materiali richiesti ma non forniti

- Dispositivi di protezione individuale in base alle raccomandazioni locali (ad esempio abito/protezione da laboratorio, maschera facciale, scudo facciale/occhialini e guanti), Timer, Contenitore per rifiuti a rischio biologico

Principi attivi dei componenti principali

- **1 Dispositivo di test** Coniugato d'oro: IgG umane specifiche verso SARS-CoV-2 Ag oro colloidale e IgY di pollo – oro colloidale. Linea di test: monoclonale di topo anti-SARS-CoV-2 Linea di controllo: monoclonale di topo anti- IgY di pollo
- **Buffer** Tricina , Cloruro di sodio, Tween 20 , Azoturo di sodio (<0,1%), Proclin 300

Conservazione e Stabilità

1. Il kit deve essere conservato a una temperatura compresa tra 2 e 30 °C. Non congelare il kit o i suoi componenti.
   Nota: Se conservato in frigorifero, tutti i componenti del kit devono essere portati a temperatura ambiente (15-30 °C) per almeno 30 minuti prima di eseguire il test. Non aprire il sacchetto mentre i componenti vengono portati a temperatura ambiente.

2. Il flacone del Buffer può essere aperto e richiuso ad ogni test. Il tappo del Buffer deve essere chiuso saldamente dopo ogni utilizzo. Il Buffer è stabile fino alla data di scadenza se conservato a 2-30 °C.
3. Eseguire l'analisi immediatamente dopo aver rimosso il dispositivo di test dalla busta di alluminio.
4. Non utilizzare il kit oltre la data di scadenza.
5. La durata di conservazione del kit è quella indicata sulla confezione esterna.
6. Non utilizzare il kit se la confezione è danneggiata o il sigillo è rotto.
7. I campioni con tampone diretto devono essere testati immediatamente dopo il prelievo. Se non è possibile effettuare il test immediatamente, il tampone di raccolta può essere conservato in una provetta di estrazione riempita con Buffer (300 µl) a temperatura ambiente (15-30 °C) per un massimo di due ore prima del test.

Avvertenze

1. Solo per uso diagnostico *in vitro*. Non riutilizzare il dispositivo di test e i componenti del kit.
2. Queste istruzioni devono essere rigorosamente seguite da un professionista sanitario qualificato per ottenere risultati accurati. Tutti gli utenti devono leggere le istruzioni prima di eseguire un test.
3. Non mangiare o fumare mentre si maneggiano i campioni.
4. Indossare guanti protettivi durante la manipolazione dei campioni e lavarsi accuratamente le mani dopo averli maneggiati.
5. Evitare spruzzi o la formazione di aerosol di campione e di Buffer.
6. Pulire accuratamente le fuoriuscite utilizzando un disinfettante appropriato.
7. Decontaminare e smaltire tutti i campioni, i kit di reazione e i materiali potenzialmente contaminati (ad es. tampone di prelievo, provetta di estrazione, dispositivo di test) in un contenitore a rischio biologico come se fossero rifiuti infettivi e smaltirli secondo le normative locali vigenti.
8. Non mescolare o scambiare campioni diversi.
9. Non mescolare reagenti di lotti diversi o di altri prodotti.
10. Non conservare il kit alla luce diretta del sole.
11. Per evitare la contaminazione, quando si apre la busta non toccare la testa del tampone di raccolta in dotazione.
12. I tamponi sterilizzati devono essere utilizzati solo per la raccolta di campioni nasali.
13. Per evitare la contaminazione incrociata, non riutilizzare i tamponi sterili per la raccolta dei campioni.
14. Non diluire il tampone raccolto con nessuna soluzione eccetto il Buffer di estrazione fornito.

15. Il tampone contiene <0,1% di azoturo di sodio come conservante che può essere tossico se ingerito. Se smaltito attraverso un lavandino, sciacquare con abbondante acqua.[7]
16. Non utilizzare il tampone di controllo positivo o negativo per la raccolta dei campioni.

Procedura del test (Fare riferimento alla Figura)

Campioni da tampone nasale

Nota: Il personale sanitario deve rispettare le linee guida di sicurezza individuale, tra cui l'uso di dispositivi di protezione individuale.

Preparazione del test

1. Lasciare che tutti i componenti del kit raggiungano una temperatura tra i 15 e i 30 °C per 30 minuti prima del test.
2. Rimuovere il dispositivo di test dal sacchetto di alluminio prima dell'uso. Posizionarlo su una superficie piana, orizzontale e pulita.
3. Tenere il flacone del Buffer in posizione verticale e riempire la provetta di estrazione con il liquido fino al raggiungimento della linea di riempimento della provetta di estrazione (300 µl).
   ⚠ **Attenzione:** Se la quantità di tampone è eccessiva o insufficiente, può verificarsi un risultato del test non corretto.
4. Posizionare la provetta di estrazione nel portaprovette.

Raccolta del campione ed Estrazione

1. Inclinare la testa del paziente indietro di 70 gradi. Mentre si ruota delicatamente il tampone, inserire il tampone per meno di un pollice (circa 2 cm) nella narice (fino a quando non si incontra la resistenza nei turbinati).
2. Ruotare il tampone cinque volte contro la parete nasale e rimuoverlo lentamente dalla narice.
3. Utilizzando lo stesso tampone ripetere la procedura di raccolta con la seconda narice.
   ⚠ **Attenzione:** se il bastoncino del tampone si rompe durante la raccolta del campione, ripetere la raccolta del campione con un nuovo tampone.
4. Ruotare la punta del tampone nel liquido all'interno della provetta di estrazione, premendolo sulla parete della provetta di estrazione almeno cinque volte e poi spremere il tampone strizzando la provetta di estrazione con le dita.
5. Spezzare il tampone nel punto di rottura e chiudere il tappo della provetta di estrazione.

Reazione con dispositivo di test

1. Aprire il tappo dell'ugello posizionato nella parte inferiore della provetta di estrazione.

2. Dispensare 5 gocce di campione estratto verticalmente nel pozzetto del campione (S) sul dispositivo. Non maneggiare o spostare il dispositivo fino a quando il test non è completo e pronto per la lettura.
   ⚠ **Attenzione:** La comparsa di bolle nella provetta di estrazione può portare a risultati imprecisi. Se non si riuscisse ad ottenere un numero di gocce sufficienti, ciò potrebbe essere causato dall'intasamento dell'ugello di erogazione. Agitare delicatamente la provetta per rimuovere l'ostruzione fino a osservare la formazione di goccia libera.
3. Chiudere l'ugello e smaltire la provetta di estrazione contenente il tampone usato secondo le normative locali e il protocollo di smaltimento dei rifiuti biologici.
4. Avviare il timer. Leggere il risultato a 15 minuti. Non leggere i risultati dopo 20 minuti.
5. Smaltire il dispositivo usato in base alle normative locali e al protocollo di smaltimento dei rifiuti per rischio biologico.

Tampone di controllo positivo / negativo
⚠ **Attenzione:** solo per l'uso del controllo. Non utilizzare il tampone di controllo positivo o negativo per la raccolta del campione.

Nota: fare riferimento alla sezione Controllo Qualità Esterno di queste Istruzioni per l'utilizzo e per la frequenza di test di tamponi di controllo qualità esterno.

1. Tenere il flacone di buffer verticalmente e riempire la provetta di estrazione con il liquido fino alla linea di riempimento della provetta di estrazione (300 µl).
   ⚠ **Attenzione:** Se la quantità di buffer è eccessiva o insufficiente, potrebbe verificarsi un risultato del test errato.
2. Posizionare la provetta di estrazione nel rack portaprovette.
3. Inserire il tampone di controllo positivo o negativo nel liquido all'interno della provetta di estrazione e immergere il tampone per 1 minuto. Ruotare la punta del tampone di controllo nel liquido all'interno della provetta di estrazione, spingendo nella parete della provetta di estrazione almeno cinque volte e poi premere il tampone strizzando la provetta di estrazione con le dita.
4. Smaltire il tampone di controllo usato in conformità con il protocollo di smaltimento dei rifiuti per rischio biologico.
5. Chiudere il tappo della provetta di estrazione.
6. Seguire la procedura di cui sopra [Reazione con dispositivo di test].

Interpretazione del test (Fare riferimento alla figura)

1. **Risultato negativo:** la presenza della sola linea di controllo (C) e nessuna

linea di test (T) all'interno della finestra del risultato indica un risultato negativo.

2. **Risultato positivo:** la presenza della linea di test (T) e della linea di controllo (C) all'interno della finestra dei risultati, indipendentemente dalla linea visualizzata per prima, indica un risultato positivo.
   ⚠ **Attenzione:** la presenza di qualsiasi linea di test (T), non importa quanto debole, indica un risultato positivo.
3. **Risultato non valido:** se la linea di controllo (C) non è visibile all'interno della finestra dei risultati dopo l'esecuzione del test, il risultato viene considerato non valido.

Limitazioni del test

1. Il contenuto di questo kit deve essere utilizzato per la rilevazione professionale e qualitativa dell'antigene SARS-CoV-2 da tampone nasale. Altri tipi di campioni possono portare a risultati errati e non devono essere utilizzati.
2. Il mancato rispetto delle istruzioni per la procedura di test e dell'interpretazione dei risultati possono influire negativamente sulle prestazioni del test e/o produrre risultati non validi.
3. Un risultato negativo può verificarsi se il campione è stato raccolto, estratto o trasportato in modo improprio. Un risultato negativo del test non esclude la possibilità di infezione da SARS-CoV-2 e deve essere confermato dalla coltura virale o da un saggio molecolare.
4. I risultati positivi dei test non escludono le co-infezioni con altri agenti patogeni.
5. I risultati dei test devono essere valutati in concomitanza con altri dati clinici a disposizione del medico.
6. Leggere i risultati del test prima di 15 minuti o dopo 20 minuti può dare risultati errati.
7. Panbio™ COVID-19 Ag Rapid Test Device non è destinato a rilevare virus difettoso (non infettivo) durante le fasi successive di mutazione virale che potrebbero essere rilevate dai test molecolari PCR.[8]
8. Risultati positivi possono verificarsi in caso di infezione da SARS-CoV.

Controllo qualità

1. **Controllo di qualità interno:**
   Il dispositivo di test ha una linea di test (T) e una linea di controllo (C) sulla superficie del dispositivo di test. Né la linea di test né la linea di controllo sono visibili nella finestra dei risultati prima di applicare un campione. La linea di controllo viene utilizzata per il controllo procedurale e deve sempre apparire se la procedura di test viene eseguita correttamente e se i reagenti del test della linea di controllo funzionano.

2. Controllo esterno di qualità:
I controlli sono formulati e fabbricati in modo specifico per garantire le prestazioni di Panbio™ COVID-19 Ag Rapid Test Device e vengono utilizzati per verificare la capacità dell'utente di eseguire correttamente il test e interpretare i risultati. Il Controllo Positivo produrrà un risultato positivo del test ed è stato fabbricato per produrre una linea di test visibile (T). Il controllo negativo produrrà un risultato negativo del test.
Una buona pratica di laboratorio suggerisce l'uso di controlli positivi e negativi per assicurarsi che:

- I reagenti del test stanno funzionando e
- Il test viene eseguito correttamente.

I controlli esterni di qualità possono essere eseguiti in una delle seguenti circostanze:

- Da un nuovo operatore prima di eseguire test su campioni di pazienti,
- Quando si riceve una nuova spedizione di test,
- A intervalli periodici come dettato dai requisiti locali, e/o dalle procedure di Controllo Qualità dell'utente.

Caratteristiche delle performance

1. Valutazione esterna di Panbio™ COVID-19 Ag Rapid Test Device
Le prestazioni cliniche di Panbio™ COVID-19 Ag Rapid Test Device sono state determinate testando 104 campioni positivi da tampone nasale e 404 campioni negativi per l'antigene SARS-CoV-2 (Ag) per avere una sensibilità del 98,1% (95% CI: 93,2-99,8%) e una specificità del 99,8% (95% CI: 98,6-100,0%). I campioni clinici sono stati determinati come positivi o negativi utilizzando un metodo di riferimento FDA EUA RT-PCR.

Risultati di Panbio™ COVID-19 Ag Rapid Test Device

		Risultato del test nasale PCR		
		Positivo	**Negativo**	**Totale**
Risultati di Panbio™ COVID-19 Ag Rapid Test Device (campione da tampone nasale)	**Positivo**	102	1	103
	Negativo	2	403	405
	Totale	104	404	508
		Sensibilità	Specificità	Percentuale di concordanza complessiva
		98,1% [93,2%;99,8%]	**99,8%** [98,6%;100,0%]	**99,4%** [98,3%;99,9%]

- I dati di performance sono stati calcolati tramite uno studio su individui sospettati di esposizione al COVID-19 o che hanno presentato sintomi

negli ultimi 7 giorni.

- La stratificazione dei campioni positivi post insorgenza di sintomi o sospetta esposizione tra 0-3 giorni ha una sensibilità del 100,0% (n=46) e a 4-7 giorni ha una sensibilità di 96,6% (n=58).
- La concordanza positiva di Panbio™ COVID-19 Ag Rapid Test Device è più alta con campioni con "valori Ct ≤ 33 con una sensibilità del 99,0%. Come suggerito nei riferimenti 8 e 9, i pazienti con valori Ct >33 non sono più contagiosi.[8, 9]
- Il dato sulla prestazione clinica è stato calcolato anche rispetto ai campioni da tampone nasofaringeo utilizzando un riferimento FDA EUA RT-PCR e ha una sensibilità del 91,1% (95% CI: 84,2-95,6%) e specificità del 99,7% (95% CI: 98,6-100,0%).

2. Limite di rilevamento

Panbio™ COVID-19 Ag Rapid Test Device è in grado di rilevare 2,5X10[1,8] $TCID_{50}$/ml di SARS-CoV-2 che è stato isolato da un paziente confermato COVID-19 in Corea.

3. Effetto gancio

Non vi è alcun effetto gancio a 1,0x10[5,8] $TCID_{50}$/ml di SARS- CoV-2 che è stato isolato da un paziente confermato COVID-19 in Corea.

4. Reattività crociata

La reattività crociata di Panbio™ COVID-19 Ag Rapid Test Device è stata valutata testando 28 virus e altri 13 microrganismi. Le concentrazioni di test finali di virus e altri microrganismi sono documentate nella tabella seguente. I seguenti virus e altri microrganismi, ad eccezione della Nucleoproteina SARS-coronavirus umana, non hanno alcun effetto sui risultati dei test di Panbio™ COVID-19 Ag Rapid Test Device. Panbio™ COVID-19 Ag Rapid Test Device ha reattività crociata con Nucleoproteina SARS-coronavirus umana ad una concentrazione di 25 ng/ml o più perché SARS-CoV ha un'omologia elevata (79,6%) al SARS-CoV-2.

No,	Tipi di campione	Sostanza di cross-reazione	Concentrazione dei test finali	Risultato del test
1	Virus	Adenovirus Tipo 1	2,2 X 10^7 $TCID_{50}$/ml	Nessuna cross reazione
2		Adenovirus Tipo 5	5,71 X 10^8 $TCID_{50}$/ml	Nessuna cross reazione
3		Adenovirus Tipo 7	2,86 X 10^9 $TCID_{50}$/ml	Nessuna cross reazione
4		Enterovirus (EV68)	2,81 X 10^7 $TCID_{50}$/ml	Nessuna cross reazione
5		Echovirus2	1,0 X $10^{6,5}$ $TCID_{50}$/ml	Nessuna cross reazione

No,	Tipi di campione	Sostanza di cross-reazione	Concentrazione dei test finali	Risultato del test
6	Virus	Echovirus11	5,0 $X10^{6,25}$ $TCID_{50}$/ml	Nessuna cross reazione
7		Enterovirus D68	2,81 $X\ 10^{7}$ $TCID_{50}$/ml	Nessuna cross reazione
8		Herpes virus umano (HSV) 1	5,0 $X\ 10^{7,5}$ $TCID_{50}$/ml	Nessuna cross reazione
9		Herpes virus umano (HSV) 2	5,0 $X\ 10^{5,75}$ $TCID_{50}$/ml	Nessuna cross reazione
10		Virus Parotite Ag	1,58 $X\ 10^{5}$ $TCID_{50}$/ml	Nessuna cross reazione
11		Virus Influenza A (H1N1) Specie (A/Virginia/ ATCC1/2009)	3,71 $X\ 10^{5}$ PFU/ml	Nessuna cross reazione
12		Virus Influenza A (H1N1) Specie (A/WS/33)	5,0 $X\ 10^{7,25}$ $TCID_{50}$/ml	Nessuna cross reazione
13		Virus Influenza A(H1N1) Specie (A/ California/08/2009/pdm09)	1,6 $X\ 10^{8}$ $TCID_{50}$/ml	Nessuna cross reazione
14		Virus Influenza B Specie (B/ Lee/40)	5,0 $X\ 10^{6,25}$ $TCID_{50}$/ml	Nessuna cross reazione
15		Parainfluenza Tipo 1	3,06 $X\ 10^{8}$ $TCID_{50}$/ml	Nessuna cross reazione
16		Parainfluenza Tipo 2	5,0 $X\ 10^{5}$ $TCID_{50}$/ml	Nessuna cross reazione
17		Parainfluenza Tipo 3	6,6 $X\ 10^{7}$ $TCID_{50}$/ml	Nessuna cross reazione
18		Parainfluenza Tipo 4A	2,81 $X\ 10^{7}$ $TCID_{50}$/ml	Nessuna cross reazione
19		Virus respiratorio sinciziale (RSV) tipo A	4,22 $X\ 10^{5}$ $TCID_{50}$/ml	Nessuna cross reazione
20		Virus respiratorio sinciziale (RSV) tipo B	5,62 $X\ 10^{5}$ $TCID_{50}$/ml	Nessuna cross reazione
21		Rinovirus A16	1,26 $X\ 10^{6}$ $TCID_{50}$/ml	Nessuna cross reazione
22		HCoV-HKU1	1,5mg/ml	Nessuna cross reazione
23		HCoV-NL63	1,7 $X\ 10^{5}$ $TCID_{50}$/ml	Nessuna cross reazione

No,	Tipi di campione	Sostanza di cross-reazione	Concentrazione dei test finali	Risultato del test
24	Virus	HCoV-OC43	8,9 X 10^5 $TCID_{50}$/ml	Nessuna cross reazione
25		HCoV-229E	1,51 X 10^6 $TCID_{50}$/ml	Nessuna cross reazione
26		Nucleoproteina SARS-coronavirus umana	25ng/ml	Cross reazione
27		Nucleoproteina MERS-CoV	0,25mg/ml	Nessuna cross reazione
28		Metapneumovirus umano (hMPV) 16 Tipo A1	1,51 X 10^6 $TCID_{50}$/ml	Nessuna cross reazione

No,	Tipi di campione	Sostanza di cross-reazione	Concentrazione dei test finali	Risultato del test
1	Altro Microorganismo	*Staphylococcus saprophyticus*	1,9 X 10^7 CFU/ml	Nessuna cross reazione
2		*Neisseria sp,(Neisseria lactamica)*	1,7 X 10^8 CFU/ml	Nessuna cross reazione
3		*Staphylococcus haemolyticus*	3,5 X 10^9 CFU/ml	Nessuna cross reazione
4		*Streptococcus salivarius*	1,96 X 10^7 CFU/ml	Nessuna cross reazione
5		*Hemophilus parahaemolyticus*	2,2 X 10^8 CFU/ml	Nessuna cross reazione
6		*Proteus vulgaris*	7,2 X 10^6 CFU/ml	Nessuna cross reazione
7		*Moraxella catarrhalis*	4,7 X 10^7 CFU/ml	Nessuna cross reazione
8		*Klebsiella pneumoniae*	5,0 X 10^6 CFU/ml	Nessuna cross reazione
9		*Fusobacterium necrophorum*	1,75 X 10^8 CFU/ml	Nessuna cross reazione
10		*Mycobacterum tuberculosis*	10mg/ml	Nessuna cross reazione
11		Lavaggio nasale umano in pool	N/A*	Nessuna cross reazione

No,	Tipi di campione	Sostanza di cross-reazione	Concentrazione dei test finali	Risultato del test
12	Altro Microorganismo	*Streptococcus pyogenes*	3,6 X 10^7 CFU/ml	Nessuna cross reazione
13		*Mycoplasma pneumoniae*	4 X 10^8 CFU/ml	Nessuna cross reazione

** Nessuna concentrazione fornita dal fornitore. È stata testata una soluzione di stock non diluito.*

5. Sostanze interferenti

Le seguenti 43 sostanze potenzialmente interferenti non hanno alcun impatto su Panbio™ COVID-19 Ag Rapid Test Device. La concentrazione finale di test delle sostanze interferenti è documentata nella tabella sotto.

No,	Tipi di campione	Sostanze interferenti	Concentrazione dei test finali	Risultato del test
1	Sostanza endogena	Mucina	0,5%	Nessuna interferenza
2		Emoglobina	100 mg/L	Nessuna interferenza
3		Trigliceridi	1,5 mg/L	Nessuna interferenza
4		Itterizia (Bilirubina)	40 mg/dL	Nessuna interferenza
5		Fattore reumatoide	200 IU/ml	Nessuna interferenza
6		Anticorpo anti-nucleo	>1:40	Nessuna interferenza
7		Gravidanza	Diluizione 1:10	Nessuna interferenza
8	Sostanza esogena	Etere glicerolo guaicolato	1 µg/ml	Nessuna interferenza
9		Albuterolo	0,005 mg/dL	Nessuna interferenza
10		Efedrina	0,1 mg/ml	Nessuna interferenza
11		Clorfenamina	0,08 mg/dL	Nessuna interferenza
12		Difenidramina	0,08 mg/dL	Nessuna interferenza
13		Ribavirina	26,7 µg /ml	Nessuna interferenza
14		Oseltamivir	0,04 mg/dL	Nessuna interferenza
15		Zanamivir	17,3 µg /ml	Nessuna interferenza
16		Fenilefrina cloridrato	15% v/v	Nessuna interferenza
17		Oximetazolina cloridrato	15% v/v	Nessuna interferenza
18		Amoxicillina	5,4 mg/dL	Nessuna interferenza
19		Acido acetilsalicilico	3 mg/dL	Nessuna interferenza
20		Ibuprofene	21,9 mg/dL	Nessuna interferenza
21		Clorotiazide	2,7 mg/dL	Nessuna interferenza
22		Indapamide	140 ng/ml	Nessuna interferenza

No,	Tipi di campione	Sostanze interferenti	Concentrazione dei test finali	Risultato del test
23	Sostanza esogena	Glimepiride (Sulfaniluree)	0,164 mg/dL	Nessuna interferenza
24		Acarbosio	0,03 mg/dL	Nessuna interferenza
25		Ivermectina	4,4 mg/L	Nessuna interferenza
26		Lopinavir	16,4 µg/L	Nessuna interferenza
27		Ritonavir	16,4 µg/L	Nessuna interferenza
28		Clorochina fosfato	0,99 mg/L	Nessuna interferenza
29		Cloruro di sodio con conservanti	4,44 mg/ml	Nessuna interferenza
30		Beclometasone	4,79 ng/ml	Nessuna interferenza
31		Desametasone	0,6 µg/ml	Nessuna interferenza
32		Flunisolide	0,61 µg/ml	Nessuna interferenza
33		Triamcinolone	1,18 ng/ml	Nessuna interferenza
34		Budesonide	2,76 ng/ml	Nessuna interferenza
35		Mometasone	1,28 ng/ml	Nessuna interferenza
36		Fluticasone	2,31 ng/ml	Nessuna interferenza
37		Zolfo	9,23 µg/ml	Nessuna interferenza
38		Benzocaina	0,13 mg/ml	Nessuna interferenza
39		Mentolo	0,15 mg/ml	Nessuna interferenza
40		Mupirocina	10 µg/ml	Nessuna interferenza
41		Tobramicina	24,03 µg/ml	Nessuna interferenza
42		Biotina	1,2 µg/ml	Nessuna interferenza
43		HAMA	63,0 ng/ml	Nessuna interferenza

6. Ripetibilità e riproducibilità

La ripetibilità e la riproducibilità di Panbio™ COVID-19 Ag Rapid Test Device sono state stabilite utilizzando pannelli di riferimento interni contenenti campioni positivi alti, positivi medi, positivi deboli e negativi. Non sono state osservate differenze all'interno della serie, tra le serie, tra i lotti, tra i siti e tra i giorni.

PREPARAZIONE

1 Consentire a tutti i componenti del kit di raggiungere una temperatura tra 15-30°C per 30 minuti prima dell'esecuzione del test.
Nota: Gli operatori sanitari devono rispettare le linee guida per la sicurezza personale, incluso l'uso di dispositivi di protezione personale.

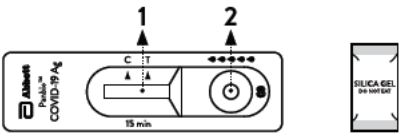
2 **Aprire la confezione e cercare quanto segue:**
1. Dispositivo di test confezionato singolarmente in busta di alluminio con essiccante
2. Buffer
3. Provetta di estrazione
4. Tappo della provetta di estrazione
5. Tampone di controllo positivo
6. Tampone di controllo negativo
7. Tamponi nasali sterilizzati per la raccolta del campione
8. Rack portaprovette
9. Guida rapida di riferimento
10. Istruzioni per l'uso

3 Leggere attentamente queste istruzioni prima di utilizzare il kit Panbio™ COVID-19 Ag Rapid Test Device.

4 Guardare la data di scadenza della scatola del kit. Se la data di scadenza è trascorsa, usare un altro kit.

5 **Aprire la busta di alluminio e cercare quanto segue:**
1. Finestra dei risultati
2. Pozzetto del campione

Quindi, etichettare il dispositivo con l'identificatore del paziente.

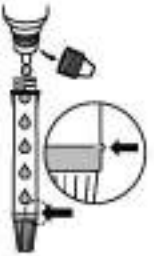


●●●●●: 5 gocce del campione estratto

PROCEDURA DEL TEST

1 Tenere il flacone del buffer verticalmente e riempire la provetta di estrazione fino alla linea di riempimento della provetta di estrazione (300 µl).

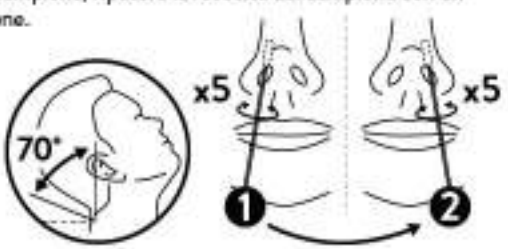
⚠ **Attenzione:** Se la quantità di buffer è eccessiva o insufficiente, potrebbe verificarsi un risultato di test errato.



2 Posizionare la provetta di estrazione nel rack portaprovette.

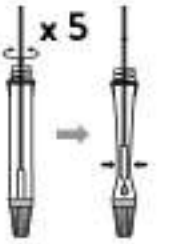
3 Inclinare la testa del paziente indietro di 70 gradi. Mentre si ruota delicatamente il tampone, inserire il tampone per meno di un pollice (circa 2 cm) nella narice (fino a quando non si incontra la resistenza nei turbinati). Ruotare il tampone cinque volte contro la parete nasale. Utilizzando lo stesso tampone ripetere la procedura di raccolta con la seconda narice. Rimuovere lentamente il tampone dalla narice.

⚠ **Attenzione:** se il bastoncino del tampone si rompe durante la raccolta del campione, ripetere la raccolta del campione con un nuovo tampone.



PROCEDURA DEL TEST

4 Inserire il tampone di campionamento nella provetta di estrazione. Ruotare la punta del tampone nel liquido all'interno della provetta di estrazione, spingendo sulla parete della provetta di estrazione almeno cinque volte e poi premere il tampone strizzando la provetta di estrazione con le dita.

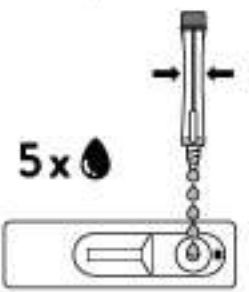


5 Spezzare il tampone nel punto di rottura e chiudere il tappo della provetta di estrazione.

6 Aprire il tappo dell'ugello posizionato nella parte inferiore della provetta di estrazione.

7 Dispensare 5 gocce di campione estratto verticalmente nel pozzetto del test (S) sul dispositivo. Non maneggiare o spostare il dispositivo fino a quando il test non è completo e pronto per la lettura.

⚠ **Attenzione:** La comparsa di bolle nella provetta di estrazione può portare a risultati imprecisi. Se non si riuscisse ad ottenere un numero di gocce sufficienti, ciò potrebbe essere causato dall'intasamento dell'ugello di erogazione. Agitare delicatamente la provetta per rimuovere l'ostruzione fino a osservare la formazione di goccia libera.



PROCEDURA DEL TEST

8 Chiudere l'ugello e smaltire la provetta di estrazione contenente il tampone usato in base alle normative locali e al protocollo di smaltimento dei rifiuti biologici.

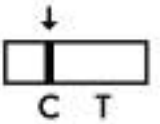
9 Avviare il timer. Leggere il risultato a 15 minuti. Non leggere i risultati dopo 20 minuti.

10 Smaltire il dispositivo usato in base alle normative locali e al protocollo di smaltimento dei rifiuti biologici.

INTERPRETAZIONE DEL TEST

NEGATIVO

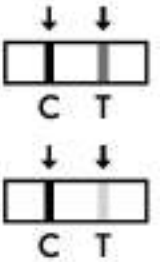
La presenza della sola linea di controllo (C) e nessuna linea di test (T) all'interno della finestra dei risultati indica un risultato negativo.



POSITIVO

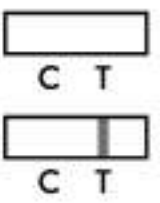
La presenza della linea di test (T) e della linea di controllo (C) all'interno della finestra dei risultati, indipendentemente dalla linea visualizzata per prima, indica un risultato positivo.

⚠ **Attenzione:** La presenza di qualsiasi linea di test (T), non importa quanto debole, indica un risultato positivo.



INVALIDO

Se la linea di controllo (C) non è visibile all'interno della finestra dei risultati dopo l'esecuzione del test, il risultato viene considerato non valido. Le istruzioni potrebbero non essere state seguite correttamente. Si consiglia di leggere nuovamente il foglietto illustrativo prima di testare nuovamente il campione con un nuovo dispositivo di test.



Sobre o Teste

PT

Introdução

A doença do Coronavírus (COVID-19) é uma doença infecciosa causada por um coronavírus recém-descoberto, coronavírus da síndrome respiratória aguda grave 2 (SARS-CoV-2)[1]. O SARS-CoV-2 é um β-coronavírus, que é um vírus de RNA com envelope de sentido positivo não segmentado[2]. É disseminado por transmissão de humano para humano através de gotículas ou contato direto, e estima-se que a infecção tenha um período médio de incubação de 6,4 dias e um número básico de reprodução de 2,24–3,58. Entre os pacientes com pneumonia causada por SARS-CoV-2, a febre foi o sintoma mais comum, seguido pela tosse[3]. Os principais ensaios IVD utilizados para COVID-19 empregam a reação em cadeia da polimerase-transcriptase reversa em tempo real (RT-PCR) que leva algumas horas[4]. A disponibilidade de um teste de diagnóstico rápido e econômico é fundamental para permitir que profissionais de saúde ajudem no diagnóstico de pacientes e previna a disseminação do vírus[5]. Os testes de antígenos desempenharão um papel crítico na luta contra a COVID-19[6].

Princípio do Teste

O dispositivo Panbio™ COVID-19 Ag Rapid Test Device contém uma tira de membrana que é pré-revestida com anticorpo anti-SARS-CoV-2 imobilizado na linha de teste e IgY monoclonal de camundongo anti-galinha na linha de controle. Dois tipos de conjugados (IgG humana específica para conjugado de ouro SARS-CoV-2 Ag (se liga à proteína do nucleocapsídeo) e conjugado de ouro IgY de frango) movem-se para cima na membrana cromatograficamente e reagem respectivamente com o anticorpo anti-SARS-CoV-2 e com o IgY monoclonal de camundongo anti-galinha revestidos na membrana. Para um resultado positivo, a IgG humana específica para o conjugado de ouro SARS-CoV-2 Ag e o anticorpo anti-SARS-CoV-2 formarão uma linha de teste na janela de resultados. Nem a linha de teste nem a linha de controle são visíveis na janela de resultados antes de aplicar a amostra do paciente. Uma linha de controle visível é necessária para indicar que um resultado de teste é válido.

Uso Pretendido

O Panbio™ COVID-19 Ag Rapid Test Device é um teste rápido de diagnóstico *in vitro* para a detecção qualitativa do antígeno SARS-CoV-2 (Ag) em amostras de esfregaço nasal humano de indivíduos que atendem aos critérios clínicos e / ou epidemiológicos COVID-19.

O Panbio™ COVID-19 Ag Rapid Test Device destina-se apenas a uso profissional e destina-se a ser usado como um auxílio no diagnóstico de infecção por SARS-CoV-2. O produto pode ser usado em qualquer ambiente laboratorial e não laboratorial que atenda aos requisitos especificados nas Instruções de Uso e regulamentação local. O teste fornece resultados de teste

preliminares. Os resultados negativos não impedem a infecção por SARS-CoV-2 e não podem ser usados como única base para o tratamento ou outras decisões de gestão. Os resultados negativos devem ser combinados com observações clínicas, histórico do paciente e informações epidemiológicas. O teste não se destina a ser usado como teste de triagem de doadores para SARS-CoV-2.

Materiais Fornecidos

- 25 dispositivos de teste com dessecante em bolsa individual
- Tampão (1 x 9 ml/frasco)
- 25 tubos de extração
- 25 tampas de tubo de extração
- 1 swab controle positivo
- 1 swab controle negativo
- 25 swabs nasais esterilizados para coleta de amostras
- 1 suporte para tubos
- 1 guia de Referência Rápida
- 1 instrução de uso

Material Necessário, Mas Não Fornecido

- Equipamento de proteção individual de acordo com a recomendações locais (exemplo: jaleco/roupa de proteção, máscara facial, protetor facial/óculos e luvas), cronômetro, recipiente para risco biológico

Ingredientes Ativos dos Componentes Principais

- **1 Dispositivo de teste** Conjugado de ouro: IgG humana específica para coloide de ouro SARS-CoV-2 Ag e IgY de galinha - coloide de ouro, linha de teste: antiSARS-CoV-2 monoclonal de camundongo Linha de controle: IgY monoclonal de camundongo antigalinha
- **Tampão** Tricina, Cloreto de Sódio, Tween 20, Azida de Sódio (<0,1%), Proclin 300

Armazenamento e Estabilidade

1. O kit de teste deve ser armazenado a uma temperatura entre 2 e 30°C. Não congele o kit ou seus componentes.
   Observação: Quando armazenados em um refrigerador, todos os componentes do kit devem estar em temperatura ambiente (15-30°C) por no mínimo 30 minutos antes de realizar o teste. Não abra a bolsa enquanto os componentes atingem a temperatura ambiente.
2. O frasco de tampão pode ser aberto e selado novamente para cada ensaio. A tampa do frasco tampão deve ser firmemente selada entre cada uso. O

tampão é estável até a data de validade se mantido entre 2 e 30°C.
3. Realize o teste imediatamente após remover o dispositivo de teste da embalagem.
4. Não use o kit de teste após o prazo de validade.
5. O prazo de validade do kit está indicado na embalagem externa.
6. Não use se o kit de teste se a bolsa estiver danificada ou se a vedação estiver violada.
7. As amostras diretas de esfregaço devem ser testadas imediatamente após a coleta. Se o teste imediato não for possível, a amostra do esfregaço pode ser mantida em um tubo de extração cheio de tampão de extração (300 µl) em temperatura ambiente (15-30°C) por até duas horas antes do teste.

Advertências

1. Somente para uso para diagnóstico *in vitro*. Não reutilize o dispositivo de teste e os componentes do kit.
2. Essas instruções devem ser estritamente seguidas por profissionais de saúde treinados, para obtenção de resultados precisos. Todos os usuários devem ler as instruções antes de realizar um teste.
3. Não coma ou fume durante o manuseio de amostras.
4. Use luvas de proteção ao manusear as amostras e lave bem as mãos em seguida.
5. Evite respingos ou formação de aerossol na amostra e no tampão.
6. Limpe bem os derramamentos usando um desinfetante apropriado.
7. Descontamine e descarte todas as amostras, kits de reação e materiais potencialmente contaminados (ou seja, swab, tubo de extração, dispositivo de teste) em um recipiente de risco biológico como se fossem resíduos infecciosos e descarte de acordo com os regulamentos locais aplicáveis.
8. Não misture ou troque amostras diferentes.
9. Não misture reagentes de lotes diferentes ou de outros produtos.
10. Não guarde o kit com exposição à luz solar direta.
11. Para evitar contaminação, não toque na ponta do swab fornecido ao abrir a bolsa do swab.
12. Os swabs esterilizados devem ser usados apenas para coleta de amostras nasais.
13. Para evitar contaminação cruzada, não reutilize os swabs esterilizados para a coleta de amostras.
14. Não dilua o swab coletado com qualquer solução, exceto o tampão de extração fornecido.
15. O tampão contém azida de sódio a <0,1% como conservante e pode ser tóxico se ingerido. Quando descartado em uma pia, lave com bastante água.[7]

16. Não use o swab de controle positivo ou negativo para a coleta de amostras.

Procedimento de Teste (consulte a figura)

Amostras de esfregaço nasal

Nota: o profissional de saúde deve cumprir as diretrizes de segurança pessoal, incluindo o uso de equipamento de proteção individual.

Preparação de Teste

1. Deixe todos os componentes do kit atingirem uma temperatura entre 15-30°C antes do teste por 30 minutos.
2. Remova o dispositivo de teste da bolsa de alumínio antes de usar. Coloque sobre uma superfície plana, horizontal e limpa.
3. Segure o frasco de tampão verticalmente e encha o tubo de extração com fluido de tampão até que ele flua até a linha de enchimento do tubo de extração (300 µl).
   ⚠ **Cuidado:** Se a quantidade de tampão for excessiva ou insuficiente, um resultado de teste impróprio pode ocorrer.
4. Coloque o tubo de extração no suporte de tubos.

Coleta e Extração de Amostras

1. Incline a cabeça do paciente 70 graus para trás. Enquanto gira suavemente o swab, introduza o swab por menos de uma polegada (cerca de 2 cm) na narina (até encontrar resistência).
2. Gire o swab cinco vezes contra a parede nasal e, em seguida, remova-o lentamente pela narina.
3. Usando o mesmo swab, repita o procedimento de coleta com a segunda narina.
   ⚠ **Cuidado:** Se o swab quebrar durante a coleta da amostra, repita a coleta da amostra com um novo swab.
4. Gire a ponta do swab no fluido tampão dentro do tubo de extração, empurrando na parede do tubo de extração pelo menos cinco vezes e, em seguida, aperte o swab apertando o tubo de extração com os dedos.
5. Quebre o swab no ponto de quebra e feche a tampa do tubo de extração.

Reação com Dispositivo de Teste

1. Abra a tampa do bico de gotejamento na parte inferior do tubo de extração.
2. Dispense 5 gotas das amostras extraídas verticalmente na cavidade da amostra (S) do dispositivo. Não manuseie ou mova o dispositivo de teste até que o teste esteja concluído e pronto para leitura.
   ⚠ **Cuidado:** As bolhas que ocorrem no tubo de extração podem levar a resultados imprecisos. Se você não conseguir criar gotas suficientes, isso pode ser causado por entupimento no bico dispensador. Agite o tubo

suavemente para liberar o bloqueio até observar a formação livre de gotas.
3. Feche o bico e descarte o tubo de extração contendo o swab usado de acordo com os regulamentos locais e o protocolo de descarte de resíduos de risco biológico.
4. Inicie o cronômetro. Leia o resultado do teste em 15 minutos. Não leia os resultados após 20 minutos.
5. Descarte o dispositivo usado de acordo com os regulamentos locais e o protocolo de descarte de resíduos de risco biológico.

Swab de Controle Positivo / Negativo

⚠ **Cuidado:** Apenas para uso de Controle. Não use o swab de controle positivo ou negativo para a coleta de amostras.

Nota: Por favor consulte a seção Controle de Qualidade Externo desta instrução de uso para saber a frequência de testagem externa da qualidade dos swabs de controle.

1. Segure o frasco de tampão verticalmente e encha o tubo de extração com fluido de tampão até que ele flua até a linha de enchimento do tubo de extração (300 µl).
   ⚠ **Cuidado:** Se a quantidade de tampão for excessiva ou insuficiente, um resultado de teste impróprio pode ocorrer.
2. Coloque o tubo de extração no suporte de tubos.
3. Insira o swab de controle positivo ou negativo no fluido tampão dentro do tubo de extração e mergulhe o swab por 1 minuto. Gire a ponta do swab de controle no fluido tampão dentro do tubo de extração, empurrando na parede do tubo de extração pelo menos cinco vezes e, em seguida, aperte o swab apertando o tubo de extração com os dedos.
4. Descarte o swab de controle usado de acordo com seu protocolo de descarte de resíduos de risco biológico.
5. Feche a tampa do tubo de extração.
6. Siga o procedimento de teste acima [Reação com Dispositivo de Teste].

Interpretação do Teste (consulte a figura)

1. **Resultado negativo:** A presença apenas da linha de controle (C) e nenhuma linha de teste (T) dentro da janela de resultado indica um resultado negativo.
2. **Resultado positivo:** A presença da linha de teste (T) e da linha de controle (C) dentro da janela de resultados, independentemente de qual linha apareça primeiro, indica um resultado positivo.
   ⚠ **Cuidado:** A presença de qualquer linha de teste (T), não importa o quão tênue, indica um resultado positivo.
3. **Resultado inválido:** Se a linha de controle (C) não estiver visível na janela de resultados após a realização do teste, o resultado é considerado inválido.

Limitações de Teste

1. O conteúdo deste kit deve ser usado para a detecção profissional e qualitativa do antígeno SARS-CoV-2 em esfregaço nasal. Outros tipos de amostra podem levar a resultados incorretos e não devem ser usados.
2. O não cumprimento das instruções para o procedimento de teste e a interpretação dos resultados do teste pode afetar adversamente o desempenho do teste e/ou produzir resultados inválidos.
3. Um resultado de teste negativo pode ocorrer se a amostra foi coletada, extraída ou transportada de forma inadequada. Um resultado de teste negativo não elimina a possibilidade de infecção por SARS-CoV-2 e deve ser confirmado por cultura viral ou um ensaio molecular.
4. Os resultados positivos dos testes não descartam coinfecções com outros patógenos.
5. Os resultados do teste devem ser avaliados em conjunto com outros dados clínicos disponíveis para o médico.
6. Ler os resultados do teste antes de 15 minutos ou depois de 20 minutos pode gerar resultados incorretos.
7. O Panbio™ COVID-19 Ag Rapid Test Device não se destina a detectar vírus defeituosos (não infecciosos) durante as fases posteriores da eliminação viral, que devem ser detectados por testes moleculares de PCR .[8]
8. Resultados positivos podem ocorrer em caso de infecção com o SARS-CoV.

Controle de Qualidade

1. **Controle de Qualidade Interno:**
   O dispositivo de teste tem uma linha de teste (T) e uma linha de controle (C) na superfície do dispositivo de teste. Nem a linha de teste nem a linha de controle são visíveis na janela de resultados antes de aplicar uma amostra. A linha de controle é usada para o controle do procedimento e deve sempre aparecer se o procedimento do teste for realizado corretamente e os reagentes do teste da linha de controle estiverem funcionando.
2. **Controle de Qualidade Externo:**
   Os controles são especificamente formulados e fabricados para garantir o desempenho do Panbio™ COVID-19 Ag Rapid Test Device e são usados para verificar a capacidade do usuário de realizar o teste de maneira adequada e interpretar os resultados. O Controle Positivo produzirá um resultado de teste positivo e foi fabricado para produzir uma linha de teste visível (T). O Controle Negativo produzirá um resultado de teste negativo. As boas práticas de laboratório sugerem o uso de controles positivos e negativos para garantir que:

- Os reagentes de teste estão funcionando; e
- O teste foi executado corretamente.
  Controles externos podem ser testados em qualquer uma das circunstâncias a seguir:
- Por um novo operador antes de realizar o teste em amostras de pacientes,
- Ao receber uma nova remessa de teste,
- Em intervalos periódicos, conforme ditado pelos requisitos locais e/ou pelos procedimentos de Controle de Qualidade do usuário.

Características de Desempenho

1. **Avaliação Externa do Panbio™ COVID-19 Ag Rapid Test Device**
   O desempenho clínico do Panbio™ COVID-19 Ag Rapid Test Device foi determinado testando 104 amostras positivas de esfregaço nasal e 404 amostras negativas para o antígeno SARS-CoV-2 (Ag) para ter uma sensibilidade de 98,1% (IC 95%: 93,2-99,8 %) e uma especificidade de 99,8% (IC 95%: 98,6-100,0%). As amostras clínicas foram consideradas positivas ou negativas usando um método de referência FDA EUA RT-PCR.

Resultados do Panbio™ COVID-19 Ag Rapid Test Device

		Resultado de teste de PCR Nasal		
		Positivo	**Negativo**	**Total**
Resultados do Panbio™ COVID-19 Ag Rapid Test Device (amostras de swab nasal)	**Positivo**	102	1	103
	Negativo	2	403	405
	Total	104	404	508
		Sensibilidade	Especificidade	Percentual de concordância Total
		98,1% [93,2%;99,8%]	**99,8%** [98,6%;100,0%]	**99,4%** [98,3%;99,9%]

- Os dados de performance foram calculados a partir de um estudo de indivíduos suspeitos de exposição a COVID-19 ou quem apresentou sintomas nos últimos 7 dias.
- Estratificação das amostras positivas após o início dos sintomas ou que tenham suspeita de exposição entre 0-3 dias tiveram uma sensibilidade de 100,0% (n=46) e entre 4-7 dias tiveram uma sensibilidade de 96,6% (n=58).
- A concordância positiva do Panbio™ COVID-19 Ag Rapid Test Device é maior com valor de Ct ≤33 com uma sensibilidade de 99,0%. Como sugerido nas referências 8 e 9, pacientes com valor de Ct> 33 não são mais contagiosos. [8, 9]

- Os dados de desempenho clínico também foram calculados em comparação a amostras de esfregaço nasofaríngeo usando uma referência FDA EUA RT-PCR e tem uma sensibilidade de 91,1% (IC 95%: 84,2-95,6%) e especificidade de 99,7% (IC 95%: 98,6-100,0 %).

2. Limite de Detecção

O Panbio™ COVID-19 Ag Rapid Test Device confirmou detectar $2,5X10^{1,8}$ $TCID_{50}$/ml de SARS-CoV-2 que foi isolado de um paciente confirmado com COVID-19 na Coreia.

3. Efeito Gancho

Não há efeito gancho em $1,0x10^{5,8}$ $TCID_{50}$/ml de SARS-CoV-2 que foi isolado de um paciente confirmado com COVID-19 na Coreia.

4. Reatividade Cruzada

A reatividade cruzada do Panbio ™ COVID-19 Ag Rapid Test Device foi avaliada testando 28 tipos de vírus e outros 13 tipos de microrganismos. As concentrações finais de vírus e outros microrganismos testados estão documentadas na Tabela abaixo. Os seguintes vírus e outros microrganismos, exceto a Nucleoproteína Humana do SARS-coronavírus, não têm efeito nos resultados de teste do Panbio ™ COVID-19 Ag Rapid Test Device. O Panbio ™ COVID-19 Ag Rapid Test Device tem reatividade cruzada com a Nucleoproteína Humana do SARS-coronavírus a uma concentração de 25 ng/ml ou mais, porque o SARS-CoV tem alta homologia (79,6%) para o SARS-CoV-2.

Nº	Tipos de Espécime	Substância com potencial reação cruzada	Concentração Final Testada	Resultado do Teste
1	Virus	Adenovírus Tipo 1	$2,2 X 10^{7}$ $TCID_{50}$/ml	Sem reação cruzada
2		Adenovírus Tipo 5	$5,71 X 10^{8}$ $TCID_{50}$/ml	Sem reação cruzada
3		Adenovírus Tipo 7	$2,86 X 10^{9}$ $TCID_{50}$/ml	Sem reação cruzada
4		Enterovirus (EV68)	$2,81 X 10^{7}$ $TCID_{50}$/ml	Sem reação cruzada
5		Echovirus2	$1,0 X 10^{6,5}$ $TCID_{50}$/ml	Sem reação cruzada
6		Echovirus11	$5,0 X10^{6,25}$ $TCID_{50}$/ml	Sem reação cruzada
7		Enterovirus D68	$2,81 X 10^{7}$ $TCID_{50}$/ml	Sem reação cruzada

Nº	Tipos de Espécime	Substância com potencial reação cruzada	Concentração Final Testada	Resultado do Teste
8	Virus	Herpesvírus humano (HSV) 1	$5,0 \times 10^{7,5}$ $TCID_{50}$/ml	Sem reação cruzada
9		Herpesvírus humano (HSV) 2	$5,0 \times 10^{5,75}$ $TCID_{50}$/ml	Sem reação cruzada
10		Vírus da caxumba Ag	$1,58 \times 10^{5}$ $TCID_{50}$/ml	Sem reação cruzada
11		Vírus influenza A (H1N1) Estirpe (A/Virginia/ATCC1/2009)	$3,71 \times 10^{5}$ PFU/ml	Sem reação cruzada
12		Vírus da gripe A (H1N1) Estirpe (A/WS/33)	$5,0 \times 10^{7,25}$ $TCID_{50}$/ml	Sem reação cruzada
13		Vírus Influenza A (H1N1) Estirpe (A/California/08/2009/pdm09)	$1,6 \times 10^{8}$ $TCID_{50}$/ml	Sem reação cruzada
14		Vírus da gripe Estirpe (B/Lee/40)	$5,0 \times 10^{6,25}$ $TCID_{50}$/ml	Sem reação cruzada
15		Parainfluenza Tipo 1	$3,06 \times 10^{8}$ $TCID_{50}$/ml	Sem reação cruzada
16		Parainfluenza Tipo 2	$5,0 \times 10^{5}$ $TCID_{50}$/ml	Sem reação cruzada
17		Parainfluenza Tipo 3	$6,6 \times 10^{7}$ $TCID_{50}$/ml	Sem reação cruzada
18		Parainfluenza Tipo 4A	$2,81 \times 10^{7}$ $TCID_{50}$/ml	Sem reação cruzada
19		Vírus sincicial respiratório (RSV) tipo A	$4,22 \times 10^{5}$ $TCID_{50}$/ml	Sem reação cruzada
20		Vírus sincicial respiratório (RSV) tipo B	$5,62 \times 10^{5}$ $TCID_{50}$/ml	Sem reação cruzada
21		Rhinovirus A16	$1,26 \times 10^{6}$ $TCID_{50}$/ml	Sem reação cruzada
22		HCoV-HKU1	1,5mg/ml	Sem reação cruzada
23		HCoV-NL63	$1,7 \times 10^{5}$ $TCID_{50}$/ml	Sem reação cruzada
24		HCoV-OC43	$8,9 \times 10^{5}$ $TCID_{50}$/ml	Sem reação cruzada
25		HCoV-229E	$1,51 \times 10^{6}$ $TCID_{50}$/ml	Sem reação cruzada
26		Nucleoproteína Humana do SARS-coronavirus	25ng/ml	Reação cruzada

Nº	Tipos de Espécime	Substância com potencial reação cruzada	Concentração Final Testada	Resultado do Teste
27	Virus	Nucleoproteína do MERS-CoV	0,25mg/ml	Sem reação cruzada
28		Metapneumovirus Humano(hMPV) 16 Tipo A1	1,51 X 10^6 $TCID_{50}$/ml	Sem reação cruzada

Nº	Tipos de Espécime	Substância com potencial reação cruzada	Concentração Final Testada	Resultado do Teste
1	Outro Microrganismo	*Staphylococcus saprophyticus*	1,9 X 10^7 CFU/ml	Sem reação cruzada
2		*Neisseria sp,(Neisseria lactamica)*	1,7 X 10^8 CFU/ml	Sem reação cruzada
3		*Staphylococcus haemolyticus*	3,5 X 10^9 CFU/ml	Sem reação cruzada
4		*Streptococcus salivarius*	1,96 X 10^7 CFU/ml	Sem reação cruzada
5		*Hemophilus parahaemolyticus*	2,2 X 10^8 CFU/ml	Sem reação cruzada
6		*Proteus vulgaris*	7,2 X 10^6 CFU/ml	Sem reação cruzada
7		*Moraxella catarrhalis*	4,7 X 10^7 CFU/ml	Sem reação cruzada
8		*Klebsiella pneumoniae*	5,0 X 10^6 CFU/ml	Sem reação cruzada
9		*Fusobacterium necrophorum*	1,75 X 10^8 CFU/ml	Sem reação cruzada
10		*Mycobacterum tuberculosis*	10mg/ml	Sem reação cruzada
11		Lavado nasal humano agrupado	N/A*	Sem reação cruzada
12		*Streptococcus pyogenes*	3,6 X 10^7 CFU/ml	Sem reação cruzada
13		*Mycoplasma pneumoniae*	4 X 10^8 CFU/ml	Sem reação cruzada

**Nenhuma concentração fornecida pelo fornecedor. A solução estoque não diluída foi testada.*

5. Substâncias Interferentes

As seguintes 43 substâncias potencialmente interferentes não têm impacto no Panbio™ COVID-19 Ag Rapid Test Device. As concentrações de teste finais das substâncias interferentes estão documentadas na Tabela abaixo.

Nº	Tipos de Espécime	Substâncias Interferentes	Concentração Final Testada	Resultado do Teste
1	Substância Endógena	Mucina	0,5%	Sem Interferência
2		Hemoglobina	100 mg/L	Sem Interferência
3		Triglicerídeos	1,5 mg/L	Sem Interferência
4		Icterícia (bilirrubina)	40 mg/dL	Sem Interferência
5		Fatores reumatoides	200 IU/ml	Sem Interferência
6		Anticorpo antinuclear	>1:40	Sem Interferência
7		Grávida	Diluição de 10 vezes	Sem Interferência
8	Substância Exógena	Guaiacol gliceril éter	1 µg/ml	Sem Interferência
9		Albuterol	0,005 mg/dL	Sem Interferência
10		Efedrina	0,1 mg/ml	Sem Interferência
11		Clorfeniramina	0,08 mg/dL	Sem Interferência
12		Difenidramina	0,08 mg/dL	Sem Interferência
13		Ribavirina	26,7 µg /ml	Sem Interferência
14		Oseltamivir	0,04 mg/dL	Sem Interferência
15		Zanamivir	17,3 µg /ml	Sem Interferência
16		Cloridrato de fenilefrina	15% v/v	Sem Interferência
17		Cloridrato de oximetazolina	15% v/v	Sem Interferência
18		Amoxicilina	5,4 mg/dL	Sem Interferência
19		Ácido acetilsalicílico	3 mg/dL	Sem Interferência
20		Ibuprofeno	21,9 mg/dL	Sem Interferência
21		Clorotiazida	2,7 mg/dL	Sem Interferência
22		Indapamida	140 ng/ml	Sem Interferência
23		Glimepirida (Sulfonilureias)	0,164 mg/dL	Sem Interferência
24		Acarbose	0,03 mg/dL	Sem Interferência
25		Ivermectina	4,4 mg/L	Sem Interferência
26		Lopinavir	16,4 µg/L	Sem Interferência
27		Ritonavir	16,4 µg/L	Sem Interferência
28		Fosfato de cloroquina	0,99 mg/L	Sem Interferência

Nº	Tipos de Espécime	Substâncias Interferentes	Concentração Final Testada	Resultado do Teste
29	Substância Exógena	Cloreto de Sódio com conservantes	4,44 mg/ml	Sem Interferência
30		Beclometasona	4,79 ng/ml	Sem Interferência
31		Dexametasona	0,6 µg/ml	Sem Interferência
32		Flunisolida	0,61 µg/ml	Sem Interferência
33		Triancinolona	1,18 ng/ml	Sem Interferência
34		Budesonida	2,76 ng/ml	Sem Interferência
35		Mometasona	1,28 ng/ml	Sem Interferência
36		Fluticasona	2,31 ng/ml	Sem Interferência
37		Enxofre	9,23 µg/ml	Sem Interferência
38		Benzocaína	0,13 mg/ml	Sem Interferência
39		Mentol	0,15 mg/ml	Sem Interferência
40		Mupirocina	10 µg/ml	Sem Interferência
41		Tobramicina	24,03 µg/ml	Sem Interferência
42		Biotina	1,2 µg/ml	Sem Interferência
43		HAMA	63,0 ng/ml	Sem Interferência

6. Repetibilidade e Reprodutibilidade

Repetibilidade e reprodutibilidade do Panbio™ COVID-19 Ag Rapid Test Device foram estabelecidas usando painéis de referência internos contendo amostras negativas e uma gama de amostras positivas. Não houve diferenças observadas dentro da execução, entre execuções, entre lotes, entre locais e entre dias.

PREPARAÇÃO

1 Deixe todos os componentes do kit atingirem uma temperatura entre 15-30°C antes do teste por 30 minutos.
Nota: Profissionais de saúde devem cumprir as diretrizes de segurança pessoal, incluindo o uso de equipamento de proteção individual.

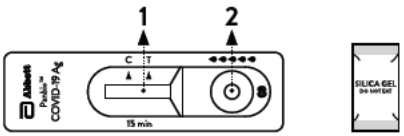
2 **Abra o pacote e observe o seguinte:**
1. Dispositivo de teste com dessecante em bolsa individual
2. Tampão
3. Tubo de extração
4. Tampa de tubos de extração
5. Swab controle positivo
6. Swab controle negativo
7. Swabs nasais esterilizados para coleta de amostra
8. Suporte para tubos
9. Guia de referência rápida
10. Instruções de uso

3 Leia atentamente estas instruções antes de usar o kit Panbio™ COVID-19 Ag Rapid Test Device.

4 Observe a data de validade da caixa do kit. Se a data de validade já passou, use outro kit.

5 **Abra a bolsa de alumínio e observe o seguinte:**
1. Janela de resultados
2. Cavidade de amostra

Em seguida, rotule o dispositivo com o identificador do paciente.

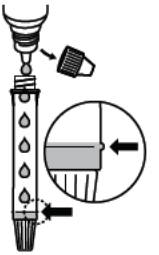


●●●●●: 5 gotas da amostra extraída

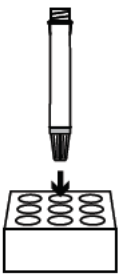
PROCEDIMENTO DE TESTE

1 Segure o frasco de tampão verticalmente e encha o tubo de extração com fluido de tampão até que ele flua até a linha de enchimento do tubo de extração (300µl).

⚠ **Cuidado:** Se a quantidade de tampão for excessiva ou insuficiente, um resultado de teste impróprio pode ocorrer.

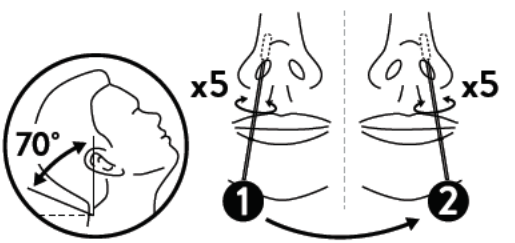


2 Coloque o tubo de extração no suporte de tubos.



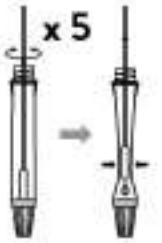
3 Incline a cabeça do paciente 70 graus para trás. Enquanto gira suavemente o swab, introduza o swab por menos de uma polegada (cerca de 2 cm) na narina (até encontrar resistência).
Gire o swab cinco vezes contra a parede nasal. Usando o mesmo swab, repita o procedimento de coleta com a segunda narina.
Remova lentamente o swab da narina.

⚠ **Cuidado:** Se o swab quebrar durante a coleta da amostra, repita a coleta da amostra com um novo swab.



PROCEDIMENTO DE TESTE

4 Insira a amostra de esfregaço no tubo de extração. Gire a ponta do swab no fluido tampão dentro do tubo de extração, empurrando na parede do tubo de extração pelo menos cinco vezes e, em seguida, aperte o swab apertando o tubo de extração com os dedos.

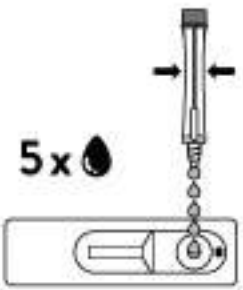


5 Quebre o swab no ponto de quebra e feche a tampa do tubo de extração.

6 Abra a tampa do bico de gotejamento na parte inferior do tubo de extração.

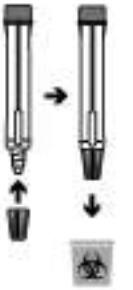
7 Dispense 5 gotas das amostras extraídas verticalmente na cavidade da amostra (S) do dispositivo. Não manuseie ou mova o dispositivo de teste até que o teste esteja concluído e pronto para leitura.

⚠ **Cuidado:** As bolhas que ocorrem no tubo de extração podem levar a resultados imprecisos. Se você não conseguir criar gotas suficientes, isso pode ser causado por entupimento no bico dispensador. Agite o tubo suavemente para liberar o bloqueio até observar a formação livre de gotas.



PROCEDIMENTO DE TESTE

8 Feche o bico e descarte o tubo de extração contendo o swab usado de acordo com os regulamentos locais e o protocolo de descarte de resíduos de risco biológico.



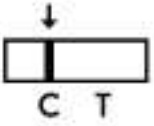
9 Inicie o cronômetro. Leia o resultado do teste em 15 minutos. Não leia os resultados após 20 minutos.

10 Descarte o dispositivo usado de acordo com os regulamentos locais e o protocolo de descarte de resíduos de risco biológico.

INTERPRETAÇÃO DE TESTE

NEGATIVO

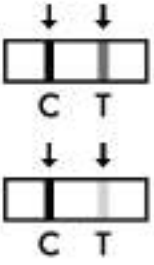
A presença apenas da linha de controle (C) e nenhuma linha de teste (T) dentro da janela de resultado indica um resultado negativo.



POSITIVO

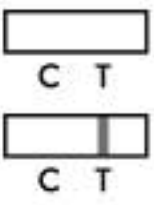
A presença da linha de teste (T) e da linha de controle (C) dentro da janela de resultados, independentemente de qual linha apareça primeiro, indica um resultado positivo.

⚠ **Cuidado:** A presença de qualquer linha de teste (T), não importa o quão tênue, indica um resultado positivo.



INVÁLIDO

Se a linha de controle (C) não estiver visível na janela de resultados após a realização do teste, o resultado é considerado inválido. As instruções podem não ter sido seguidas corretamente. É recomendável ler o a instrução de uso novamente antes de testar novamente a amostra com um novo dispositivo de teste.



PORTUGUÊS

О тесте

RU

Введение

Болезнь, вызванная коронавирусом (COVID-19), является инфекционным заболеванием, вызываемым недавно обнаруженным коронавирусом 2 группы (SARS-CoV-2)[1], связанным с тяжелым синдромом острой дыхательной недостаточности. SARS-CoV-2 — это β-коронавирус, который представляет собой оболочечный вирус с несегментированной положительно-полярной нитью РНК[2]. Он распространяется путем передачи от человека человеку воздушно-капельным путем или при прямом контакте; по оценкам, инкубационный период инфекции составляет в среднем 6,4 дня, а базовое репродуктивное число — 2,24-3,58. Среди пациентов с пневмонией, вызванной SARS-CoV-2, лихорадка была наиболее распространенным симптомом, после которого следует кашель[3]. В основных анализах, используемых для *in vitro* диагностики инфекции COVID-19, используется полимеразная цепная реакция с обратной транскриптазой (ОТ-ПЦР; RT-PCR) в реальном времени, которая занимает несколько часов[4]. Наличие экономичного и быстрого диагностического теста в месте оказания медицинской помощи имеет решающее значение для того, чтобы медицинские работники могли помочь в диагностике пациентов и предотвратить дальнейшее распространение вируса[5]. Тесты на антигены будут играть важнейшую роль в борьбе с COVID-19[6].

Принцип теста

Экспресс-тест Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) содержит мембранную полоску, предварительно покрытую иммобилизованным анти-SARS-CoV-2 антителом на тестовой линии, и мышиным моноклональным анти-куриным IgY на контрольной линии. Два типа конъюгатов (человеческий IgG, специфичный для конъюгата антигена SARS-CoV-2 на золотой подложке (связывается с белком нуклеокапсида), и конъюгат куриного IgY на золотой подложке) движутся вверх по мембране хроматографически и реагируют с анти-SARS-CoV-2 антителом и с предварительно покрытым мышиным моноклональным анти-куриным IgY, соответственно. Для получения положительного результата человеческий IgG, специфичный к конъюгату антигена SARS-CoV-2 на золотой подложке и анти-SARS-CoV-2 антитела, образуют в окне результата тестовую линию. Ни тестовая, ни контрольная линии в окне результата до нанесения образца, полученного у пациента, не видны. Видимая контрольная линия необходима, чтобы показать, что результат анализа действителен.

Назначение

Экспресс-тест Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) - это экспресс-тест *in vitro* для качественного определения антигена SARS-CoV-2 (Ag) в образцах мазков из носа, полученных у пациентов, соответствующих клиническим и / или эпидемиологическим критериям COVID-19. Экспресс-тест Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) предназначен только для профессионального применения в качестве помощи при диагностике инфекции, вызванной вирусом SARS-CoV-2. Медицинское изделие может использоваться в любой лабораторной и не лабораторной среде, которая соответствует требованиям, указанным в инструкции по применению и местным нормам. Тестирование представляет предварительные результаты тестирования. Отрицательные результаты не исключают инфицирование SARS-CoV-2, и их нельзя использовать в качестве единственного основания для лечения или принятия другого решения в рамках ведения пациента. Отрицательные результаты должны соответствовать клиническим наблюдениям, данным анамнеза заболевания и эпидемиологической информации. Тест не предназначен для использования в качестве скринингового теста доноров на SARS-CoV-2.

Предоставляемые материалы

- 25 тест-кассет в индивидуальной вакуумной упаковке с осушителем
- Буфер (1 x 9 мл / флакон)
- 25 пробирок экстракционные
- 25 колпачков для пробирок экстракционных
- 1 Положительный контрольный образец
- 1 Отрицательный контрольный образец
- 25 Стерильных назальный тампонов (тупферов) для сбора образцов
- 1 Штатив
- 1 Краткое руководство
- 1 Инструкция по применению

Необходимые, но не предоставляемые материалы

- Средства индивидуальной защиты в соответствии с местными рекомендациями (халат / лабораторный халат, маска для лица, защитный экран для лица / очки и перчатки), таймер, контейнер для биологических опасных отходов

Активные ингредиенты основных компонентов

- **Тест-кассета** Подложка для конъюгата: человеческий IgG, специфичный к антигену SARS-CoV-2 конъюгат с золотом и IgY куриного желтка - конъюгат с золотом Тестовая линия: Моноклональные мышиные антитела к антигену SARS-CoV-2; Контрольная линия: Мышиные моноклональные антитела к IgY куриного желтка
- **Буфер** Трицин, хлорид натрия , Твин 20 , Азид натрия (<0,1%), Проклин 300

Хранение и стабильность

1. Набор следует хранить при температуре от 2 до 30 °C. Не замораживайте набор или его компоненты.
   Примечание: При хранении в холодильнике все компоненты набора должны быть приведены к комнатной температуре (15-30 °C) минимум за 30 минут до проведения теста. Не открывайте тест-кассету, пока компоненты не дойдут до комнатной температуры.
2. Флакон с буфером флакон можно открывать и запечатывать заново для каждого анализа. Крышка флакона с буфером должна быть плотно закрыта между использованиями. Буфер стабилен до истечения срока годности, если хранится при температуре 2-30 °C.
3. Выполните тест сразу же после извлечения тест-кассеты из индивидуальной упаковки.
4. Не используйте набор после истечения срока годности.
5. Срок годности набора указан на наружной упаковке.
6. Не используйте набор, если индивидуальная упаковка повреждена или ее герметичность нарушена.
7. Тампоны (тупферы) с образцами должны быть протестированы сразу же после взятия. Если немедленное тестирование невозможно, тампон (тупфер) с образцом можно хранить в экстракционной пробирке, заполненной экстракционным буфером (300 мкл), при комнатной температуре (15-30 °C) в течение двух часов до начала анализа.

Меры предосторожности

1. Предназначен только для диагностики *in vitro*. Не используйте повторно тест-кассету и компоненты набора.
2. Эти инструкции должны строго соблюдаться обученным медицинским работником для достижения точных результатов.

Все пользователи должны перед выполнением анализа прочитать инструкцию.

3. Не принимайте пищу и не курите при обращении с образцами.
4. При работе с образцами наденьте защитные перчатки, а после - тщательно вымойте руки.
5. Избегайте разбрызгивания или образования аэрозолей образцов и буфера.
6. Тщательно удалите пролитую жидкость с помощью соответствующего дезинфицирующего средства.
7. Необходимо обеззараживать и утилизировать все образцы, наборы и потенциально загрязненные материалы (тампон, экстракционная пробирка, тест-кассета) в контейнере для биологически опасных отходов, по правилам для инфицированных отходов, в соответствии с местным законодательством.
8. Различные образцы не должны смешиваться или взаимозаменяться.
9. Не смешивайте реагенты различных серий или реагенты для других медицинских изделий.
10. Не храните набор под прямыми солнечными лучами.
11. Во избежание загрязнения не прикасайтесь к головке прилагаемого тампона (тупфера) при открывании упаковки тампона (тупфера).
12. Стерильные тампоны следует использовать только для взятия мазков из носа.
13. Во избежание перекрестного загрязнения не следует повторно использовать стерильные тампоны для получения мазков.
14. Не смешивайте тампон с образцом с какими-либо растворами, кроме поставляемого экстракционного буфера.
15. Буфер содержит <0,1% азида натрия в качестве консерванта, который может быть токсичным при проглатывании. При утилизации в водопровод промойте его большим количеством воды.[7]
16. Не используйте положительный или отрицательный контрольный образцы для сбора образцов.

Процедура проведения теста (см. рисунок)

Образцы мазков из носа

Примечание: Медицинский работник должен соблюдать правила техники безопасности, включая использование средств индивидуальной защиты.

Подготовка

1. Перед тестированием выдержите все компоненты набора в течение 30 минут при температуре 15-30 °C.
2. Извлеките тест-кассету из индивидуальной упаковки перед использованием. Поместите ее на ровную, горизонтальную и чистую поверхность.
3. Держа флакон с буфером вертикально наполните экстракционную пробирку буферным раствором, пока она не дойдет до линии заполнения экстракционной пробирки (300 мкл).
   ⚠ **Предупреждение:** Если объем буфера чрезмерен или недостаточен, результат теста может быть неправильным.
4. Установите экстракционную пробирку в штатив.

Сбор образцов и экстракция

1. Наклоните голову пациента назад на 70 градусов. Осторожно вращая тампон, введите тампон на расстояние менее одного дюйма (около 2 см) в ноздрю (до тех пор, пока не возникнет сопротивление носовых раковин).
2. Поверните тампон пять раз так, чтобы он плотно касался поверхности стенки носа, затем медленно удалите его из ноздри.
3. Используя тот же тампон, повторите процедуру сбора со второй ноздри.
   ⚠ **Предупреждение:** Внимание! Если палочка тампона сломалась во время отбора мазка, повторите сбор мазка с новым тампоном.

4. Наконечник тампона проворачивают в буферном растворе внутри экстракционной пробирки, вдавливая его в стенку экстракционной пробирки не менее пяти раз, а затем тампон выжимают, сдавливая экстракционную пробирку пальцами.
5. Тампон разламывают в точке разлома, и колпачок для пробирки экстракционной закрывают.

Реакция с тест-кассетой

1. Откройте крышку колпачка - капельницы в нижней части экстракционной пробирки.
2. Внесите 5 капель раствора из экстракционной пробирки вертикально в ячейку для образца (S) на тест-кассете. Не трогайте и не перемещайте тест-кассету, пока тест не будет завершен и готов к считыванию.
   ⚠ **Предупреждение:** Пузырьки, возникающие в экстракционной пробирке, могут привести к неточным результатам. Если

отмерить достаточное количество капель не удается, это может быть вызвано засорением колпачка-капельницы. Осторожно встряхните пробирку, чтобы устранить обструкцию, пока не образуются свободные капли.

3. Закройте колпачок -капельницу, и утилизируйте экстракционную пробирку, содержащую использованный тампон в соответствии с местными правилами и протоколом утилизации биологически опасных отходов.
4. Запустите таймер. Результат можно считывать через 15 минут. Не считывайте результаты, если прошло 20 минут и больше.
5. Использованную тест-кассету утилизируют в соответствии с местными правилами и протоколом утилизации биологически опасных отходов.

Положительный / Отрицательный контрольные образцы

⚠ **Предупреждение:** Контролируемое использование. Не используйте положительный или отрицательный контрольный образцы для сбора образцов.

Примечание: См. Раздел «Внешний контроль качества» данной инструкции, чтобы узнать, как часто использовать контрольные образцы для внешнего контроля качества.

1. Держа флакон с буфером вертикально наполните экстракционную пробирку буферным раствором, пока она не дойдет до линии заполнения экстракционной пробирки (300 мкл).

   ⚠ **Предупреждение:** Если объем буфера чрезмерен или недостаточен, результат теста может быть неправильным.
2. Установите экстракционную пробирку в штатив.
3. Поместите положительный или отрицательный контрольный образец в буферный раствор внутри экстракционной пробирки и замочите образец на 1 минуту. Наконечник контрольного образца проворачивают в буферном растворе внутри экстракционной пробирки, вдавливая его в стенку экстракционной пробирки не менее пяти раз, а затем образец выжимают, сдавливая экстракционную пробирку пальцами.
4. Использованный контрольный образец утилизируют в соответствии с местными правилами и протоколом утилизации биологически опасных отходов.
5. Закройте колпачок экстракционной пробирки.
6. Выполните описанную выше процедуру испытания [Реакция с тест-кассетой].

Интерпретация теста (см. рисунок)

1. **Отрицательный результат:** Наличие только контрольной линии (C) и отсутствие тестовой линии (T) в окошке для считывания указывает на отрицательный результат теста.
2. **Положительный результат:** Наличие тестовой (T) и контрольной (C) линии в окне результата, независимо от того, какая линия появляется первой, указывает на положительный результат.
   ⚠ **Предупреждение:** Наличие тестовой линии (T), какой бы слабой она ни была, свидетельствует о положительном результате.
3. **Неверный результат:** Если контрольная линия (C) не видна в окне результатов после выполнения теста, результат считается неверным.

Ограничения теста

1. Содержимое этого набора должно использоваться для профессионального и качественного определения антигена SARS-CoV-2 в мазке из носа. Другие типы образцов могут привести к неправильным результатам и не должны использоваться.
2. Несоблюдение инструкций по проведению анализа и интерпретации его результатов может отрицательно повлиять на проведение анализа и/или привести к неверным результатам.
3. Отрицательный результат теста может быть получен, если образец был собран, экстрагирован или транспортирован неправильно. Отрицательный результат теста не исключает возможности заражения SARS-CoV-2 и должен быть подтвержден посевом на вирус или молекулярным анализом.
4. Положительные результаты теста не исключают коинфекций другими возбудителями.
5. Результаты анализа должны оцениваться в сочетании с другими клиническими данными, доступными врачу.
6. Считывание результатов теста раньше, чем через 15 минут или позже, чем через 20 минут, может привести к получению неверных результатов.
7. Экспресс-тест Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) не предназначено для обнаружения дефектного (неинфекционного) вируса на более поздних стадиях выделения вируса, которое может быть обнаружено с помощью молекулярных тестов ПЦР.[8]
8. Положительный результат может быть получен в случае инфицирования SARS-CoV.

Контроль качества

1. **Внутренний контроль качества:**
   На поверхности тест-кассеты имеются тестовая линия (T) и контрольная линия (C). Ни тестовая, ни контрольная линии не видны в окне результатов до нанесения образца. Контрольная линия используется для контроля проведения процедуры и должна появляться всегда, если процедура испытания проводится должным образом, а реагенты контрольной линии работают.
2. **Внешний контроль качества:**
   Контрольные линии специально разработаны и изготовлены для обеспечения работы Экспресс-теста Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) и используются для проверки способности пользователя правильно проводить анализ и интерпретировать результаты. Положительный контроль дает положительный результат теста и был изготовлен для получения видимой тестовой линии (T). Отрицательный контроль приведет к отрицательному результату теста.
   Согласно требованиям Надлежащей лабораторной практики, предполагается использование положительного и отрицательного контролей, чтобы убедиться в том, что:

- Реагенты для анализа работают, и
- Анализ выполнен правильно.

Внешний контроль может быть проведен при любых следующих обстоятельствах:

- Новым оператором перед проведением анализа образцов от пациентов,
- При получении новой партии набора,
- Периодически, в соответствии с местными требованиями и/или процедурами контроля качества, применяемыми пользователем.

Эксплуатационные характеристики

1. **Внешняя оценка Экспресс-теста Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device)**
   Клиническая эффективность Экспресс-тест Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device)
   была определена путем тестирования 104 положительных и 404 отрицательных образцов мазков из носа на антиген SARS-CoV-2 (Ag) с чувствительностью 98,1% (95% CI: 93,2-99,8%) и специфичностью 99,8% (95% CI: 98,6-100,0%). Клинические образцы были определены как положительные или отрицательные с использованием эталонного метода ОТ-ПЦР, разрешенного FDA на использование в чрезвычайных ситуациях.

Результаты для Экспресс-тест Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device)

		Результаты теста ПЦР мазков из носа		
		Положительный результат	**Отрицательный результат**	**Итого**
Экспресс-тест Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) (мазки из носа)	**Положительный результат**	102	1	103
	Отрицательный результат	2	403	405
	Итого	104	404	508
		Чувствительностью	Специфичностью	Общая процентная согласованность
		98,1% [93,2%;99,8%]	**99,8%** [98,6%;100,0%]	**99,4%** [98,3%;99,9%]

- Данные о производительности были рассчитаны на основе исследования лиц, подозреваемых в контакте с COVID-19 или у которых в течение последних 7 дней проявлялись симптомы.
- Стратификация положительных образцов после появления симптомов или подозрения на контакт между 0–3 днями имеет чувствительность 100,0% (n=46), а 4–7 дней - чувствительность 96,6% (n=58).
- Положительный отклик Экспресс-теста Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) выше для образцов пациентов со значением порогового цикла Ct≤33 - чувствительность 99,0%. Как указано в рекомендациях 8 и 9, пациенты со значением порогового цикла Ct>33не являются вирулентными.[8, 9]
- Данные клинической эффективности также были рассчитаны по сравнению с образцами мазков из носоглотки с использованием эталонного метода ОТ-ПЦР, разрешённого FDA на использование в чрезвычайных ситуациях (для положительных и отрицательных образцов) и имеют чувствительность 91,1% (95% ДИ: 84,2-95,6%) и специфичность 99,7% (95% ДИ: 98,6-100,0 %).

2. Предел обнаружения

Подтверждено, что Экспресс-тест Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) обеспечивает обнаружение $2,5X10^{1,8}$ $ТЦД_{50}$/мл SARS-CoV-2, выделенного у пациента с подтвержденной инфекцией COVID-19 в Корее.

3. Эффект высокой дозы (Hook Effect)

При дозе $1{,}0x10^{5,8}$ $ТЦД_{50}$/мл SARS- CoV-2, выделенного у пациента с подтвержденной инфекцией COVID-19 в Корее, эффект высокой дозы отсутствует.

4. Перекрестная реактивность

Перекрестную реактивность Экспресс-теста Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) оценивали путем тестирования 28 вирусов и 13 других микроорганизмов. Окончательные тестовые концентрации вирусов и других микроорганизмов приведены в таблице ниже. Следующие вирусы и другие микроорганизмы, кроме Нуклеопротеина человеческого SARS-коронавирус, не влияют на результаты анализа с помощью Экспресс-теста Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device). Существует перекрестная реактивность Экспресс-теста Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) с Нуклеопротеином человеческим SARS-коронавирус в концентрации 25 нг / мл или более, поскольку SARS-CoV имеет высокую гомологичность (79,6%) с SARS-CoV-2.

№	Типы образцов	Вещество, вызывающее перекрестную реакцию	Окончательная тестовая концентрация	Результаты теста
1	Вирус	Аденовирус тип 1	$2{,}2 \times 10^{7}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
2		Аденовирус тип 5	$5{,}71 \times 10^{8}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
3		Аденовирус тип 7	$2{,}86 \times 10^{9}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
4		Эховирус (EV68)	$2{,}81 \times 10^{7}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
5		Эховирус 2	$1{,}0 \times 10^{6,5}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
6		Эховирус 11	$5{,}0 \times 10^{6,25}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
7		Эховирус D68	$2{,}81 \times 10^{7}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
8		Герпесвирус человека (HSV) 1	$5{,}0 \times 10^{7,5}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
9		Герпесвирус человека (HSV) 2	$5{,}0 \times 10^{5,75}$ $ТЦД_{50}$/мл	Нет перекрестной реакции

№	Типы образцов	Вещество, вызывающее перекрестную реакцию	Окончательная тестовая концентрация	Результаты теста
10	Вирус	Антиген парамиксофируса	1,58 X 10^5 $ТЦД_{50}$/мл	Нет перекрестной реакции
11		Штамм вируса гриппа A (H1N1) (A/Virginia/ ATCC1/2009)	3,71 X 10^5 PFU/ мл	Нет перекрестной реакции
12		Штамм вируса гриппа A (H1N1) (A/WS/33)	5,0 X $10^{7,25}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
13		Штамм вируса гриппа A (H1N1) A/ California/08/2009/ pdm09	1,6 X 10^8 $ТЦД_{50}$/ мл	Нет перекрестной реакции
14		Штамм вируса гриппа B (B/Lee/40)	5,0 X $10^{6,25}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
15		Вирус парагриппа типа 1	3,06 X 10^8 $ТЦД_{50}$/мл	Нет перекрестной реакции
16		Вирус парагриппа типа 2	5,0 X 10^5 $ТЦД_{50}$/ мл	Нет перекрестной реакции
17		Вирус парагриппа типа 3	6,6 X 10^7 $ТЦД_{50}$/ мл	Нет перекрестной реакции
18		Вирус парагриппа типа 4A	2,81 X 10^7 $ТЦД_{50}$/мл	Нет перекрестной реакции
19		Респираторно-синцитиальный вирус (RSV) типа A	4,22 X 10^5 $ТЦД_{50}$/мл	Нет перекрестной реакции
20		Респираторно-синцитиальный вирус (RSV) типа B	5,62 X 10^5 $ТЦД_{50}$/мл	Нет перекрестной реакции
21		Риновирус A16	1,26 X 10^6 $ТЦД_{50}$/мл	Нет перекрестной реакции
22		HCoV-HKU1	1,5мг/мл	Нет перекрестной реакции
23		HCoV-NL63	1,7 X 10^5 $ТЦД_{50}$/ мл	Нет перекрестной реакции
24		HCoV-OC43	8,9 X 10^5 $ТЦД_{50}$/ мл	Нет перекрестной реакции

№	Типы образцов	Вещество, вызывающее перекрестную реакцию	Окончательная тестовая концентрация	Результаты теста
25	Вирус	HCoV-229E	1,51 X 10^6 $ТЦД_{50}$/мл	Нет перекрестной реакции
26		Нуклеопротеин человеческий SARS-коронавирус	25нг/мл	Перекрестная реакция
27		Нуклеопротеин коронавируса БВРС	0,25мг/мл	Нет перекрестной реакции
28		Метапневмовирус человека (hMPV) 16 Тип A1	1,51 X 10^6 $ТЦД_{50}$/мл	Нет перекрестной реакции

№	Типы образцов	Вещество, вызывающее перекрестную реакцию	Окончательная тестовая концентрация	Результаты теста
1	Другой микроорганизм	*Staphylococcus saprophyticus*	1,9 X 10^7 КОЕ/мл	Нет перекрестной реакции
2		*Neisseria sp.(Neisseria lactamica)*	1,7 X 10^8 КОЕ/мл	Нет перекрестной реакции
3		*Staphylococcus haemolyticus*	3,5 X 10^9 КОЕ/мл	Нет перекрестной реакции
4		*Streptococcus salivarius*	1,96 X 10^7 КОЕ/мл	Нет перекрестной реакции
5		*Hemophilus parahaemolyticus*	2,2 X 10^8 КОЕ/мл	Нет перекрестной реакции
6		*Proteus vulgaris*	7,2 X 10^6 КОЕ/мл	Нет перекрестной реакции
7		*Moraxella catarrhalis*	4,7 X 10^7 КОЕ/мл	Нет перекрестной реакции
8		*Klebsiella pneumoniae*	5,0 X 10^6 КОЕ/мл	Нет перекрестной реакции
9		*Fusobacterium necrophorum*	1,75 X 10^8 КОЕ/мл	Нет перекрестной реакции
10		*Микобактерии туберкулеза*	10мг/мл	Нет перекрестной реакции

№	Типы образцов	Вещество, вызывающее перекрестную реакцию	Окончательная тестовая концентрация	Результаты теста
11	Другой микроорганизм	Пул образцов жидкости, собранных при промывании носа	N/A*	Нет перекрестной реакции
12		*Streptococcus pyogenes*	3,6 X 10^7 КОЕ/мл	Нет перекрестной реакции
13		*Mycoplasma pneumoniae*	4 X 10^8 КОЕ/мл	Нет перекрестной реакции

**Поставщик не предоставил концентрации. Был протестирован неразбавленный исходный раствор.*

5. Интерферирующие вещества

Следующие 43 потенциально интерферирующих веществ не оказывают никакого влияния на Экспресс-тест Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device). Окончательные тестовые концентрации интерферирующих веществ задокументированы в нижеприведенной таблице.

№	Типы образцов	Интерферирующие вещества	Окончательная тестовая концентрация	Результаты теста
1	Эндогенная субстанция	Муцин	0,5%	Нет влияния
2		Гемоглобин	100 мг/л	Нет влияния
3		Триглицериды	1,5 мг/л	Нет влияния
4		Билирубин	40 мг/дл	Нет влияния
5		Ревматоидный фактор	200 МЕ/мл	Нет влияния
6		Антиядерное антитело	>1:40	Нет влияния
7		Беременность	10-кратное разведение	Нет влияния
8	Экзогенная субстанция	Глицериловый эфир гваяколя	1 мкг/мл	Нет влияния
9		Альбутерол	0,005 мг/дл	Нет влияния
10		Эфедрин	0,1 мг/мл	Нет влияния
11		Хлорфенирамин	0,08 мг/дл	Нет влияния
12		Дифенгидрамин	0,08 мг/дл	Нет влияния
13		Рибавирин	26,7 мкг/мл	Нет влияния
14		Осельтамивир	0,04 мг/дл	Нет влияния
15		Занамивир	17,3 мкг/мл	Нет влияния

№	Типы образцов	Интерферирующие вещества	Окончательная тестовая концентрация	Результаты теста
16	Экзогенная субстанция	Фенилэфрина гидрохлорид	15% об,/об,	Нет влияния
17		Оксиметазолина гидрохлорид	15% об,/об,	Нет влияния
18		Амоксициллин	5,4 мг/дл	Нет влияния
19		Ацетилсалициловая кислота	3 мг/дл	Нет влияния
20		Ибупрофен	21,9 мг/дл	Нет влияния
21		Хлортиазид	2,7 мг/дл	Нет влияния
22		Индапамид	140 нг/мл	Нет влияния
23		Глимепирид (Сульфонилмочевина)	0,164 мг/дл	Нет влияния
24		Акарбоза	0,03 мг/дл	Нет влияния
25		Ивермектин	4,4 мг/л	Нет влияния
26		Лопинавир	16,4 мкг/л	Нет влияния
27		Ритонавир	16,4 мкг/л	Нет влияния
28		Хлорохина фосфат	0,99 мг/л	Нет влияния
29		Хлорид натрия с консервантами	4,44 мг/мл	Нет влияния
30		Беклометазон	4,79 нг/мл	Нет влияния
31		Дексаметазон	0,6 мкг/мл	Нет влияния
32		Флунизолид	0,61 мкг/мл	Нет влияния
33		Триамцинолон	1,18 нг/мл	Нет влияния
34		Будесонид	2,76 нг/мл	Нет влияния
35		Мометазон	1,28 нг/мл	Нет влияния
36		Флутиказон	2,31 нг/мл	Нет влияния
37		Сера	9,23 мкг/мл	Нет влияния
38		Бензокаин	0,13 мг/мл	Нет влияния
39		Ментол	0,15 мг/мл	Нет влияния
40		Мупироцин	10 мкг/мл	Нет влияния
41		Тобрамицин	24,03мкг/мл	Нет влияния
42		Биотин	1,2 мкг/мл	Нет влияния
43		HAMA (человеческие анти-мышиные антитела)	63,0 нг/мл	Нет влияния

6. Повторяемость и воспроизводимость

Повторяемость и воспроизводимость Экспресс-тест Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) была определена с использованием собственных эталонных панелей, содержащих отрицательные образцы и ряд положительных образцов. Различий в внутри одной серии, между сериями, между центрами и между днями не наблюдали.

ПОДГОТОВКА

1 Перед тестированием выдержите все компоненты набора в течение 30 минут при температуре 15-30 °C
Примечание: Медицинский работник должен соблюдать правила техники безопасности, включая использование средств индивидуальной защиты.

2 **Откройте упаковку и проверьте комплектность:**

1. Тест-кассета в индивидуальной вакуумной упаковке с осушителем
2. Буфер
3. Пробирка экстракционная
4. Колпачок для пробирки экстракционной
5. Положительный контрольный образец
6. Отрицательный контрольный образец
7. Стерильные назальные тампоны для сбора образцов
8. Штатив
9. Краткое руководство
10. Инструкция по применению

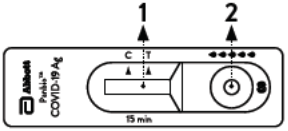
3 Перед использованием Экспресс-теста Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) внимательно прочитайте данные инструкции.

4 Проверьте срок годности набора. Если срок годности прошел, используйте другой набор.

5 **Откройте индивидуальную упаковку тест-кассеты и проверьте комплектность:**

1. Окно результата
2. Ячейка для образца

Затем наклейте на тест-кассету идентификатор пациента.

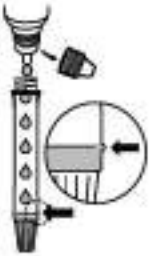


●●●●●: 5 капель раствора из экстракционной пробирки

ПРОЦЕДУРА ТЕСТИРОВАНИЯ

1 Держа флакон с буфером вертикально наполните экстракционную пробирку буферным раствором, пока она не дойдет до линии заполнения экстракционной пробирки (300 мкл).

⚠ **Предупреждение:** Если объем буфера чрезмерен или недостаточен, результат теста может быть неправильным.



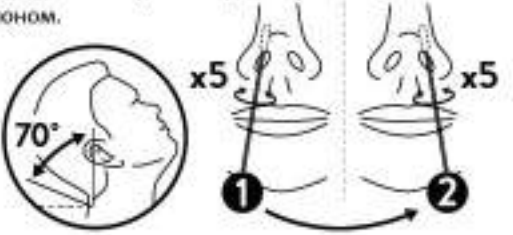
2 Установите экстракционную пробирку в штатив.

3 Наклоните голову пациента назад на 70 градусов. Осторожно вращая тампон, введите тампон на расстояние менее одного дюйма (около 2 см) в ноздрю (до тех пор, пока не возникнет сопротивление носовых раковин).

Поверните тампон пять раз так, чтобы он плотно касался поверхности стенки носа, затем медленно удалите его из ноздри.

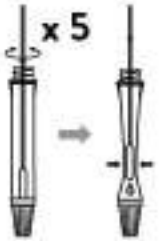
Используя тот же тампон, повторите процедуру сбора со второй ноздри.

⚠ **Предупреждение:** Внимание! Если палочка тампона сломалась во время отбора мазка, повторите сбор мазка с новым тампоном.



ПРОЦЕДУРА ТЕСТИРОВАНИЯ

4 Вставьте тампон с образцом в экстракционную пробирку. Наконечник тампона проворачивают в буферном растворе внутри экстракционной пробирки, вдавливая его в стенку экстракционной пробирки не менее пяти раз, а затем тампон выжимают, сдавливая экстракционную пробирку пальцами.

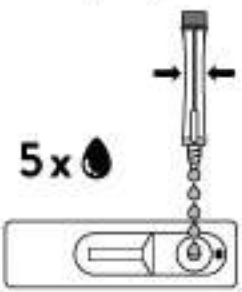


5 Тампон разламывают в точке разлома, и колпачок для пробирки экстракционной закрывают.

6 Откройте крышку колпачка - капельницы в нижней части экстракционной пробирки.

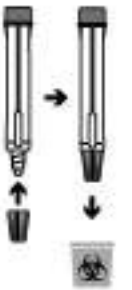
7 Внесите 5 капель раствора из экстракционной пробирки вертикально в ячейку для образца (S) на тест-кассете. Не трогайте и не перемещайте тест-кассету, пока тест не будет завершен и готов к считыванию.

⚠ **Предупреждение:** Пузырьки, возникающие в экстракционной пробирке, могут привести к неточным результатам. Если отмерить достаточное количество капель не удается, это может быть вызвано засорением колпачка-капельницы. Осторожно встряхните пробирку, чтобы устранить обструкцию, пока не образуются свободные капли.



ПРОЦЕДУРА ТЕСТИРОВАНИЯ

8 Закройте колпачок-капельницу, и утилизируйте экстракционную пробирку, содержащую использованный тампон в соответствии с местными правилами и протоколом утилизации биологически опасных отходов.



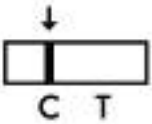
9 Запустите таймер. Результат можно считывать через 15 минут. Не считывайте результаты, если прошло 20 минут и больше.

10 Использованную тест-кассету утилизируют в соответствии с местными правилами и протоколом утилизации биологически опасных отходов.

ИНТЕРПРЕТАЦИЯ ТЕСТА

ОТРИЦАТЕЛЬНЫЙ

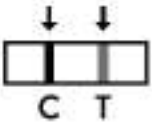
Наличие только контрольной линии (C) и отсутствие тестовой линии (T) в окошке для считывания указывает на отрицательный результат теста.

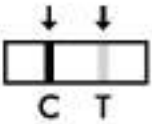


ПОЛОЖИТЕЛЬНЫЙ

Положительный результат: Наличие тестовой (T) и контрольной (C) линии в окне результата, независимо от того, какая линия появляется первой, указывает на положительный результат.

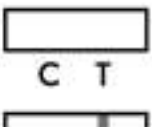
⚠ **Предупреждение:** Наличие тестовой линии (T), какой бы слабой она ни была, свидетельствует о положительном результате.

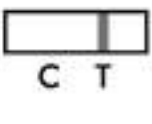




НЕВЕРНЫЙ РЕЗУЛЬТАТ

Если контрольная линия (C) не видна в окне результатов после выполнения теста, результат считается неверным. Инструкции могли быть выполнены неправильно. В этом случае рекомендуется снова прочитать инструкцию по применению перед повторным тестированием образца с использованием новой тест-кассетой.





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GLOSSARY OF SYMBOLS / SYMBOLVERZEICHNIS / GLOSARIO DE SÍMBOLOS / GLOSSAIRE DES SYMBOLES / GLOSSARIO DEI SIMBOLI / GLOSSÁRIO DE SÍMBOLOS / ГЛОССАРИЙ ОБОЗНАЧЕНИЙ

	Temperature limitation Temperaturbegrenzung Limitación de temperatura Limitation de température Limitazione di temperatura Limitação de temperatura Температурный диапазон
IVD	For *in vitro* diagnostic use only Medizinprodukt für *in-vitro* Diagnostik Sólo para uso diagnóstico *in vitro* Pour un usage de diagnostic *in vitro* uniquement Ad uso esclusivo diagnostico *in vitro* Somente para uso para diagnóstico *in vitro* Медицинское изделие для диагностики *In Vitro*
	Do not reuse Nicht wiederverwenden No reutilizar Ne pas réutiliser Non riutilizzare Não reutilizar Не использовать повторно
	Do not use if package is damaged Bei beschädigter Verpackung nicht verwenden No lo use si el paquete está dañado Ne pas utiliser si le colis est endommagé Non utilizzare se la confezione è danneggiata Não use se o pacote estiver danificado Не используйте, если упаковка повреждена

LOT	Lot Number Chargencode Número de lote Numéro de lot Numero di lotto Número de Lote Номер серии
REF	Catalog Number Artikelnummer Número de catalogo Numéro de catalogue Numero di catalogo Número no Catálogo Каталожный номер
	Consult instructions for use Gebrauchsanleitung beachten Consultar instrucciones de uso Consulter les instructions d'utilisation Consultare le istruzioni per l'uso Consulte as instruções de uso См. Инструкцию по применению
	Keep dry Trocken aufbewahren Mantener seco Garder au sec Mantenere asciutto Manter seco Хранить в сухом месте
	Biological Risks Biologisches Risiko Riesgos biológicos Risques biologiques Rischi biologici Riscos Biológicos Биологическая опасность
	Use By Verwendbar bis Usar por Utiliser par Utilizzare per Usar até Использовать до

	Manufacturer Hersteller Fabricante Fabricant Produttore Fabricante Производитель
	Date of manufacture Herstellungsdatum Fecha de manufactura Date de fabrication Data di produzione Data de fabricação Дата производства
	Keep away from sunlight Von Sonnenlicht fernhalten Mantener alejado de la luz solar Tenir à l'écart de la lumière du soleil Tenere lontano dalla luce solare Manter longe da luz solar Беречь от попадания солнечных лучей
	CE mark CE Zeichen Marca CE Marquage CE Marcatura CE Marca CE Знак соответствия продукции техническим регламентам ЕС
	Contains sufficient for X tests Ausreichend für X Prüfungen Contiene suficiente para X pruebas Contient suffisamment pour les tests X Contenuto sufficiente per X test Contém suficiente para X testes Содержит материалы, достаточные для выполнения X тестов
	Caution Achtung Precaución Attention Attenzione Cuidado Предупреждение

STERILE EO	Sterilized using ethylene oxide Sterilisiert mit Ethylenoxid Esterilizado con óxido de etileno. Stérilisé à l'oxyde d'éthylène Sterilizzato con ossido di etilene Esterilizado com óxido de etileno Стерилизовано окисидом этилена
STERILE R	Sterilized using irradiation Sterilisiert durch Bestrahlung Esterilizado mediante irradiación. Stérilisé par irradiation Sterilizzato con irradiazione Esterilizado por irradiação Стерилизовано с использованием облучения
2	Do not re-sterilize Nicht sterilisieren No volver a esterilizar Ne pas re-stériliser Non risterilizzare Não reesterilize Не стерилизуйте повторно
CONTROL -	Negative control Negative Kontrolle Control negativo Contrôle négatif Controllo negativo Controle negativo Отрицательный контроль
CONTROL +	Positive control Positive Kontrolle Control positivo Contrôle positif Controllo positivo Controle positivo Положительный контроль

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Europe & Middle East / Europa & Mittlerer Osten / Europa y Medio Oriente / Europe & Moyen Orient / Europe & Middle East / Europa e Oriente Médio / Европа, Ближний Восток	+44 161 483 9032 EMEproductsupport@abbott.com
Africa, Russia & CIS / Afrika, Russland & CIS / África, Rusia y CEI / Afrique, Russie & CIS / Africa, Russia & CIS / África, Rússia e CEI / Африка, Россия и СНГ	+27 10 500 9700 ARCISproductsupport@abbott.com
Asia Pacific / Asien Pazifik / Asia Pacífico / Asie Pacifique / Asia Pacific / Ásia-Pacífico / Азия, Океания	+61 7 3363 7711 APproductsupport@abbott.com
Latin America / Lateinamerika / America Latina / Amérique Latine / Latin America / América Latina / Латинская Америка	+57 2 661 8797 LAproductsupport@abbott.com

Abbott Rapid Diagnostics Jena GmbH
Orlaweg 1, D-07743 Jena, Germany
abbott.com/poct

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Abbott

REF 41FK10

CE

Panbio™

COVID-19 Ag Rapid Test Device

(NASOPHARYNGEAL)

In vitro **diagnostic rapid test for qualitative detection of SARS-CoV-2 antigen (Ag)**

In-vitro **diagnostischer Schnelltest zum qualitativen Nachweis von SARS-CoV-2 Antigen (Ag)**

Prueba rápida de diagnóstico *In vitro* para la detección cualitativa del antígeno (Ag) del SARS-CoV-2

Test rapide de diagnostic *in vitro* pour la détection qualitative de l'antigène SARS-CoV-2 (Ag)

Test diagnostico rapido *in vitro* per la ricerca qualitativa dell'antigene SARS-CoV-2 (Ag)

Teste rápido de diagnóstico *in vitro* para detecção qualitativa do antígeno SARS-CoV-2 (Ag)

Экспресс-тест *in vitro* для качественного определения антигена SARS-CoV-2 (Ag)

About the Test

EN

Introduction

The Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. The SARS-CoV-2 is a β-coronavirus, which is an enveloped non-segmented positive-sense RNA virus[2]. It is spread by human-to-human transmission via droplets or direct contact, and infection has been estimated to have a mean incubation period of 6.4 days and a basic reproduction number of 2.24-3.58. Among patients with pneumonia caused by SARS-CoV-2, fever was the most common symptom, followed by cough[3]. The main IVD assays used for COVID-19 employ real-time reverse transcriptase-polymerase chain reaction (RT-PCR) that takes a few hours[4]. The availability of a cost-effective, rapid point-of-care diagnostic test is critical to enable healthcare professionals to aid in the diagnosis of patients and prevent further spread of the virus[5]. Antigen tests will play a critical role in the fight against COVID-19[6].

Test Principle

Panbio™ COVID-19 Ag Rapid Test Device contains a membrane strip, which is pre-coated with immobilized anti-SARS-CoV-2 antibody on the test line and mouse monoclonal anti-chicken IgY on the control line. Two types of conjugates (human IgG specific to SARS-CoV-2 Ag gold conjugate and chicken IgY gold conjugate) move upward on the membrane chromatographically and react with anti-SARS-CoV-2 antibody and pre-coated mouse monoclonal anti-chicken IgY respectively. For a positive result, human IgG specific to SARS-CoV-2 Ag gold conjugate and anti-SARS-CoV-2 antibody will form a test line in the result window. Neither the test line nor the control line are visible in the result window prior to applying the patient specimen. A visible control line is required to indicate a test result is valid.

Intended Use

Panbio™ COVID-19 Ag Rapid Test Device is an *in vitro* diagnostic rapid test for the qualitative detection of SARS-CoV-2 antigen (Ag) in human nasopharyngeal swab specimens from individuals who meet COVID-19 clinical and / or epidemiological criteria. Panbio™ COVID-19 Ag Rapid Test Device is for professional use only and is intended to be used as an aid in the diagnosis of SARS-CoV-2 infection. The product may be used in any laboratory and non-laboratory environment that meets the requirements specified in the Instructions for Use and local regulation. The test provides preliminary test results. Negative results don't preclude SARS-CoV-2 infection and they cannot be used as the sole basis for treatment or other management decisions. Negative results must be

combined with clinical observations, patient history, and epidemiological information. The test is not intended to be used as a donor screening test for SARS-CoV-2.

Materials Provided

- 25 Test devices with desiccant in individual foil pouch
- Buffer (1 x 9 ml/bottle)
- 25 Extraction tubes
- 25 Extraction tube caps
- 1 Positive control swab
- 1 Negative control swab
- 25 Sterilized nasopharyngeal swabs for sample collection
- 1 Tube rack
- 1 Quick reference guide (Nasopharyngeal)
- 1 Instructions for use

Materials Required but not Provided

- Personal Protective Equipment per local recommendations (i.e. gown/lab coat, face mask, face shield/eye goggles and gloves), Timer, Biohazard container

Active Ingredients of Main Components

- **1 Test device** Gold conjugate: Human IgG specific to SARS-CoV-2 Ag gold colloid and Chicken IgY - gold colloid, Test line: Mouse monoclonal anti-SARS-CoV-2, Control line: Mouse monoclonal anti-Chicken IgY
- **Buffer** Tricine, Sodium Chloride, Tween 20, Sodium Azide (<0.1%), Proclin 300

Storage and Stability

1. The test kit should be stored at a temperature between 2-30 °C. Do not freeze the kit or its components.
   Note: When stored in a refrigerator, all kit components must be brought to room temperature (15-30 °C) for a minimum of 30 minutes prior to performing the test. Do not open the pouch while components come to room temperature.
2. The Buffer bottle may be opened and resealed for each assay. The Buffer cap should be firmly sealed between each use. The Buffer is stable until expiration date if kept at 2-30 °C.
3. Perform the test immediately after removing the test device from the foil pouch.

4. Do not use the test kit beyond its expiration date.
5. The shelf life of the kit is as indicated on the outer package.
6. Do not use the test kit if the pouch is damaged or the seal is broken.
7. Direct swab specimens should be tested immediately after collection. If immediate testing is not possible, the swab specimen can be kept in an extraction tube filled with extraction buffer (300 µl) at room temperature (15-30 °C) for up to two hours prior to testing.

Warnings

1. For *in vitro* diagnostic use only. Do not reuse the test device and kit components.
2. These instructions must be strictly followed by a trained healthcare professional to achieve accurate results. All users have to read the instruction prior to performing a test.
3. Do not eat or smoke while handling specimens.
4. Wear protective gloves while handling specimens and wash hands thoroughly afterwards.
5. Avoid splashing or aerosol formation of specimen and buffer.
6. Clean up spills thoroughly using an appropriate disinfectant.
7. Decontaminate and dispose of all specimens, reaction kits and potentially contaminated materials (i.e. swab, extraction tube, test device) in a biohazard container as if they were infectious waste and dispose according to applicable local regulations.
8. Do not mix or interchange different specimens.
9. Do not mix reagent of different lots or those for other products.
10. Do not store the test kit in direct sunlight.
11. To avoid contamination, do not touch the head of provided swab when opening the swab pouch.
12. The provided sterilized swabs in the package should be used only for nasopharyngeal specimen collection.
13. To avoid cross-contamination, do not reuse the sterilized swabs for specimen collection.
14. Do not dilute the collected swab with any solution except for the provided extraction buffer.
15. The buffer contains <0.1% sodium azide as a preservative which may be toxic if ingested. When disposed of through a sink, flush with a large volume of water.[7]

Test Procedure (Refer to Figure)

Nasopharyngeal Swab Specimens

Note: Healthcare professionals should comply with personal safety guidelines including the use of personal protective equipment.

Test Preparation

1. Allow all kit components to reach a temperature between 15-30 °C prior to testing for 30 minutes.
2. Remove the test device from the foil pouch prior to use. Place on a flat, horizontal and clean surface.
3. Hold the buffer bottle vertically and fill the extraction tube with buffer fluid until it flows up to the Fill-line of the extraction tube (300 µl).

⚠ **Caution:** If the amount of buffer is excessive or insufficient, an improper test result may occur.

4. Place the extraction tube in the tube rack.

Specimen Collection & Extraction

1. Tilt the patient's head back slightly about 45°-70° to straighten the passage from the front of the nose.
2. Insert the swab with a flexible shaft through the nostril parallel to the palate.

⚠ **Caution:** Use dedicated nasopharyngeal swab for specimen collection.

3. Swab should reach depth equal to distance from nostrils to outer opening of the ear.

⚠ **Caution:** If resistance is encountered during insertion of the swab, remove it and attempt insertion in the opposite nostril.

4. Gently rub and roll the swab, 3-4 times. Leave the swab in place for several seconds to absorb secretions.
5. Slowly remove swab while rotating it and insert into the extraction tube.
6. Swirl the swab tip in the buffer fluid inside the extraction tube, pushing into the wall of the extraction tube at least five times and then squeeze out the swab by squeezing the extraction tube with your fingers.
7. Break the swab at the breakpoint and close the cap of extraction tube.

Reaction with Test Device

1. Open the dropping nozzle cap at the bottom of the extraction tube.
2. Dispense 5 drops of extracted specimens vertically into the specimen well (S) on the device. Do not handle or move the test device until the test is complete and ready for reading.

⚠ **Caution:** Bubbles that occur in the extraction tube can lead to

inaccurate results. If you are unable to create sufficient drops, this may be caused by clogging in the dispensing nozzle. Shake the tube gently to release the blockage until you observe free drop formation.

3. Close the nozzle and dispose of the extraction tube containing the used swab according to your local regulations and biohazard waste disposal protocol.
4. Start timer. Read result at 15 minutes. Do not read results after 20 minutes.
5. Dispose of the used device according to your local regulations and biohazard waste disposal protocol.

Positive / Negative Control Swab

Note: Please refer to the External Quality Control section of this Instructions for use for the frequency of testing external quality control swabs.

1. Hold the buffer bottle vertically and fill the extraction tube with buffer fluid until it flows up to the Fill-line of the extraction tube (300 µl).

⚠ **Caution:** If the amount of buffer is excessive or insufficient, an improper test result may occur.

2. Place the extraction tube in the tube rack.
3. Insert the positive or negative control swab in the buffer fluid inside of the extraction tube and soak the swab for 1 minute. Swirl the control swab tip in the buffer fluid inside of the extraction tube, pushing into the wall of the extraction tube at least five times and then squeeze out the swab by squeezing the extraction tube with your fingers.
4. Dispose of the used control swab in accordance with your biohazard waste disposal protocol.
5. Close the cap of the extraction tube.
6. Follow the above test procedure [Reaction with Test Device].

Test Interpretation (Refer to Figure)

1. Negative result: The presence of only the control line (C) and no test line (T) within the result window indicates a negative result.
2. Positive result: The presence of the test line (T) and the control line (C) within the result window, regardless of which line appears first, indicates a positive result.

⚠ **Caution:** The presence of any test line (T), no matter how faint, indicates a positive result.

3. Invalid result: If the control line (C) is not visible within the result window after performing the test, the result is considered invalid.

Test Limitations

1. The contents of this kit are to be used for the professional and qualitative detection of SARS-CoV-2 antigen from nasopharyngeal swab. Other specimen types may lead to incorrect results and must not be used.
2. Failure to follow the instructions for test procedure and interpretation of test results may adversely affect test performance and/or produce invalid results.
3. A negative test result may occur if the specimen was collected, extracted or transported improperly. A negative test result does not eliminate the possibility of SARS-CoV-2 infection and should be confirmed by viral culture or a molecular assay.
4. Positive test results do not rule out co-infections with other pathogens.
5. Test results must be evaluated in conjunction with other clinical data available to the physician.
6. Reading the test results earlier than 15 minutes or later than 20 minutes may give incorrect results.
7. Panbio™ COVID-19 Ag Rapid Test Device is not intended to detect from defective (non-infectious) virus during the later stages of viral shedding that might be detected by PCR molecular tests.[8]
8. Positive results may occur in cases of infection with SARS-CoV.

Quality Control

1. Internal Quality Control:

The test device has a test line (T) and a control line (C) on the surface of the test device. Neither the test line nor the control line are visible in the result window before applying a specimen. The control line is used for procedural control and should always appear if the test procedure is performed properly and the test reagents of the control line are working.

2. External Quality Control:

The controls are specifically formulated and manufactured to ensure performance of the Panbio™ COVID-19 Ag Rapid Test Device and are used to verify the user's ability to properly perform the test and interpret the results. The Positive Control will produce a positive test result and has been manufactured to produce a visible test line (T). The Negative Control will produce a negative test result.

Good laboratory practice suggests the use of positive and negative controls to ensure that:

- Test reagents are working, and
- The test is correctly performed.

The external controls can be run under any of the following circumstances:

- By a new operator prior to performing testing on patient specimens,
- When receiving a new test shipment,
- At periodic intervals as dictated by local requirements, and/or by the user's Quality Control procedures.

Performance Characteristics

1. External evaluation of Panbio™ COVID-19 Ag Rapid Test Device

Clinical performance of Panbio™ COVID-19 Ag Rapid Test Device was determined by testing 140 positive and 445 negative specimens for SARS-CoV-2 antigen (Ag) to have a sensitivity of 91.4% (95% CI: 85.5-95.5%) and specificity of 99.8% (95% CI: 98.8-100%). Clinical specimens were determined to be positive or negative using an FDA EUA RT-PCR reference method.

Panbio™ COVID-19 Ag Rapid Test Device Results

		PCR Test Result		
		Positive	**Negative**	**Total**
Panbio™ COVID-19 Ag Rapid Test Device Results	**Positive**	128	1	129
	Negative	12	444	456
	Total	140	445	585
		Sensitivity	Specificity	Overall Percent Agreement
		91.4% [85.5%;95.5%]	**99.8%** [98.8%;100%]	**97.8%** [96.2%;98.8%]

- Performance data was calculated from a study of individuals suspected of exposure to COVID-19 or who have presented with symptoms in the last 7 days.
- Stratification of the positive specimens post onset of symptoms or suspected exposure between 0-3 days has a sensitivity of 94.9% (n=39) and 4-7 days has a sensitivity of 90.1% (n=101).
- Positive agreement of the Panbio™ COVID-19 Ag Rapid Test Device is higher with samples of Ct values ≤33 with a sensitivity of 94.1%. As suggested in References 8 and 9, patients with Ct value >33 are no longer contagious.[8, 9]

2. Detection Limit

Panbio™ COVID-19 Ag Rapid Test Device was confirmed to detect $2.5X10^{1.8}$ $TCID_{50}$/ml of SARS-CoV-2 which was isolated from a COVID-19 confirmed patient in Korea.

3. **Hook Effect**
   There is no hook effect at $1.0x10^{5.8}$ $TCID_{50}$/ml of SARS-CoV-2 which was isolated from a COVID-19 confirmed patient in Korea.
4. **Cross Reactivity**
   Cross-reactivity of Panbio™ COVID-19 Ag Rapid Test Device was evaluated by testing 25 viruses and 14 other microorganisms. The final test concentrations of viruses and other microorganisms are documented in the Table below. The following viruses and other microorganisms except the Human SARS-coronavirus Nucleoprotein have no effect on the test results of Panbio™ COVID-19 Ag Rapid Test Device. Panbio™ COVID-19 Ag Rapid Test Device has cross-reactivity with Human SARS-coronavirus Nucleoprotein at a concentration of 25 ng/ml or more because SARS-CoV has high homology (79.6%) to the SARS-CoV-2.

No.	Types of Specimen	Cross Reaction Substance	Final Test Concentration	Test Result
1	Virus	Adenovirus Type3	$2.0 X 10^{6.5}$ $TCID_{50}$/ml	No cross reaction
2		Adenovirus Type7	$2.0 X 10^{4.75}$ $TCID_{50}$/ml	No cross reaction
3		Echovirus2	$1.0 X 10^{6.5}$ $TCID_{50}$/ml	No cross reaction
4		Echovirus11	$2.0 X10^{5.25}$ $TCID_{50}$/ml	No cross reaction
5		Human herpesvirus (HSV) 1	$2.0 X 10^{6.25}$ $TCID_{50}$/ml	No cross reaction
6		Human herpesvirus (HSV) 2	$2.0 X 10^{4.75}$ $TCID_{50}$/ml	No cross reaction
7		Mumps Virus Ag	$2.0 X 10^{3.5}$ $TCID_{50}$/ml	No cross reaction
8		Influenza virus A (H1N1) Strain (A/Virginia/ATCC1/2009)	$2.6 X 10^{5.0}$ PFU/ml	No cross reaction
9		Influenza virus A (H1N1) Strain (A/WS/33)	$5.0 X 10^{7.25}$ $TCID_{50}$/ml	No cross reaction
10		Influenza virus A(H3N2) Strain (A/Hong Kong/8/68)	N/A*	No cross reaction

No.	Types of Specimen	Cross Reaction Substance	Final Test Concentration	Test Result
11	Virus	Influenza virus B Strain (B/Lee/40)	2.0 X $10^{5.25}$ $TCID_{50}$/ml	No cross reaction
12-14		Parainfluenza Type 1, Parainfluenza Type 2, Parainfluenza Type 3	N/A*	No cross reaction
15		Parainfluenza Type 4A	1.97 X $10^{7.0}$ PFU/ml	No cross reaction
16		Respiratory syncytial virus (RSV) type A	4.22 X $10^{5.0}$ $TCID_{50}$/ml	No cross reaction
17		Respiratory syncytial virus (RSV) type B	5.62 X $10^{5.0}$ $TCID_{50}$/ml	No cross reaction
18		HCoV-HKU1	10 µg/ml	No cross reaction
19		Rhinovirus A16	8.8 X $10^{5.0}$ PFU/ml	No cross reaction
20		HCoV-NL63	1.7 X $10^{5.0}$ $TCID_{50}$/ml	No cross reaction
21		HCoV-OC43	8.9 X $10^{5.0}$ $TCID_{50}$/ml	No cross reaction
22		HCoV-229E	1.51 X $10^{6.0}$ $TCID_{50}$/ml	No cross reaction
23		Human SARS-coronavirus Nucleoprotein	25 ng/ml	Cross reaction
24		MERS-CoV Nucleoprotein	0.25 mg/ml	No cross reaction
25		Human Metapneumovirus (hMPV) 16 Type A1	1.06 X $10^{6.0}$ PFU/ml	No cross reaction

No.	Types of Specimen	Cross Reaction Substance	Final Test Concentration	Test Result
1	Other Microorganism	*Staphylococcus aureus*	1.0 X $10^{6.0}$ CFU/ml	No cross reaction
2		*Staphylococcus saprophyticus*	1.0 X $10^{6.0}$ CFU/ml	No cross reaction
3		*Neisseria sp.(Neisseria lactamica)*	1.0 X $10^{6.0}$ CFU/ml	No cross reaction
4		*Escherichia coli*	1.0 X $10^{6.0}$ CFU/ml	No cross reaction
5		*Staphylococcus haemolyticus*	1.0 X $10^{6.0}$ CFU/ml	No cross reaction
6		*Streptococcus pyogenes*	1.0 X $10^{6.0}$ CFU/ml	No cross reaction
7		*Streptococcus salivarius*	1.0 X $10^{6.0}$ CFU/ml	No cross reaction
8		*Hemophilus parahaemolyticus*	1.0 X $10^{6.0}$ CFU/ml	No cross reaction
9		*Proteus vulgaris*	1.0 X $10^{6.0}$ CFU/ml	No cross reaction
10		*Moraxella catarrhalis*	1.0 X $10^{6.0}$ CFU/ml	No cross reaction
11		*Klebsiella pneumoniae*	1.0 X $10^{6.0}$ CFU/ml	No cross reaction
12		*Fusobacterium necrophorum*	1.0 X $10^{6.0}$ CFU/ml	No cross reaction
13		*Mycobacterum tuberculosis*	10 mg/ml	No cross reaction
14		*Pooled human nasal wash*	N/A*	No cross reaction

** No concentration provided by supplier. Undiluted stock solution was tested.*

5. Interfering Substances

The following 42 potentially interfering substances have no impact on Panbio™ COVID-19 Ag Rapid Test Device. The final test concentrations of the interfering substances are documented in the Table below.

No.	Types of Specimen	Interfering Substances	Final Test Concentration	Test Result
1	Endogenous Substance	Mucin	0.5%	No Interference
2		Hemoglobin	100 mg/L	No Interference
3		Triglycerides	1.5 mg/L	No Interference
4		Icteric (Bilirubin)	40 mg/dL	No Interference
5		Rheumatoid factor	200 IU/ml	No Interference
6		Anti-nuclear antibody	>1:40	No Interference
7		Pregnant	10-fold dilution	No Interference
8	Exogenous Substance	Guaiacol glyceryl ether	1 µg/ml	No Interference
9		Albuterol	0.005 mg/dL	No Interference
10		Ephedrine	0.1 mg/ml	No Interference
11		Chlorpheniramine	0.08 mg/dL	No Interference
12		Diphenhydramine	0.08 mg/dL	No Interference
13		Ribavirin	26.7 µg /ml	No Interference
14		Oseltamivir	0.04 mg/dL	No Interference
15		Zanamivir	17.3 µg /ml	No Interference
16		Phenylephrine hydrochloride	15% v/v	No Interference
17		Oxymetazolin hydrochloride	15% v/v	No Interference
18		Amoxicillin	5.4 mg/dL	No Interference
19		Acetylsalicylic acid	3 mg/dL	No Interference
20		Ibuprofen	21.9 mg/dL	No Interference
21		Chlorothiazide	2.7 mg/dL	No Interference

No.	Types of Specimen	Interfering Substances	Final Test Concentration	Test Result
22	Exogenous Substance	Indapamide	140 ng/ml	No Interference
23		Glimepiride (Sulfonylureas)	0.164 mg/dL	No Interference
24		Acarbose	0.03 mg/dL	No Interference
25		Ivermectin	4.4 mg/L	No Interference
26		Lopinavir	16.4 µg/L	No Interference
27		Ritonavir	16.4 µg/L	No Interference
28		Chloroquine phosphate	0.99 mg/L	No Interference
29		Sodium chloride with preservatives	4.44 mg/ml	No Interference
30		Beclomethasone	4.79 ng/ml	No Interference
31		Dexamethasone	0.6 µg/ml	No Interference
32		Flunisolide	0.61 µg/ml	No Interference
33		Triamcinolone	1.18 ng/ml	No Interference
34		Budesonide	2.76 ng/ml	No Interference
35		Mometasone	1.28 ng/ml	No Interference
36		Fluticasone	2.31 ng/ml	No Interference
37		Sulfur	9.23 µg/ml	No Interference
38		Benzocaine	0.13 mg/ml	No Interference
39		Menthol	0.15 mg/ml	No Interference
40		Mupirocin	10 µg/ml	No Interference
41		Tobramycin	24.03 µg/ml	No Interference
42		Biotin	1.2 µg/ml	No Interference

6. Repeatability & Reproducibility

Repeatability & Reproducibility of Panbio™ COVID-19 Ag Rapid Test Device was established using in-house reference panels containing negative specimens and a range of positive specimens. There were no differences observed within-run, between-run, between-lots, between-sites, and between-days.

PREPARATION

1 Allow all kit components to reach a temperature between 15-30°C prior to testing for 30 minutes.
Note: Healthcare professionals should comply with personal safety guidelines including the use of personal protective equipment.

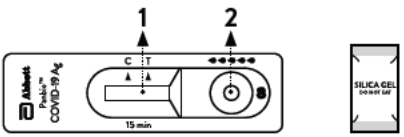
2 **Open the package and look for the following:**
1. Test device with desiccant in individual foil pouch
2. Buffer
3. Extraction tube
4. Extraction tube cap
5. Positive control swab
6. Negative control swab
7. Sterilized nasopharyngeal swabs for sample collection
8. Tube rack
9. Quick reference guide (Nasopharyngeal)
10. Instructions for use

3 Carefully read these instructions prior to using Panbio™ COVID-19 Ag Rapid Test Device kit.

4 Look at the expiration date of the kit box. If the expiration date has passed, use another kit.

5 **Open the foil pouch and look for the following:**
1. Result window
2. Specimen well

Then, label the device with the patient identifier.



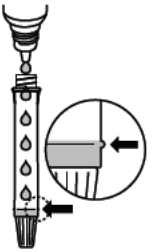
: 5 drops of the extracted specimen

ENGLISH

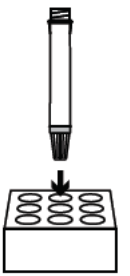
TEST PROCEDURE

1 Hold the buffer bottle vertically and fill the extraction tube with buffer fluid until it flows up to the Fill-line of the extraction tube (300µl).

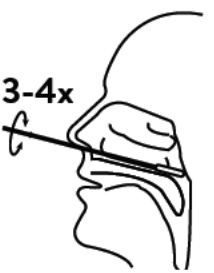
⚠ **Caution:** If the amount of buffer is excessive or insufficient, an improper test result may occur.



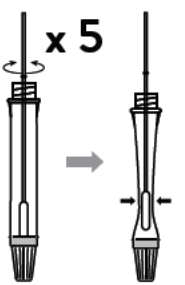
2 Place the extraction tube in the tube rack.



3 Tilt the patient's head back. Insert the swab through the nostril. Gently rub and roll the swab, 3-4 times. Leave the swab in place for several seconds. Slowly remove swab.

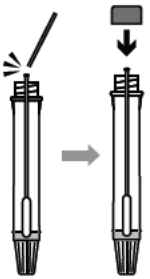


4 Insert the swab specimen in the extraction tube. Swirl the swab tip in the buffer fluid inside the extraction tube, pushing into the wall of the extraction tube at least five times and then squeeze out the swab by squeezing the extraction tube with your fingers.



TEST PROCEDURE

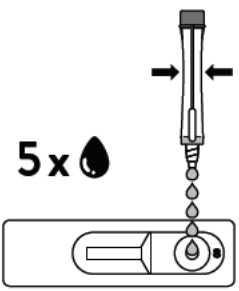
5 Break the swab at the breakpoint and close the cap of extraction tube.



6 Open the dropping nozzle cap at the bottom of the extraction tube.

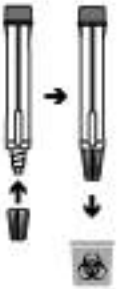
7 Dispense 5 drops of extracted specimens vertically into the specimen well (S) on the device. Do not handle or move the test device until the test is complete and ready for reading.

⚠ **Caution:** Bubbles that occur in the extraction tube can lead to inaccurate results. If you are unable to create sufficient drops, this may be caused by clogging in the dispensing nozzle. Shake the tube gently to release the blockage until you observe free drop formation.



TEST PROCEDURE

8 Close the nozzle and dispose of the extraction tube containing the used swab according to your local regulations and biohazard waste disposal protocol.



9 Start timer. Read result at 15 minutes. Do not read results after 20 minutes.

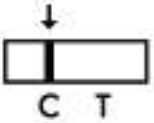
10 Dispose of the used device according to your local regulations and biohazard waste disposal protocol.

ENGLISH

TEST INTERPRETATION

NEGATIVE

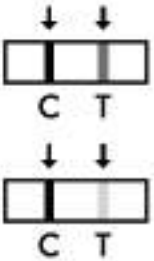
The presence of only the control line (C) and no test line (T) within the result window indicates a negative result.



POSITIVE

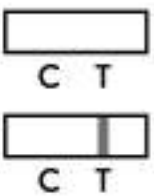
The presence of the test line (T) and the control line (C) within the result window, regardless of which line appears first, indicates a positive result.

⚠ **Caution**: The presence of any test line (T), no matter how faint, indicates a positive result.



INVALID

If the control line (C) is not visible within the result window after performing the test, the result is considered invalid. Instructions may not have been followed correctly. It is recommended to read the IFU again before re-testing the specimen with a new test device.



ENGLISH

Über den Test

DE

Übersicht

Die Coronavirus Krankheit (Covid-19) ist eine Infektionskrankheit. Sie wird verursacht durch das neuartige Coronavirus, das schwere akute respiratorische Syndrom Coronavirus 2 (SARS-CoV-2)[1]. SARS-CoV-2 gehört der Gattung β an, bei dem es sich um ein umhülltes, nicht segmentiertes RNA-Virus mit positiver Polarität handelt[2]. Es wird über Tröpfchen oder direkten Kontakt von Mensch zu Mensch übertragen. Für die Infektion wurde eine Inkubationszeit von 6,4 Tagen ermittelt und die geschätzte Reproduktionszahl liegt bei 2,24-3,58. Bei Patienten mit einer durch SARS-CoV-2 verursachten Lungenentzündung war Fieber das häufigste Symptom, gefolgt von Husten[3]. Der am häufigsten für COVID-19 verwendete IVD-Assay ist die Reverse Transkriptase-Polymerase-Kettenreaktion (RT-PCR) in Echtzeit, die nur wenige Stunden dauert[4]. Die Verfügbarkeit eines kostengünstigen, schnellen diagnostischen Point-of-Care-Diagnosetests ist von entscheidender Bedeutung für die Unterstützung des medizinischen Fachpersonals bei der Diagnose von Patienten und somit für die Verhinderung einer weiteren Verbreitung des Virus[5]. Antigentests werden im Kampf gegen COVID-19 eine entscheidende Rolle spielen[6].

Testprinzip

Panbio™ COVID-19 Ag Rapid Test Device beinhaltet einen Membranstreifen, der auf der Testlinie mit immobilisiertem Anti-SARS-CoV-2-Antikörpern und auf der Kontrolllinie mit monoklonalem Anti-Huhn-IgY der Maus vorbeschichtet ist. Zwei Arten von Konjugaten (humanes IgG, spezifisch für SARS-CoV-2 Ag Goldkonjugat und Hühner-IgY-Goldkonjugat) bewegen sich chromatographisch auf der Membran nach oben und reagieren mit dem Anti-SARS-CoV-2-Antikörper bzw. dem vorbeschichteten monoklonalen Anti-Hühner-IgY der Maus. Bei einem positiven Ergebnis bildet humanes IgG, das spezifisch für das Goldkonjugat SARS-CoV-2 Ag ist mit dem Anti-SARS-CoV-2-Antikörper eine Testlinie im Testergebnislesefenster. Weder die Testlinie noch die Kontrolllinie sind vor dem Auftragen der Patientenprobe im Testergebnislesefenster sichtbar. Eine sichtbare Kontrolllinie weist nach, dass das Testergebnis valide ist.

In-vitro diagnostischer Gebrauch

Der Panbio™ COVID-19 Ag Rapid Test Device ist ein in-vitro diagnostischer Schnelltest zum qualitativen Nachweis von SARS-CoV-2 Antigen (Ag) in menschlichen nasopharyngealen Abstrichproben von Personen, die die klinischen und / oder epidemiologischen Kriterien von COVID-19 erfüllen. Der Panbio™ COVID-19 Ag Rapid Test Device ist nur für den professionellen Gebrauch bestimmt und dient als Hilfsmittel zur Diagnose einer SARS-CoV-2 Infektion. Das Produkt kann in jeder Laborumgebung sowie Umgebungen außerhalb des Labors eingesetzt werden, die den Anforderungen aus der Gebrauchsanweisung und den vor Ort geltenden, regulatorischen

Anforderungen entsprechen. Der Test liefert vorläufige Testergebnisse.
Negative Testergebnisse schließen eine SARS CoV-2 Infektion nicht aus und dürfen nicht als alleinige Grundlage für eine weitere Behandlung oder andere Managemententscheidungen herangezogen werden.
Negative Ergebnisse müssen mit klinischen Beobachtungen, Patientenanamnesen und epidemiologischen Informationen abgeglichen werden.
Der Test ist nicht für das SARS-CoV-2 Screening von Blutspendern vorgesehen.

Bereitgestellte Materialien

- 25 Testkassetten verpackt in Folienbeutel mit Trockenmittel
- Puffer (1x 9 ml/Fläschchen)
- 25 Extraktionsröhrchen
- 25 Deckel für Extraktionsröhrchen
- 1 Positivkontrolltupfer
- 1 Negativkontrolltupfer
- 25 Sterilisierte nasopharyngeale Tupfer zur Probenahme
- 1 Ständer für Röhrchen
- 1 Kurzanleitung (Nasopharyngeal)
- 1 Gebrauchsanweisung

Zusätzlich benötigte Materialien

- Persönliche Schutzausrüstung gemäß den örtlichen Empfehlungen (d.h. Laborkittel, Gesichtsmaske, Gesichtsschutz / Schutzbrille und Handschuhe), Uhr, Biohazard-Abfallbehälter

Aktive Bestandteile der Hauptkomponenten

- **Testkassette** Goldkonjugat: Human-IgG spezifisch für SARS-CoV-2 Ag Goldkolloid und Hühner-IgY - Goldkolloid, Testlinie: Maus-monoklonales anti-SARS-CoV-2, Kontrolllinie: Maus-monoklonales Anti-Huhn IgY
- **Puffer** Tricin, Natriumchlorid, Tween 20, Natriumazid (<0,1%), Proclin 300

Lagerung und Stabilität

1. Das Test-Kit ist bei einer Temperatur von 2-30 °C zu lagern. Die Testkassette und die Komponenten des Test-Kits dürfen nicht eingefroren werden.
   Hinweis: Bei Lagerung im Kühlschrank müssen alle Komponenten mindestens 30 Minuten vor der Testdurchführung auf Raumtemperatur (15-30 °C) gebracht werden. Öffnen Sie die Verpackung nicht, während die Komponenten auf Raumtemperatur gebracht werden.

2. Die Pufferflasche kann für jeden Test geöffnet und wieder verschlossen werden. Die Kappe der Pufferflasche ist nach jedem Gebrauch fest zu verschließen. Der Puffer ist bis zum Verfallsdatum anwendbar und stabil bei einer Aufbewahrung bei 2-30 °C.
3. Führen Sie den Test umgehend nach Entnahme der Testkassette aus der Verpackung durch.
4. Verwenden Sie den Test nicht nach Ablauf des Verfallsdatums.
5. Das Verfallsdatum des Kits ist sichtbar gedruckt auf der äußeren Verpackung.
6. Verwenden Sie den Test nicht, wenn die Verpackung oder Verpackungssiegel beschädigt sind.
7. Direkte Abstrichproben sollten unmittelbar nach der Entnahme getestet werden. Wenn ein sofortiger Test nicht möglich ist, kann die Abstrichprobe in einem mit Extraktionspuffer (300 µl) gefüllten Extraktionsröhrchen bei Raumtemperatur (15-30 °C) bis zu zwei Stunden vor dem Test aufbewahrt werden.

Warnhinweise

1. Nur für den Einsatz in der In-vitro Diagnostik. Die Testkassette und die Komponenten des Kits dürfen nicht wiederverwendet werden.
2. Diese Gebrauchsanweisung ist von einer ausgebildeten, medizinischen Fachkraft strikt zu befolgen, um genaue Ergebnisse zu erzielen. Alle Anwender müssen die Anleitung vor der Test-Durchführung sorgfältig lesen.
3. Essen und Trinken Sie nicht beim Umgang mit Proben.
4. Tragen Sie bei der Handhabung der Proben Schutzhandschuhe und waschen Sie anschließend die Hände gründlich.
5. Vermeiden Sie Spritzer oder Aerosolbildung von Proben und Puffer.
6. Reinigen Sie verschüttete Flüssigkeiten gründlich mit geeigneten Desinfektionsmitteln.
7. Dekontaminieren und entsorgen Sie alle Proben, Reaktionskits und potenziell kontaminierten Materialien (d. h. Tupfer, Extraktionsröhrchen, Testkassette) in einem Behälter für biologische Gefahrenstoffe, als ob sie infektiöser Abfall wären, und entsorgen Sie sie gemäß den geltenden örtlichen Vorschriften.
8. Proben dürfen nicht gemischt werden. Stellen Sie sicher, dass Proben nicht vertauscht werden.
9. Reagenzien von verschiedenen Chargen dürfen nicht gemischt werden. Mischen Sie diese auch nicht mit anderen Produkten.
10. Test-Kits dürfen nicht unter direkter Sonneneinstrahlung gelagert werden.
11. Um Kontaminationen zu vermeiden, berühren Sie nicht beim Öffnen des Tupferbeutels die Spitze des Tupfers.

12. Die im Lieferumfang enthaltenen, sterilen Tupfer sind nur für die Entnahme von nasopharyngealen Abstrichen zu verwenden.
13. Um eine Kreuzkontamination zu vermeiden, dürfen die sterilen Tupfer nicht zur wiederholten Probenentnahme verwendet werden.
14. Verdünnen Sie den Tupfer nicht mit einer anderen Lösung als dem mitgelieferten Extraktionspuffer.
15. Der Puffer enthält <0,1% Natriumazid als Konservierungsmittel, das bei Verschlucken giftig sein kann. Bei einer Entsorgung über das Waschbecken, ist das Mittel mit einer großen Wassermenge weg zu spülen.[7]

Testablauf (siehe Abbildung)

Nasopharyngeale Proben

Hinweis: Persönliche Sicherheitsrichtlinien einschließlich der Verwendung persönlicher Schutzausrüstung sind durch das Fachpersonal einzuhalten.

Testvorbereitung

1. Stellen Sie 30 Minuten vor Testbeginn sicher, dass alle Testkomponenten Raumtemperatur haben.
2. Entfernen Sie die Testkassette aus der Verpackung. Platzieren Sie die Testkassette auf einer flachen und sauberen Oberfläche.
3. Halten Sie das Pufferfläschchen vertikal und füllen Sie das Extraktionsröhrchen mit Pufferflüssigkeit, bis die Fülllinie des Extraktionsröhrchens erreicht ist (300 µl).

⚠ **Achtung:** Bei einer zu hohen oder geringen Puffermenge sind falsche Testergebnisse möglich.

4. Stellen Sie das Extraktionsröhrchen in den Röhrchenständer.

Probensammlung und -Extraktion

1. Neigen Sie den Kopf des Patienten leicht um 45°-70° nach hinten, um den Durchgang von der Nasenvorderseite aus zu ebnen.
2. Führen Sie den Tupfer mit dem flexiblen Schaft durch das Nasenloch parallel zum Gaumen ein.

⚠ **Achtung:** Verwenden Sie zur Probenentnahme den speziellen nasopharyngealen Tupfer.

3. Der Abstrich sollte eine Tiefe erreichen, die dem Abstand von den Nasenlöchern bis zur äußeren Öffnung des Ohres entspricht.

⚠ **Achtung:** Wenn beim Einführen des Tupfers ein Widerstand spürbar ist, entfernen Sie den Tupfer und versuchen Sie, ihn in das gegenüberliegende Nasenloch einzuführen.

4. Reiben und drehen Sie den Tupfer vorsichtig 3-4 Mal. Lassen Sie den Tupfer einige Sekunden an Ort und Stelle, um Sekrete aufzunehmen.
5. Entfernen Sie den Tupfer langsam mit rotierender Bewegung und führen Sie ihn in das Extraktionsröhrchen ein.

6. Schwenken Sie die Tupferspitze in der Pufferflüssigkeit im Inneren des Extraktionsröhrchens. Drücken Sie dabei mindestens fünfmal gegen die Wand des Extraktionsröhrchens und drücken Sie anschließend denn Tupfer aus, indem Sie mit den Fingern das Extraktionsröhrchen zusammendrücken.
7. Brechen Sie den Tupferstiel an der Bruchstelle ab und schließen Sie die Kappe des Extraktionsröhrchens.

Reaktion mit der Test-Kassette

1. Öffnen Sie die Kappe der Dosieröffnung am Boden des Extraktionsröhrchens.
2. Geben Sie 5 Tropfen der extrahierten Probe senkrecht in die Probenvertiefung (S) der Testkassette. Bewegen Sie die Testkassette nicht, bis der Test abgeschlossen und zum Ablesen bereit ist.

⚠ **Achtung:** Blasen, die im Extraktionsröhrchen auftreten, können zu ungenauen Ergebnissen führen. Wenn es nicht möglich ist, genügend Tropfen zu erzeugen, kann dies an einer Verstopfung der Dosieröffnung liegen. Schütteln Sie das Röhrchen leicht, um die Verstopfung zu lösen, bis Sie eine freie Tropfenbildung beobachten können.

3. Schließen Sie die Dosieröffnung und entsorgen Sie das Extraktionsröhrchen mit dem gebrauchten Tupfer gemäß den örtlichen Vorschriften und dem Entsorgungsprotokoll für biologisch gefährliche Abfälle.
4. Starten Sie die Uhr und lesen Sie das Ergebnis nach 15 Minuten ab. Lesen Sie das Ergebnis nicht mehr nach 20 Minuten ab.
5. Entsorgen Sie die gebrauchte Testkassette gemäß den örtlichen Vorschriften und dem Entsorgungsprotokoll für biologisch gefährlichen Abfall.

Positive/ Negative Kontrolltupfer

Hinweis: Informationen zur Häufigkeit der Prüfung externer Qualitätskontrolltupfer finden Sie im Abschnitt Externe Qualitätskontrolle dieser Gebrauchsanweisung.

1. Halten Sie das Pufferfläschchen vertikal und füllen Sie das Extraktionsröhrchen mit Pufferflüssigkeit, bis die Fülllinie des Extraktionsröhrchens erreicht ist (300 µl).

⚠ **Achtung:** Bei einer zu hohen oder geringen Puffermenge sind falsche Testergebnisse möglich.

2. Stellen Sie das Extraktionsröhrchen in den Röhrchenständer.
3. Führen Sie den Positiv- oder Negativkontrolltupfer in die Pufferflüssigkeit des Extraktionsröhrchens ein und weichen Sie den Tupfer 1 Minute lang ein. Schwenken Sie die Spitze des Kontrolltupfers in der Pufferflüssigkeit im Inneren des Extraktionsröhrchens. Drücken Sie dabei den Tupfer mindestens fünfmal gegen die Wand des Extraktionsröhrchens und drücken Sie anschließend den Tupfer aus, indem Sie mit den Fingern das Extraktionsröhrchen zusammendrücken.

4. Entsorgen Sie den gebrauchten Kontrolltupfer gemäß dem Entsorgungsprotokoll für biologisch gefährliche Abfälle.
5. Schließen Sie den Deckel des Extraktionsröhrchens.
6. Befolgen Sie anschließend das obige Testverfahren [siehe Reaktion mit der Testkassette].

Testinterpretation (siehe Abbildung)

1. Negatives Ergebnis: Erscheinen eine Kontrolllinie (C) und keine Testlinie (T) innerhalb des Testergebnislesefensters, ist das Ergebnis negativ.
2. Positives Ergebnis: Erscheinen eine Kontrolllinie (C) und eine Testlinie (T) innerhalb des Testergebnislesefensters, unabhängig davon, welche Linie zuerst erscheint, ist das Ergebnis positiv.

⚠ **Achtung:** Jede Testlinie (T), unabhängig davon, wie schwach diese Linie ist, ist als positives Testergebnis zu bewerten.

3. Ungültiges Ergebnis: Ist die Kontrolllinie (C) nach der Testdurchführung innerhalb des Testergebnislesefensters nicht sichtbar, ist das Ergebnis ungültig.

Einschränkungen

1. Der Inhalt dieses Test-Kits ist für den professionellen und qualitativen Nachweis von SARS-CoV-2 Antigen aus nasopharyngealen Abstrichproben zu verwenden. Andere Probentypen können zu falschen Ergebnissen führen und dürfen nicht verwendet werden.
2. Die Nichtbeachtung der Anweisungen zum Testverfahren und zur Interpretation der Testergebnisse kann die Testleistung beeinträchtigen und/oder zu ungültigen Ergebnissen führen.
3. Ein negatives Testergebnis kann auftreten, wenn die Probe nicht ordnungsgemäß entnommen, extrahiert oder transportiert wurde. Ein negatives Testergebnis schließt die Möglichkeit einer SARS-CoV-2-Infektion nicht aus und sollte durch eine Viruskultur oder einen molekularen Assay bestätigt werden.
4. Ein positives Testergebnis schließt eine Co-Infektion mit anderen Erregern nicht aus.
5. Die Testergebnisse müssen in Verbindung mit anderen klinischen Daten bewertet werden, die dem Arzt zur Verfügung stehen.
6. Das Ablesen der Testergebnisse früher als 15 Minuten oder später als 20 Minuten kann zu falschen Ergebnissen führen.
7. Panbio™ COVID-19 Ag Rapid Test Device ist nicht zum Nachweis von defekten (nicht infektiösen) Viren in den späteren Stadien der Virusabgabe bestimmt, die durch PCR-Molekulartests nachgewiesen werden könnten. [8]
8. Eine Infektion mit SARS-CoV kann zu positiven Ergebnissen führen.

Qualitätskontrolle

1. Interne Qualitätskontrolle:

Die Testkassette besitzt eine Testlinie (T) und eine Kontrolllinie (C) auf der Oberfläche der Testvorrichtung. Die Testlinie und die Kontrolllinie sind vor dem Aufbringen einer Probe im Testergebnislesefensters nicht sichtbar. Die Kontrolllinie dient zur Verfahrenskontrolle und sollte immer dann erscheinen, wenn der Test ordnungsgemäß durchgeführt wird und die Testreagenzien der Kontrolllinie funktionieren.

2. Externe Qualitätskontrolle:

Die Kontrollen sind speziell formuliert und hergestellt, um die Leistung des Panbio™ COVID-19 Ag Rapid Tests zu gewährleisten, und dienen dazu, die Fähigkeit des Anwenders zu überprüfen, Tests korrekt durchzuführen und deren Ergebnisse richtig zu interpretieren. Die Positivkontrolle liefert ein positives Testergebnis und wurde hergestellt, um eine sichtbare Testlinie (T) zu erzeugen. Die Negativkontrolle liefert ein negatives Testergebnis.

Gute Laborpraxis empfiehlt die Verwendung von Positiv- und Negativkontrollen, um sicher zu stellen, dass:

- Testreagenzien funktionieren, und
- der Test korrekt durchgeführt wird.

Die externen Kontrollen können unter den folgenden Umständen durchgeführt werden:

- Von einem neuen Anwender vor der Durchführung von Tests an Patientenproben,
- Wenn Sie eine neue Sendung an Tests erhalten,
- In regelmäßigen Abständen gemäß den lokalen Vorschriften und / oder den Qualitätskontrollverfahren des Anwenders.

Leistungsmerkmale

1. Externe Bewertung des Panbio™ COVID-19 Ag Rapid Test Device

Die klinische Leistung von Panbio™ COVID-19 Ag Rapid Test Device wurde durch das Testen von 140 SARS-CoV-2 Antigen (Ag)-positiven und 445 -negativen Proben mit einer Sensitivität von 91,4% (95% CI: 85,5-95,5%) und einer Spezifität von 99,8% (95% CI: 98,8-100%) bestimmt, Positivität und Negativität von Proben wurden mit einer FDA-EUA RT-PCR Referenzmethode ermittelt,

Ergebnis für Panbio™ COVID-19 Ag Rapid Test Device

		PCR Testergebnis		
		Positiv	**Negativ**	**Gesamt**
Ergebnis für Panbio™ COVID-19 Ag Rapid Test Device	**Positiv**	128	1	129
	Negativ	12	444	456
	Gesamt	140	445	585
		Sensitivität	Spezifität	Kombinierte prozentale Übereinstimmung
		91,4% [85,5%;95,5%]	**99,8%** [98,8%;100%]	**97,8%** [96,2%;98,8%]

- Die Leistungsdaten wurden aus einer Studie mit Personen berechnet, bei denen der Verdacht auf Exposition mit COVID-19 bestand oder die in den letzten 7 Tagen Symptome zeigten.
- Die Stratifizierung der positiven Proben nach dem Auftreten von Symptomen oder einer vermuteten Exposition zwischen 0-3 Tagen ergibt eine Sensitivität von 94,9% (n=39) und zwischen 4-7 Tagen eine Sensitivität von 90,1% (n=101).
- Die positive Übereinstimmung des Panbio™ COVID-19 Ag Rapid Test Device ist mit einer Sensitivität von 98,2% höher für Proben mit Ct Werten ≤33. Referenzen 8 und 9 legen nahe, dass Patienten mit Ct Werten >33 nicht mehr ansteckend sind.[8, 9]

2. Nachweisgrenze

Es wurde bestätigt, dass Panbio™ COVID-19 Ag Rapid Test Device in der Lage ist 2,5X10[1,8] $TCID_{50}$/ml SARS-CoV-2 nachzuweisen, das aus einem COVID-19 bestätigten Patienten in Korea isoliert wurde.

3. Hook Effekt Hook Effect

Es gibt keinen Hook Effekt bei 1,0x10[5,8] $TCID_{50}$/ml of SARS- CoV-2, das aus einem COVID-19 bestätigten Patienten in Korea isoliert wurde.

4. Kreuzreaktionen

Die Kreuzreaktivität des Panbio™ COVID-19 Ag Rapid Test Device wurde anhand von Tests mit 25 Viren und 14 anderen Mikroorganismen bewertet. Die finalen Testkonzentrationen von Viren und anderen Mikroorganismen sind in der folgenden Tabelle dokumentiert. Die folgenden Viren und andere Mikroorganismen mit Ausnahme des humanen SARS-Coronavirus-Nukleoproteins haben keinen Einfluss auf die Testergebnisse des Panbio™ COVID-19 Ag Rapid Test Device. Panbio™ COVID-19 Ag Rapid Test Device zeigt Kreuzreaktivität mit dem humanen SARS-Coronavirus-Nukleoprotein bei einer

Konzentration von 25 ng/ml oder mehr, da SARS-CoV eine hohe Homologie (79,6%) zu SARS-CoV-2 aufweist.

Nr,	Art der Probe	Kreuzreaktion Substanz	Finale Testkonzentration	Testergebnis
1	Virus	Adenovirus Type3	2,0 X $10^{6,5}$ $TCID_{50}$/ml	Keine Kreuzreaktion
2		Adenovirus Type7	2,0 X $10^{4,75}$ $TCID_{50}$/ml	Keine Kreuzreaktion
3		Echovirus2	1,0 X $10^{6,5}$ $TCID_{50}$/ml	Keine Kreuzreaktion
4		Echovirus11	2,0 X$10^{5,25}$ $TCID_{50}$/ml	Keine Kreuzreaktion
5		Menschliches Herpesvirus (HSV) 1	2,0 X $10^{6,25}$ $TCID_{50}$/ml	Keine Kreuzreaktion
6		Menschliches Herpesvirus (HSV) 2	2,0 X $10^{4,75}$ $TCID_{50}$/ml	Keine Kreuzreaktion
7		Mumps Virus Ag	2,0 X $10^{3,5}$ $TCID_{50}$/ml	Keine Kreuzreaktion
8		Influenza-Virus A (H1N1) Stamm (A/Virginia/ ATCC1/2009)	2,6 X $10^{5,0}$ PFU/ml	Keine Kreuzreaktion
9		Influenza-Virus A (H1N1) Stamm (A/WS/33)	5,0 X $10^{7,25}$ $TCID_{50}$/ml	Keine Kreuzreaktion
10		Influenza-Virus A(H3N2) Stamm (A/Hong Kong/8/68)	N/A*	Keine Kreuzreaktion
11		Influenza-Virus B Stamm (B/Lee/40)	2,0 X $10^{5,25}$ $TCID_{50}$/ml	Keine Kreuzreaktion
12-14		Parainfluenza Type 1, Parainfluenza Type 2, Parainfluenza Type 3	N/A*	Keine Kreuzreaktion
15		Parainfluenza Typ 4A	1,97 X $10^{7,0}$ PFU/ml	Keine Kreuzreaktion
16		Respiratorisches Synzytialvirus (RSV) type A	4,22 X $10^{5,0}$ $TCID_{50}$/ml	Keine Kreuzreaktion
17		Respiratorisches Synzytialvirus (RSV) type B	5,62 X $10^{5,0}$ $TCID_{50}$/ml	Keine Kreuzreaktion
18		HCoV-HKU1	10 µg/ml	Keine Kreuzreaktion
19		Rhinovirus A16	8,8 X $10^{5,0}$ PFU/ml	Keine Kreuzreaktion

Nr,	Art der Probe	Kreuzreaktion Substanz	Finale Testkonzentration	Testergebnis
20	Virus	HCoV-NL63	1,7 X $10^{5,0}$ $TCID_{50}$/ml	Keine Kreuzreaktion
21		HCoV-OC43	8,9 X $10^{5,0}$ $TCID_{50}$/ml	Keine Kreuzreaktion
22		HCoV-229E	1,51 X $10^{6,0}$ $TCID_{50}$/ml	Keine Kreuzreaktion
23		Humanes SARS-Coronavirus Nukleoprotein	25 ng/ml	Kreuzreaktion
24		MERS-CoV Nukleoprotein	0,25 mg/ml	Keine Kreuzreaktion
25		Humanes Metapneumovirus (hMPV) 16 Typ A1	1,06 X $10^{6,0}$ PFU/ml	Keine Kreuzreaktion

Nr.	Art der Probe	Kreuzreaktion Substanz	Finale Testkonzentration	Testergebnis
1	Andere Mikroorganismen	*Staphylococcus aureus*	1,0 X $10^{6,0}$ CFU/ml	Keine Kreuzreaktion
2		*Staphylococcus saprophyticus*	1,0 X $10^{6,0}$ CFU/ml	Keine Kreuzreaktion
3		*Neisseria sp,(Neisseria lactamica)*	1,0 X $10^{6,0}$ CFU/ml	Keine Kreuzreaktion
4		*Escherichia coli*	1,0 X $10^{6,0}$ CFU/ml	Keine Kreuzreaktion
5		*Staphylococcus haemolyticus*	1,0 X $10^{6,0}$ CFU/ml	Keine Kreuzreaktion
6		*Streptococcus pyogenes*	1,0 X $10^{6,0}$ CFU/ml	Keine Kreuzreaktion
7		*Streptococcus salivarius*	1,0 X $10^{6,0}$ CFU/ml	Keine Kreuzreaktion
8		*Hemophilus parahaemolyticus*	1,0 X $10^{6,0}$ CFU/ml	Keine Kreuzreaktion
9		*Proteus vulgaris*	1,0 X $10^{6,0}$ CFU/ml	Keine Kreuzreaktion
10		*Moraxella catarrhalis*	1,0 X $10^{6,0}$ CFU/ml	Keine Kreuzreaktion
11		*Klebsiella pneumoniae*	1,0 X $10^{6,0}$ CFU/ml	Keine Kreuzreaktion

Nr.	Art der Probe	Kreuzreaktion Substanz	Finale Testkonzentration	Testergebnis
12	Andere Mikroorganismen	*Fusobacterium necrophorum*	1,0 X $10^{6,0}$ CFU/ml	Keine Kreuzreaktion
13		*Mycobacterum tuberculosis*	10 mg/ml	Keine Kreuzreaktion
14		*Humane Nasalspülung (gepoolt)*	N/A*	Keine Kreuzreaktion

** Keine Konzentrationsangabe durch den Lieferanten. Unverdünnte Stammlösung wurde getestet.*

5. Interferierende Substanzen

Die folgenden 42 potenziell interferierenden Substanzen haben keinen Einfluss auf Panbio™ COVID-19 Ag Rapid Test Device. Die endgültigen Testkonzentrationen der Störsubstanzen sind in der folgenden Tabelle dokumentiert.

Nr,	Art der Probe	Interferierende Substanzen	Finale Testkonzentration	Testergebnis
1	Endogene Substanz	Mucin	0,5%	Keine Interferenz
2		Hämoglobin	100 mg/L	Keine Interferenz
3		Triglyceride	1,5 mg/L	Keine Interferenz
4		Icteric (Bilirubin)	40 mg/dL	Keine Interferenz
5		Rheuma-Faktor	200 IU/ml	Keine Interferenz
6		Anti-nuklearer Antikörper	>1:40	Keine Interferenz
7		Schwanger	10-fach verdünnt	Keine Interferenz
8	Exogene Substanz	Guajakol-Glyceryl-Ether	1 µg/ml	Keine Interferenz
9		Albuterol	0,005 mg/dL	Keine Interferenz
10		Ephedrin	0,1 mg/ml	Keine Interferenz
11		Chlorpheniramin	0,08 mg/dL	Keine Interferenz
12		Diphenhydramin	0,08 mg/dL	Keine Interferenz
13		Ribavirin	26,7 µg /ml	Keine Interferenz
14		Oseltamivir	0,04 mg/dL	Keine Interferenz
15		Zanamivir	17,3 µg /ml	Keine Interferenz
16		Phenylephrin-Hydrochlorid	15% v/v	Keine Interferenz
17		Oxymetazolin-Hydrochlorid	15% v/v	Keine Interferenz
18		Amoxicillin	5,4 mg/dL	Keine Interferenz

Nr,	Art der Probe	Interferierende Substanzen	Finale Testkonzentration	Testergebnis
19	Exogene Substanz	Acetylsalicylsäure	3 mg/dL	Keine Interferenz
20		Ibuprofen	21,9 mg/dL	Keine Interferenz
21		Chlorothiazid	2,7 mg/dL	Keine Interferenz
22		Indapamid	140 ng/ml	Keine Interferenz
23		Glimepirid (Sulfonylharnstoffe)	0,164 mg/dL	Keine Interferenz
24		Acarbose	0,03 mg/dL	Keine Interferenz
25		Ivermectin	4,4 mg/L	Keine Interferenz
26		Lopinavir	16,4 µg/L	Keine Interferenz
27		Ritonavir	16,4 µg/L	Keine Interferenz
28		Chloroquinphosphat	0,99 mg/L	Keine Interferenz
29		Natriumchlorid mit Konservierungsstoffen	4,44 mg/ml	Keine Interferenz
30		Beclomethason	4,79 ng/ml	Keine Interferenz
31		Dexamethason	0,6 µg/ml	Keine Interferenz
32		Flunisolid	0,61 µg/ml	Keine Interferenz
33		Triamcinolon	1,18 ng/ml	Keine Interferenz
34		Budesonid	2,76 ng/ml	Keine Interferenz
35		Mometason	1,28 ng/ml	Keine Interferenz
36		Fluticason	2,31 ng/ml	Keine Interferenz
37		Sulfur	9,23 µg/ml	Keine Interferenz
38		Benzocain	0,13 mg/ml	Keine Interferenz
39		Menthol	0,15 mg/ml	Keine Interferenz
40		Mupirocin	10 µg/ml	Keine Interferenz
41		Tobramycin	24,03 µg/ml	Keine Interferenz
42		Biotin	1,2 µg/ml	Keine Interferenz

6. Wiederholbarkeit & Reproduzierbarkeit

Die Wiederholbarkeit und Reproduzierbarkeit von Panbio™ COVID-19 Ag Rapid Test Device wurde unter Verwendung eines internen Referenzpanels mit negativen Proben und einer Reihe positiver Proben festgestellt. Es wurden keine Unterschiede innerhalb der Testreihe, zwischen den Testreihen, zwischen den Chargen, zwischen den Standorten und zwischen den Tagen festgestellt.

VORBEREITUNG

1 Lassen Sie alle Komponenten des Test-Kits 30 Minuten vor Beginn des Testens eine Temperatur von 15-30°C erreichen.
Hinweis: Das medizinische Personal sollte die persönlichen Sicherheitsrichtlinien einschließlich der Verwendung persönlicher Schutzausrüstung einhalten.

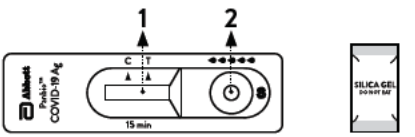
2 **Öffnen Sie die Verpackung und Entnehmen Sie Folgendes:**
1. Testkassetten verpackt in Folienbeutel mit Trockenmittel
2. Puffer
3. Extraktionsröhrchen
4. Deckel für Extraktionsröhrchen
5. Positivkontrolltupfer
6. Negativkontrolltupfer
7. Sterilisierte nasopharyngeale Tupfer zur Probenahme
8. Ständer für Röhrchen
9. Kurzanleitung (Nasopharyngeal)
10. Gebrauchsanweisung

3 Lesen Sie diese Anleitung vor Verwendung des Panbio™ COVID-19 Ag Rapid Test Device sorgfältig durch.

4 Beachten Sie das Verfallsdatum der Kit-Box. Wenn das Verfallsdatum abgelaufen ist, verwenden Sie einen anderen Kit

5 **Öffnen Sie den Folienbeutel und schauen Sie nach Folgendem:**
1. Testergebnislesefenster
2. Probenvertiefung

Beschriften Sie die Testkassette mit der Patient-ID.



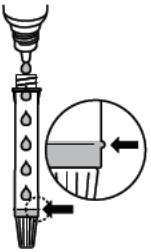
●●●●● : 5 Tropfen der extrahierten Probe

DEUTSCH

TESTVERFAHREN

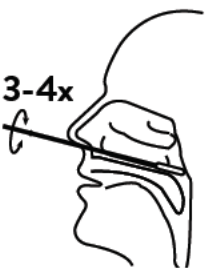
1 Halten Sie das Pufferfläschchen vertikal und füllen Sie das Extraktionsröhrchen mit Pufferflüssigkeit, bis die Fülllinie des Extraktionsröhrchens erreicht ist (300 µl).

⚠ **Achtung:** Bei einer zu hohen oder geringen Puffermenge sind falsche Testergebnisse möglich.

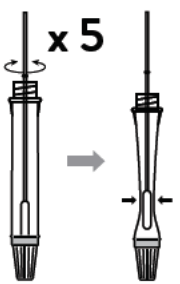


2 Stellen Sie das Extraktionsröhrchen in den Röhrchenständer.

3 Neigen Sie den Kopf des Patienten nach hinten. Führen Sie den Tupfer durch das Nasenloch ein. Reiben und rollen Sie den Tupfer vorsichtig 3-4 Mal. Lassen Sie den Tupfer für einige Sekunden an Ort und Stelle. Entfernen Sie den Tupfer langsam.



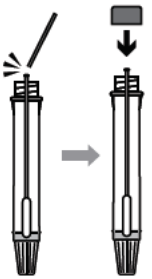
4 Führen Sie die Abstrichprobe in das Extraktionsröhrchen ein. Schwenken Sie die Tupferspitze in der Pufferflüssigkeit des Extraktionsröhrchens. Drücken Sie dabei den Tupfer mindestens fünfmal an die Wand des Extraktionsröhrchens und drücken Sie anschließend denn Tupfer aus, indem Sie mit den Fingern das Extraktionsröhrchen zusammendrücken.



DEUTSCH

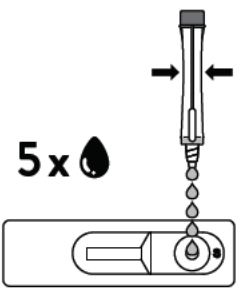
TESTVERFAHREN

5 Brechen Sie den Tupfer an der Bruchstelle ab und schließen Sie den Deckel des Extraktionssröhrchens.



6 Öffnen Sie die Kappe der Dosieröffnung am Boden des Extraktionsröhrchens.

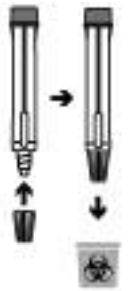
7 Geben Sie 5 Tropfen der extrahierten Proben senkrecht in die Probenvertiefung (S) der Testkassette. Bewegen Sie die Testkassette nicht, bis der Test abgeschlossen und zum Ablesen bereit ist.



⚠ **Achtung:** Blasen, die im Extraktionsröhrchen auftreten, können zu ungenauen Ergebnissen führen. Wenn Sie nicht in der Lage sind, genügend Tropfen zu erzeugen, kann dies an einer Verstopfung der Dosieröffnung liegen. Schütteln Sie das Röhrchen leicht, um die Verstopfung zu lösen, bis Sie eine freie Tropfenbildung beobachten können.

TESTVERFAHREN

8 Schließen Sie die Dosieröffnung und entsorgen Sie das Extraktionsröhrchen mit dem gebrauchten Tupfer gemäß den örtlichen Vorschriften und dem Entsorgungsprotokoll für biologisch gefährliche Abfälle.



9 Starten Sie die Uhr und lesen Sie das Ergebnis nach 15 Minuten ab. Lesen Sie das Ergebnis nicht mehr nach 20 Minuten ab.

10 Entsorgen Sie die gebrauchte Testkassette gemäß den örtlichen Vorschriften und dem Entsorgungsprotokoll für biologisch gefährlichen Abfall.

TEST INTERPRETATION

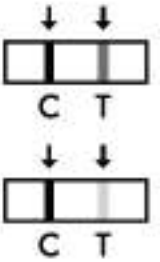
NEGATIV

Erscheinen eine Kontrolllinie (C) und keine Testlinie (T) innerhalb des Testergebnislesefensters, ist das Ergebnis negativ.

POSITIV

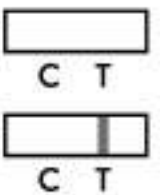
Erscheinen eine Kontrolllinie (C) und eine Testlinie (T) innerhalb des Testergebnislesefensters, unabhängig davon, welche Linie zuerst erscheint, ist das Ergebnis positiv.

⚠ **Achtung:** Jede Testlinie (T), unabhängig davon, wie schwach diese Linie ist, ist als positives Testergebnis zu bewerten.



UNGÜLTIG

Ist die Kontrolllinie (C) nach der Testdurchführung innerhalb des Testergebnislesefensters nicht sichtbar, ist das Ergebnis ungültig.
Die Anweisungen wurden möglicherweise nicht korrekt befolgt. Es wird empfohlen, die IFU erneut zu lesen, bevor die Probe mit einer neuen Testkassette erneut getestet wird.



Acerca de la prueba

ES

Introducción

La enfermedad por coronavirus (COVID-19) es una enfermedad infecciosa causada por un coronavirus recién descubierto, el síndrome respiratorio agudo severo coronavirus 2 (SARS-CoV-2) [1]. El SARS-CoV-2 es un β-coronavirus, que es un virus de ARN de sentido positivo no segmentado con envoltura[2]. Se transmite de persona a persona a través de gotitas o contacto directo, y se ha estimado que la infección tiene un período de incubación medio de 6,4 días y un número de reproducción básico de 2,24 a 3,58. Entre los pacientes con neumonía causada por SARS-CoV-2, la fiebre fue el síntoma más común, seguido de la tos[3]. Los principales ensayos de DIV utilizados para COVID-19 emplean la reacción en cadena de la polimerasa con transcriptasa inversa en tiempo real (RT-PCR) que tarda unas pocas horas[4]. La disponibilidad de una prueba de diagnóstico rápida y costo efectiva en el lugar de atención es fundamental para que los profesionales de la salud puedan ayudar en el diagnóstico de los pacientes y prevenir una mayor propagación del virus[5]. Las pruebas de antígeno jugarán un papel fundamental en la lucha contra COVID-19[6].

Principio de la prueba

Panbio™ COVID-19 Ag Rapid Test Device contiene una tira de membrana, que está pre-revestido con anticuerpo anti-SARS-CoV-2 inmovilizado en la línea de prueba e IgY anti-pollo monoclonal de ratón en la línea de control. Dos tipos de conjugados (IgG humana específica para el conjugado de oro de SARS-CoV-2 Ag y el conjugado de oro de IgY de pollo) se desplazan hacia arriba en la membrana cromatográficamente y reaccionan con el anticuerpo anti-SARS-CoV-2 y el anticuerpo monoclonal de ratón anti-IgY de pollo pre-revestido respectivamente. Para obtener un resultado positivo, la IgG humana específica para el conjugado de oro SARS-CoV-2 Ag y el anticuerpo anti-SARS-CoV-2 formarán una línea de prueba en la ventana de resultados. Ni la línea de prueba, ni la línea de control son visibles en la ventana de resultados antes de aplicar la muestra del paciente. Se requiere una línea de control visible para indicar que el resultado de una prueba es válido.

Uso Indicado

Panbio™ COVID-19 Ag Rapid Test Device es una prueba rápida de diagnóstico *in vitro* para la detección cualitativa del antígeno (Ag) del SARS-CoV-2 en muestras de hisopado nasofaríngeos humanos de individuos que cumplen con los criterios clínicos y / o epidemiológicos de COVID-19. Panbio™ COVID-19 Ag Rapid Test Device es solo para uso profesional y está destinado a ser utilizado como ayuda en el diagnóstico

de la infección por SARS-CoV-2. El producto se puede utilizar en cualquier entorno de laboratorio y no laboratorio que cumpla con los requisitos especificados en las Instrucciones de uso y la normativa local. La prueba proporciona resultados preliminares de la prueba. Los resultados negativos no excluyen la infección por SARS-CoV-2 y no pueden usarse como la única base para el tratamiento u otras decisiones de manejo. Los resultados negativos deben combinarse con observaciones clínicas, historial del paciente e información epidemiológica. La prueba no está destinada a utilizarse como prueba de detección de donantes para el SARS-CoV-2.

Materiales Suministrados

- 25 dispositivos de prueba con desecante en bolsa de aluminio individual
- Solución tampón (1 x 9 ml / frasco)
- 25 tubos de extracción
- 25 tapas de tubos de extracción
- 1 hisopo control positivo
- 1 hisopo control negativo
- 25 hisopos nasofaríngeos esterilizados para la recolección de muestras
- 1 gradilla para tubos
- 1 guía de referencia rápida (nasofaríngea)
- 1 Instrucciones de uso

Materiales Requeridos pero NO suministrados

- Elementos de protección personal según las recomendaciones locales (es decir, bata/bata de laboratorio, mascarilla, careta/gafas y guantes), temporizador, contenedor de riesgo biológico

Ingredientes Activos de los componentes principales

- **1 Dispositivo de prueba** Conjugado de oro: IgG humana específica para el coloide de oro SARS-CoV-2 Ag y coloide de oro IgY de pollo, línea de prueba: anti-SARS-CoV-2 monoclonal de ratón, línea control: IgY anti-pollo monoclonal de ratón
- **Tampón** Tricina, Cloruro de sodio, Tween 20, Azida de sodio (<0,1%), Proclin 300

Almacenamiento y estabilidad

1. El kit de prueba debe almacenarse a una temperatura entre 2 y 30 ° C. No congele el kit ni sus componentes.

Nota: Cuando se almacena en un refrigerador, todos los componentes del kit deben llevarse a temperatura ambiente (15-30 °C) durante un mínimo de 30 minutos antes de realizar la prueba. No abra la bolsa mientras los componentes alcancen la temperatura ambiente.

2. La botella de tampón se puede abrir y volver a sellar para cada prueba. La tapa del tampón debe sellarse firmemente entre cada uso. El tampón es estable hasta la fecha de caducidad si se mantiene a 2-30 °C.
3. Realice la prueba inmediatamente después de extraer el dispositivo de prueba de la bolsa de aluminio.
4. No use el kit de prueba después de su fecha de vencimiento.
5. La vida útil del kit es la indicada en el empaque exterior.
6. No utilice el kit de prueba si la bolsa está dañada o el sello está roto.
7. Las muestras de hisopo directo deben analizarse inmediatamente después de la recolección. Si la prueba inmediata no es posible, la muestra de hisopo se puede mantener en un tubo de extracción lleno de tampón de extracción (300 µl) a temperatura ambiente (15-30 °C) hasta dos horas antes de la prueba.

Advertencias

1. Solo para uso diagnóstico *in vitro*. No reutilice el dispositivo de prueba ni los componentes del kit.
2. Estas instrucciones deben seguirse estrictamente por profesionales de la salud entrenados para lograr resultados precisos. Todos los usuarios deben leer las instrucciones antes de realizar una prueba.
3. No coma ni fume mientras manipula las muestras.
4. Utilice guantes protectores al manipular las muestras y lávese bien las manos después.
5. Evite las salpicaduras o la formación de aerosoles en la muestra y el tampón.
6. Limpie los derrames a fondo con un desinfectante adecuado.
7. Descontamine y deseche todas las muestras, kits de reacción y materiales potencialmente contaminados (es decir, hisopo, tubo de extracción, dispositivo de prueba) en un contenedor de riesgo biológico como si fueran desechos infecciosos y elimínelos de acuerdo con las regulaciones locales aplicables.
8. No mezcle ni intercambie muestras diferentes.
9. No mezcle reactivos de diferentes lotes o de otros productos.
10. No almacene el kit de prueba a la luz solar directa.
11. Para evitar la contaminación, no toque la cabeza del hisopo suministrado al abrir la bolsa del hisopo.

12. Los hisopos esterilizados suministrados en el paquete deben usarse solo para la recolección de muestras nasofaríngeas.
13. Para evitar la contaminación cruzada, no reutilice los hisopos esterilizados para la recolección de muestras.
14. No diluya el hisopo recogido con ninguna solución excepto el tampón de extracción proporcionado.
15. El tampón contiene azida sódica <0,1% como conservante que puede ser tóxico si se ingiere. Cuando se deseche a través de un fregadero, enjuague con una gran cantidad de agua.[7]

Procedimiento de prueba (consulte la figura)

Muestras de hisopado nasofaríngeo

Note: El profesional de la salud debe cumplir con las pautas de seguridad personal, incluido el uso de equipo de protección personal.

Preparación de la prueba

1. Permita que todos los componentes del kit alcancen una temperatura entre 15 y 30 °C durante 30 minutos antes de realizar la prueba.
2. Extraiga el dispositivo de prueba de la bolsa de aluminio antes de usarlo. Colocar sobre una superficie plana, horizontal y limpia.
3. Sostenga el frasco de tampón verticalmente y llene el tubo de extracción con solución tampón hasta que fluya hasta la línea de llenado del tubo de extracción (300 µl).

⚠ **Precaución:** Si la cantidad de tampón es excesiva o insuficiente, puede producirse un resultado de prueba incorrecto.

4. Coloque el tubo de extracción en la gradilla de tubos.

Recolección y extracción de la muestra

1. Incline la cabeza del paciente ligeramente hacia atrás entre 45° y 70° para enderezar el pasaje desde la parte delantera de la nariz.
2. Inserte el hisopo con un eje flexible a través de la fosa nasal paralela al paladar.

⚠ **Precaución:** Utilice un hisopo nasofaríngeo específico para la recolección de muestras.

3. El hisopo debe alcanzar una profundidad igual a la distancia desde las fosas nasales hasta la abertura exterior del oído.

⚠ **Precaución:** Si encuentra resistencia durante la inserción del hisopo, retírelo e intente insertarlo en la fosa nasal opuesta.

4. Frote y gire suavemente el hisopo, 3 a 4 veces. Deje el hisopo en su lugar durante varios segundos para que absorba las secreciones.
5. Retire lentamente el hisopo mientras lo gira e insértelo en el tubo de extracción.

6. Gire la punta del hisopo en la solución tampón dentro del tubo de extracción, empujando hacia la pared del tubo de extracción al menos cinco veces y luego exprima el hisopo apretando el tubo de extracción con los dedos.
7. Quiebre el hisopo en el punto de ruptura y cierre la tapa del tubo de extracción.

Reacción con dispositivo de prueba

1. Abra la tapa de la boquilla de goteo en la parte inferior del tubo de extracción.
2. Dispense 5 gotas de la muestra extraída de manera vertical en el pocillo de muestra (S) del dispositivo. No manipule ni mueva el dispositivo de prueba hasta que la prueba esté completa y lista para leer.

⚠ **Precaución:** Las burbujas que se forman en el tubo de extracción pueden dar lugar a resultados inexactos. Si no puede crear suficientes gotas, esto puede deberse a una obstrucción en la boquilla dispensadora. Agite el tubo suavemente para liberar el bloqueo hasta que observe la formación de gotas libres.

3. Cierre la boquilla y deseche el tubo de extracción que contiene el hisopo usado de acuerdo con las regulaciones locales y el protocolo de eliminación de desechos de riesgo biológico.
4. De inicio al temporizador. Lea el resultado a los 15 minutos. No lea los resultados después de 20 minutos.
5. Deseche el dispositivo usado de acuerdo con las regulaciones locales y el protocolo de eliminación de desechos de riesgo biológico.

Hisopo de control positivo / negativo

Nota: Consulte la sección Control de calidad externo de estas Instrucciones de uso para conocer la frecuencia de las pruebas con hisopos de control de calidad externos.

1. Sostenga el frasco de tampón verticalmente y llene el tubo de extracción con solución tampón hasta que fluya hasta la línea de llenado del tubo de extracción (300 µl).

⚠ **Precaución:** Si la cantidad de tampón es excesiva o insuficiente, puede producirse un resultado de prueba incorrecto.

2. Coloque el tubo de extracción en la gradilla de tubos.
3. Inserte el hisopo de control positivo o negativo en el líquido tampón dentro del tubo de extracción y empape el hisopo durante 1 minuto. Gire la punta del hisopo de control en la solución tampón dentro del tubo de extracción, empuje hacia la pared del tubo de extracción al menos cinco veces y luego exprima el hisopo apretando el tubo de extracción con los dedos.

4. Deseche el hisopo de control usado de acuerdo con su protocolo de eliminación de desechos de riesgo biológico.
5. Cierre la tapa del tubo de extracción.
6. Siga el procedimiento de prueba anterior [Reacción con dispositivo de prueba].

Interpretación de la prueba (consulte la figura)

1. **Resultado negativo:** La presencia de solo la línea de control (C) y ninguna línea de prueba (T) dentro de la ventana de resultados indica un resultado negativo.
2. **Resultado positivo:** La presencia de la línea de prueba (T) y la línea de control (C) dentro de la ventana de resultados, independientemente de la línea que aparezca primero, indica un resultado positivo.

⚠ **Precaución:** La presencia de cualquier línea de prueba (T), no importa cuán débil sea, indica un resultado positivo.

3. **Resultado no válido:** si la línea de control (C) no es visible dentro de la ventana de resultados después de realizar la prueba, el resultado se considera no válido.

Limitaciones de la prueba

1. El contenido de este kit está indicado para uso profesional y para la detección cualitativa del antígeno del SARS-CoV-2 a partir de un hisopado nasofaríngeo. Otros tipos de muestras pueden dar lugar a resultados incorrectos y no deben utilizarse.
2. No seguir las instrucciones para el procedimiento de prueba y la interpretación de los resultados de la prueba puede afectar adversamente el desempeño de la prueba y/o producir resultados no válidos.
3. Puede producirse un resultado negativo de la prueba si la muestra se recolectó, extrajo o transportó incorrectamente. Un resultado negativo de la prueba no elimina la posibilidad de infección por SARS-CoV-2 y debería ser confirmado mediante cultivo viral o un ensayo molecular.
4. Los resultados positivos de las pruebas no descartan coinfecciones con otros patógenos.
5. Los resultados de la prueba deben evaluarse junto con otros datos clínicos disponibles para el médico.
6. La lectura de resultados de la prueba antes de 15 minutos o después de 20 minutos puede dar resultados incorrectos.
7. Panbio™ COVID-19 Ag Rapid Test Device no está destinado para detectar virus defectuosos (no infecciosos) en etapas tardías de la diseminación viral que podrían detectarse mediante pruebas moleculares de PCR.[8]

8. Pueden producirse resultados positivos en casos de infección por SARS-CoV.

Control de calidad

1. Control de calidad interno:

el dispositivo de prueba tiene una línea de prueba (T) y una línea de control (C) en la superficie del dispositivo de prueba. Ni la línea de prueba, ni la línea de control son visibles en la ventana de resultados antes de aplicar una muestra. La línea de control se utiliza para el control del procedimiento y siempre debe aparecer si el procedimiento de prueba se realiza correctamente y los reactivos de prueba de la línea de control están funcionando.

2. Control de calidad externo:

Los controles están específicamente formulados y fabricados para garantizar el rendimiento de Panbio™ COVID-19 Ag Rapid Test Device y se utilizan para verificar la capacidad del usuario para realizar correctamente la prueba e interpretar los resultados. El control positivo producirá un resultado de prueba positivo y ha sido fabricado para producir una línea de prueba visible (T). El control negativo producirá un resultado de prueba negativo.

Las buenas prácticas de laboratorio sugieren el uso de controles positivos y negativos para asegurarse de que:

- Los reactivos de prueba están funcionando y
- La prueba se realiza correctamente.

Los controles externos se pueden ejecutar en cualquiera de las siguientes circunstancias:

- Por un nuevo operador antes de realizar pruebas en muestras de pacientes,
- Al recibir un nuevo envío de prueba,
- A intervalos periódicos según lo dicten los requisitos locales, y/o los procedimientos de control de calidad del usuario.

Características de desempeño

1. Evaluación externa de Panbio™ COVID-19 Ag Rapid Test Device

El desempeño clínico de Panbio™ COVID-19 Ag Rapid Test Device se determinó analizando 140 muestras positivas y 445 negativas para el antígeno (Ag) del SARS-CoV-2 para tener una sensibilidad de 91,4% (95% CI: 85,5-95,5%) y una especificidad de 99,8% (95% CI: 98,8-100%). Se determinó que las muestras clínicas eran positivas o negativas utilizando un método de referencia FDA EUA RT-PCR.

Resultados de Panbio™ COVID-19 Ag Rapid Test Device

		Resultado de prueba PCR		
		Positiva	**Negativa**	**Total**
Resultados de Panbio™ COVID-19 Ag Rapid Test Device	**Positiva**	128	1	129
	Negativa	12	444	456
	Total	140	445	585
		Sensibilidad	Especificidad	Porcentaje de concordancia total
		91,4% [85,5%;95,5%]	**99,8%** [98,8%;100%]	**97,8%** [96,2%;98,8%]

- Los datos de desempeño se calcularon a partir de un estudio de individuos sospechosos de exposición a COVID-19 o que presentaron síntomas en los últimos 7 días.
- La estratificación de las muestras positivas después de la aparición de los síntomas o la presunta exposición entre 0-3 días tiene una sensibilidad de 94,9% (n=39) y 4-7 días tiene una sensibilidad de 90,1% (n=101).
- La concordancia positiva de Panbio™ COVID-19 Ag Rapid Test Device es mayor con valores de Ct ≤33 con una sensibilidad del 98,2%. Como se sugiere en las referencias 8 y 9, los pacientes con un valor de Ct >33 ya no son contagiosos.[8, 9]

2. Límite de detección

Panbio™ COVID-19 Ag Rapid Test Device confirmó detectar $2,5X10^{1,8}$ $TCID_{50}$/ml de SARS-CoV-2 el cual fue aislado de un paciente confirmado por COVID-19 en Corea.

3. Efecto gancho

No hay efecto de gancho a $1,0x10^{5,8}$ $TCID_{50}$/ml de SARS-CoV-2 que se aisló de un paciente confirmado por COVID-19 en Corea.

4. Reactividad cruzada

La reactividad cruzada de Panbio™ COVID-19 Ag Rapid Test Device se evaluó analizando 25 virus y otros 14 microorganismos. Las concentraciones finales de prueba de virus y otros microorganismos se documentan en la siguiente tabla. Los siguientes virus y otros microorganismos, excepto la nucleoproteína del coronavirus del SARS humano, no tienen ningún efecto sobre los resultados de la prueba del dispositivo de prueba rápida Panbio ™ COVID-19 Ag. Panbio™ COVID-19 Ag Rapid Test Device tiene reactividad cruzada con la nucleoproteína de coronavirus SARS humano a una

concentración de 25 ng/ml o más porque el SARS-CoV tiene una alta homología (79,6%) con el SARS-CoV-2.

No,	Tipo de muestra	Sustancia de reacción cruzada	Concentración final de la prueba	Resultado de la prueba
1	Virus	Adenovirus Tipo3	$2,0 \times 10^{6,5}$ $TCID_{50}$/ml	Sin reacción cruzada
2		Adenovirus Tipo7	$2,0 \times 10^{4,75}$ $TCID_{50}$/ml	Sin reacción cruzada
3		Echovirus2	$1,0 \times 10^{6,5}$ $TCID_{50}$/ml	Sin reacción cruzada
4		Echovirus11	$2,0 \times 10^{5,25}$ $TCID_{50}$/ml	Sin reacción cruzada
5		Virus del herpes humano (HSV) 1	$2,0 \times 10^{6,25}$ $TCID_{50}$/ml	Sin reacción cruzada
6		Virus del herpes humano (HSV) 2	$2,0 \times 10^{4,75}$ $TCID_{50}$/ml	Sin reacción cruzada
7		Ag Virus Paperas	$2,0 \times 10^{3,5}$ $TCID_{50}$/ml	Sin reacción cruzada
8		Virus de la Influenza A (H1N1) cepa (A/Virginia/ATCC1/2009)	$2,6 \times 10^{5,0}$ PFU/ml	Sin reacción cruzada
9		Virus de la Influenza A (H1N1) cepa (A/WS/33)	$5,0 \times 10^{7,25}$ $TCID_{50}$/ml	Sin reacción cruzada
10		Virus de la Influenza A (H3N2) cepa (A/Hong Kong/8/68)	N/A*	Sin reacción cruzada
11		Virus de la Influenza B cepa (B/Lee/40)	$2,0 \times 10^{5,25}$ $TCID_{50}$/ml	Sin reacción cruzada
12-14		Parainfluenza Tipo 1, Parainfluenza Tipo 2, Parainfluenza Tipo 3	N/A*	Sin reacción cruzada
15		Parainfluenza Tipo 4A	$1,97 \times 10^{7,0}$ PFU/ml	Sin reacción cruzada
16		Virus sincitial respiratorio (RSV) tipo A	$4,22 \times 10^{5,0}$ $TCID_{50}$/ml	Sin reacción cruzada
17		Virus sincitial respiratorio (RSV) tipo B	$5,62 \times 10^{5,0}$ $TCID_{50}$/ml	Sin reacción cruzada
18		HCoV-HKU1	10 µg/ml	Sin reacción cruzada

No,	Tipo de muestra	Sustancia de reacción cruzada	Concentración final de la prueba	Resultado de la prueba
19	Virus	Rinovirus A16	$8,8 \times 10^{5,0}$ PFU/ml	Sin reacción cruzada
20		HCoV-NL63	$1,7 \times 10^{5,0}$ $TCID_{50}$/ml	Sin reacción cruzada
21		HCoV-OC43	$8,9 \times 10^{5,0}$ $TCID_{50}$/ml	Sin reacción cruzada
22		HCoV-229E	$1,51 \times 10^{6,0}$ $TCID_{50}$/ml	Sin reacción cruzada
23		Nucleoproteína del coronavirus del SARS humano	25 ng/ml	Reacción cruzada
24		Nucleoproteina del MERS-CoV	0,25 mg/ml	Sin reacción cruzada
25		Metaneumovirus humano (hMPV) 16 tipo A1	$1,06 \times 10^{6,0}$ PFU/ml	Sin reacción cruzada

No,	Tipo de muestra	Sustancia de reacción cruzada	Concentración final de la prueba	Resultado de la prueba
1	Otros Microorganismos	*Staphylococcus aureus*	$1,0 \times 10^{6,0}$ CFU/ml	Sin reacción cruzada
2		*Staphylococcus saprophyticus*	$1,0 \times 10^{6,0}$ CFU/ml	Sin reacción cruzada
3		*Neisseria sp,(Neisseria lactamica)*	$1,0 \times 10^{6,0}$ CFU/ml	Sin reacción cruzada
4		*Escherichia coli*	$1,0 \times 10^{6,0}$ CFU/ml	Sin reacción cruzada
5		*Staphylococcus haemolyticus*	$1,0 \times 10^{6,0}$ CFU/ml	Sin reacción cruzada
6		*Streptococcus pyogenes*	$1,0 \times 10^{6,0}$ CFU/ml	Sin reacción cruzada
7		*Streptococcus salivarius*	$1,0 \times 10^{6,0}$ CFU/ml	Sin reacción cruzada
8		*Hemophilus parahaemolyticus*	$1,0 \times 10^{6,0}$ CFU/ml	Sin reacción cruzada
9		*Proteus vulgaris*	$1,0 \times 10^{6,0}$ CFU/ml	Sin reacción cruzada
10		*Moraxella catarrhalis*	$1,0 \times 10^{6,0}$ CFU/ml	Sin reacción cruzada

No,	Tipo de muestra	Sustancia de reacción cruzada	Concentración final de la prueba	Resultado de la prueba
11	Otros Microorganismos	*Klebsiella pneumoniae*	1,0 X $10^{6,0}$ CFU/ml	Sin reacción cruzada
12		*Fusobacterium necrophorum*	1,0 X $10^{6,0}$ CFU/ml	Sin reacción cruzada
13		*Tuberculosis micobacteriana*	10 mg/ml	Sin reacción cruzada
14		*Lavado nasal humano agrupado*	N/A*	Sin reacción cruzada

** Sin concentración proporcionada por el proveedor. Se evaluó la solución madre sin diluir.*

5. Sustancias interferentes

Las siguientes 42 sustancias potencialmente interferentes no tienen ningún impacto en Panbio™ COVID-19 Ag Rapid Test Device. Las concentraciones de prueba finales de las sustancias interferentes se documentan en la siguiente tabla.

No,	Tipo de muestra	Sustancias Interferentes	Concentración final de la prueba	Resultado de la prueba
1	Sustancia Endógena	Mucina	0,5%	Sin interferencia
2		Hemoglobina	100 mg/L	Sin interferencia
3		Triglicéridos	1,5 mg/L	Sin interferencia
4		Icterico (Bilirrubina)	40 mg/dL	Sin interferencia
5		Factor reumatoide	200 IU/ml	Sin interferencia
6		Anticuerpo antinuclear	>1:40	Sin interferencia
7		Embarazo	Dilución de 10 veces	Sin interferencia
8	Sustancia Exógena	Éter de glicerilo guayacol	1 µg/ml	Sin interferencia
9		Albuterol	0,005 mg/dL	Sin interferencia
10		Efedrina	0,1 mg/ml	Sin interferencia
11		Clorfeniramina	0,08 mg/dL	Sin interferencia
12		Difenhidramina	0,08 mg/dL	Sin interferencia
13		Ribavirina	26,7 µg /ml	Sin interferencia
14		Oseltamivir	0,04 mg/dL	Sin interferencia
15		Zanamivir	17,3 µg /ml	Sin interferencia
16		Clorhidrato de fenilefrina	15% v/v	Sin interferencia
17		Clorhidrato de oximetazolina	15% v/v	Sin interferencia
18		Amoxicilina	5,4 mg/dL	Sin interferencia

No,	Tipo de muestra	Sustancias Interferentes	Concentración final de la prueba	Resultado de la prueba
19	Sustancia Exógena	Ácido acetilsalicílico	3 mg/dL	Sin interferencia
20		Ibuprofeno	21,9 mg/dL	Sin interferencia
21		Clorotiazida	2,7 mg/dL	Sin interferencia
22		Indapamida	140 ng/ml	Sin interferencia
23		Glimepirida (sulfonilureas)	0,164 mg/dL	Sin interferencia
24		Acarbose	0,03 mg/dL	Sin interferencia
25		Ivermectina	4,4 mg/L	Sin interferencia
26		Lopinavir	16,4 µg/L	Sin interferencia
27		Ritonavir	16,4 µg/L	Sin interferencia
28		Fosfato de cloroquina	0,99 mg/L	Sin interferencia
29		Cloruro de sodio con conservantes	4,44 mg/ml	Sin interferencia
30		Beclometasona	4,79 ng/ml	Sin interferencia
31		Dexametasona	0,6 µg/ml	Sin interferencia
32		Flunisolida	0,61 µg/ml	Sin interferencia
33		Triamcinolona	1,18 ng/ml	Sin interferencia
34		Budesonida	2,76 ng/ml	Sin interferencia
35		Mometasona	1,28 ng/ml	Sin interferencia
36		Fluticasona	2,31 ng/ml	Sin interferencia
37		Azufre	9,23 µg/ml	Sin interferencia
38		Benzocaína	0,13 mg/ml	Sin interferencia
39		Mentol	0,15 mg/ml	Sin interferencia
40		Mupirocina	10 µg/ml	Sin interferencia
41		Tobramicina	24,03 µg/ml	Sin interferencia
42		Biotina	1,2 µg/ml	Sin interferencia

6. Repetibilidad y reproducibilidad

La repetibilidad y reproducibilidad de Panbio™ COVID-19 Ag Rapid Test Device se estableció utilizando paneles de referencia internos que contienen muestras negativas y una variedad de muestras positivas. No se observaron diferencias dentro de las evaluaciones, entre evaluaciones, entre lotes, entre sitios y entre días.

PREPARACIÓN

1 Permita que todos los componentes del kit alcancen una temperatura entre 15 y 30 °C durante 30 minutos antes de realizar la prueba.
Note: Los profesional de la salud deben cumplir con las pautas de seguridad personal, incluido el uso de equipo de protección personal.

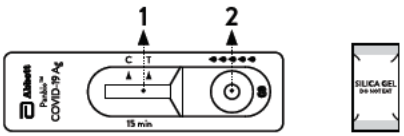
2 **Abra el paquete y revise los siguientes componentes:**
1. Dispositivo de prueba con desecante en bolsa de aluminio individual
2. Solución tampón
3. Tubo de extracción
4. Tapa de tubos de extracción
5. Hisopo control positivo
6. Hisopo control negativo
7. Hisopos nasofaríngeos esterilizados para la recolección de muestras
8. Gradilla para tubos
9. Guía de referencia rápida (nasofaríngea)
10. Instrucciones de uso

3 Lea cuidadosamente estas instrucciones de uso antes de usar Panbio™ COVID-19 Ag Rapid Test Device kit.

4 Revise la fecha de vencimiento de la caja del kit. Si la fecha de vencimiento ha pasado, use otro kit.

5 **Abra la bolsa de aluminio y revise lo siguiente:**
1. Ventana de resultados
2. Pocillo de muestra

Luego, rotule el dispositivo con el identificador del paciente.



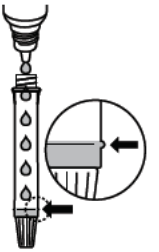
●●●●● : 5 gotas de la muestra extraída

ESPAÑOL

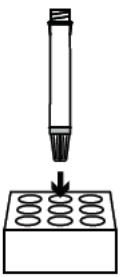
PROCEDIMIENTO DE LA PRUEBA

1 Sostenga el frasco de tampón verticalmente y llene el tubo de extracción con solución tampón hasta que fluya hasta la línea de llenado del tubo de extracción (300µl).

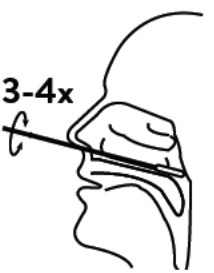
⚠ **Precaución:** Si la cantidad de tampón es excesiva o insuficiente, puede producirse un resultado de prueba incorrecto.



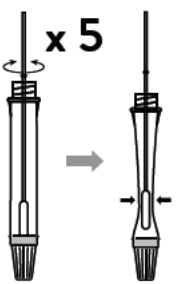
2 Coloque el tubo de extracción en la gradilla para tubos.



3 Incline la cabeza del paciente hacia atrás. Inserte el hisopo a través de la fosa nasal. Frote y gire suavemente el hisopo, 3 a 4 veces. Deje el hisopo en su lugar durante varios segundos. Retire lentamente el hisopo.

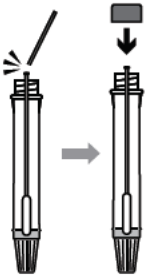


4 Inserte la muestra de hisopado en el tubo de extracción. Gire la punta del hisopo en la solución tampón dentro del tubo de extracción, empujando hacia la pared del tubo de extracción al menos cinco veces y luego exprima el hisopo apretando el tubo de extracción con los dedos.



PROCEDIMIENTO DE LA PRUEBA

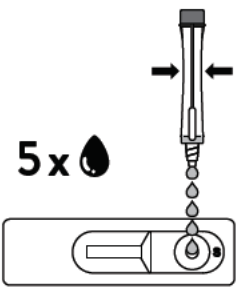
5 Quiebre el hisopo en el punto de ruptura y cierre la tapa del tubo de extracción.



6 Abra la tapa de la boquilla de goteo en la parte inferior del tubo de extracción.

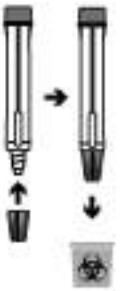
7 Dispense 5 gotas de las muestras extraídas verticalmente en el pocillo de la muestra (S) en el dispositivo. No manipule ni mueva el dispositivo de prueba hasta que la prueba esté completa y lista para leer.

⚠ **Precaución:** Las burbujas que se forman en el tubo de extracción pueden dar lugar a resultados incorrectos. Si no puede crear suficientes gotas, esto puede deberse a una obstrucción en la boquilla dispensadora. Agite el tubo suavemente para liberar el bloqueo hasta que observe la formación de gotas libres.



PROCEDIMIENTO DE LA PRUEBA

8 Cierre la boquilla y deseche el tubo de extracción que contiene el hisopo usado de acuerdo con las regulaciones locales y el protocolo de eliminación de desechos de riesgo biológico.



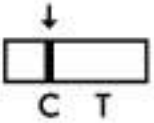
9 De inicio al temporizador. Leer resultado a los 15 minutos. No lea los resultados después de 20 minutos.

10 Deseche el dispositivo usado de acuerdo con las regulaciones locales y el protocolo de eliminación de desechos de riesgo biológico.

INTERPRETACIÓN DE LA PRUEBA

NEGATIVA

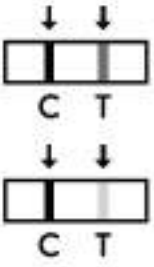
La presencia de solo la línea de control (C) y ninguna línea de prueba (T) dentro de la ventana de resultados indica un resultado negativo.



POSITIVA

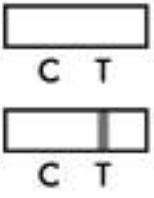
La presencia de la línea de prueba (T) y la línea de control (C) dentro de la ventana de resultados, independientemente de la línea que aparezca primero, indica un resultado positivo.

⚠ **Precaución:** La presencia de cualquier línea de prueba (T), no importa cuán débil sea, indica un resultado positivo.



NO VÁLIDA

Si la línea de control (C) no está visible dentro de la ventana de resultados después de realizar la prueba, el resultado se considera inválido. Es posible que las instrucciones no se hayan seguido correctamente. Se recomienda volver a leer las instrucciones de uso antes de volver a analizar la muestra con un nuevo dispositivo de prueba.



ESPAÑOL

A propos du Test

FR

Introduction

La maladie à coronavirus (COVID-19) est une maladie infectieuse causée par un coronavirus nouvellement découvert, le coronavirus du syndrome respiratoire aigu sévère 2 (SARS-CoV-2)[1]. Le SARS-CoV-2 est un β-coronavirus, qui est un virus à ARN sens positif non segmenté enveloppé[2]. Il se propage par transmission interhumaine via des gouttelettes ou par contact direct, et l'infection a été estimée avoir une période d'incubation moyenne de 6,4 jours et un nombre de reproduction de base de 2,24 à 3,58. Parmi les patients atteints de pneumonie causée par le SARS-CoV-2, la fièvre était le symptôme le plus courant, suivie de la toux [3]. Les principaux dosages IVD utilisés pour le COVID-19 utilisent une réaction en chaîne transcriptase-polymérase inverse en temps réel (RT-PCR) qui prend quelques heures[4]. La disponibilité d'un test efficient de diagnostic rapide en biologie délocalisée est primordial aux professionnels de santé. Pour leurs permettre d'aider au diagnostic des patients et d'empêcher la propagation du virus [5]. Les tests d'antigènes joueront un rôle essentiel dans la lutte contre le COVID-19 [6].

Principe du Test

Panbio™ COVID-19 Ag Rapid Test Device contient une bande de membrane pré-enduite d'anticorps anti-SARS-CoV-2 immobilisés sur la ligne de test et un anticorps IgY monoclonal de souris anti-poulet sur la ligne de contrôle. Deux types de conjugués (IgG humaine spécifique au SARS-CoV-2 Ag conjugué d'Or et IgY Poulet conjugué d'Or) se déplacent vers le haut sur la membrane par chromatographie et réagissent respectivement avec l'anticorps anti-SARS-CoV-2 et l'IgY monoclonal de souris anti-poulet pré-enduit. Pour un résultat positif, l'IgG humaine spécifique au conjugué SARS-CoV-2 Ag et l'anticorps anti-SARS-CoV-2 formeront une ligne de test dans la fenêtre de résultat. Ni la ligne de test ni la ligne de contrôle ne sont visibles dans la fenêtre de résultat avant l'application de l'échantillon du patient. Une ligne de contrôle visible est requise pour indiquer qu'un résultat de test est valide.

Utilisation prévue

Panbio™ COVID-19 Ag Rapid Test Device est un test de diagnostic rapide *in vitro* pour la détection qualitative de l'antigène SARS-CoV-2 (Ag) dans des échantillons sur écouvillons nasopharyngés humains provenant de personnes répondant aux critères cliniques et / ou épidémiologiques du COVID-19. Panbio™ COVID-19 Ag Rapid Test Device est destiné à un usage professionnel uniquement et est destiné à être utilisé comme une aide au diagnostic de l'infection par le

SARS-CoV-2. Le produit peut être utilisé dans tout environnement de laboratoire et hors laboratoire qui répond aux exigences spécifiées dans le mode d'emploi et dans la réglementation locale. Le test fournit des résultats de test préliminaires. Les résultats négatifs n'empêchent pas l'infection par le SARS-CoV-2 et ils ne peuvent pas être utilisés comme seule base de traitement ou d'autres décisions de prise en charge. Les résultats négatifs doivent être associés aux observations cliniques, aux antécédents du patient et aux informations épidémiologiques. Le test n'est pas destiné à être utilisé comme test de dépistage des donneurs pour le SARS-CoV-2.

Matériel fourni

- 25 appareils de test avec dessiccateur dans une pochette individuelle en aluminium
- Solution tampon (1 x 9 ml / flacon)
- 25 tubes d'extraction
- 25 bouchons pour les tubes d'extraction
- 1 écouvillon de contrôle positif
- 1 écouvillon de contrôle négatif
- 25 écouvillons nasopharyngés stérilisés pour le prélèvement d'échantillons
- 1 porte tubes
- 1 guide de référence rapide (nasopharyngé)
- 1 Notice d'utilisation

Matériel requis mais non fourni

- Équipement de protection individuelle selon les recommandations locales (ex : blouse de laboratoire, masque facial, écran facial / lunettes et gants), minuterie, conteneur à déchets

Ingrédients actifs des principaux composants

- **1 test** Conjugué or : IgG humaines spécifiques au colloïde d'or SARS-CoV-2 Ag et IgY de poulet - colloïde d'or, Ligne de test : anti-SARS-CoV-2 monoclonale de souris, Ligne de contrôle : IgY monoclonale de souris anti-poulet
- **Tampon** Tricine, chlorure de sodium, Tween 20 , azide de sodium (<0,1%), Proclin 300

Stockage et stabilité

1. Le kit de test doit être conservé à une température comprise entre 2 et 30 ° C. Ne congelez pas le kit ou ses composants.

Remarque : Lorsqu'ils sont conservés au réfrigérateur, tous les composants du kit doivent être portés à température ambiante (15-30° C) pendant au moins 30 minutes avant d'effectuer le test. N'ouvrez pas la pochette tant que les composants ne sont pas à température ambiante.

2. Le flacon de tampon peut être ouvert et refermé pour chaque test. Le bouchon du tampon doit être fermement scellé entre chaque utilisation. Le tampon est stable jusqu'à la date d'expiration s'il est conservé entre 2 et 30 ° C.
3. Effectuez le test immédiatement après avoir retiré le dispositif de test de la pochette en aluminium.
4. N'utilisez pas le kit de test au-delà de sa date d'expiration.
5. La durée de conservation du kit est celle indiquée sur l'emballage extérieur.
6. N'utilisez pas le kit de test si la pochette est endommagée ou si le sceau est brisé.
7. Les échantillons directs sur écouvillon doivent être testés immédiatement après le prélèvement. Si un test immédiat n'est pas possible, l'échantillon sur écouvillon peut être conservé dans un tube d'extraction rempli de tampon d'extraction (300 µl) à température ambiante (15-30° C) jusqu'à deux heures avant le test.

Précautions d'usage

1. Pour usage de diagnostic *in vitro* uniquement. Ne réutilisez pas le dispositif de test et les composants du kit.
2. Ces instructions doivent être strictement suivies par un professionnel de santé qualifié pour obtenir des résultats précis. Tous les utilisateurs doivent lire les instructions avant d'effectuer un test.
3. Ne pas manger ni fumer pendant la manipulation des échantillons.
4. Portez des gants de protection lors de la manipulation des échantillons et lavez-vous soigneusement les mains par la suite.
5. Évitez les éclaboussures ou la formation d'aérosols sur l'échantillon et le tampon.
6. Nettoyez soigneusement les déversements en utilisant un désinfectant approprié.
7. Décontaminer et éliminer tous les échantillons, kits de réaction et matériaux potentiellement contaminés (c'est-à-dire écouvillon, tube d'extraction, dispositif de test) dans un récipient contenant des risques biologiques comme s'il s'agissait de déchets infectieux et éliminer conformément aux réglementations locales applicables.
8. Ne pas mélanger ni échanger différents échantillons.
9. Ne mélangez pas les réactifs de lots différents ou ceux d'autres produits.

10. Ne stockez pas le kit de test à la lumière directe du soleil.
11. Pour éviter toute contamination, ne touchez pas la tête de l'écouvillon fourni lors de l'ouverture de la poche de l'écouvillon.
12. Les écouvillons stérilisés fournis dans l'emballage ne doivent être utilisés que pour le prélèvement d'échantillons nasopharyngés.
13. Pour éviter toute contamination croisée, ne réutilisez pas les écouvillons stérilisés pour le prélèvement d'échantillons.
14. Ne diluez pas l'écouvillon collecté avec une solution à l'exception du tampon d'extraction fourni.
15. Le tampon contient < 0,1% d'azide de sodium comme agent de conservation qui peut être toxique en cas d'ingestion. Lorsqu'il est éliminé dans un évier, rincez avec un grand volume d'eau[7].

Procédure de test (reportez-vous au schéma)

Échantillons sur écouvillon nasopharyngé

Remarque : le professionnel de santé doit se conformer aux directives de sécurité personnelle, y compris l'utilisation d'équipements de protection individuelle.

Préparation du test

1. Laisser tous les composants du kit atteindre une température comprise entre 15 et 30 ° C avant le test pendant 30 minutes.
2. Retirez le dispositif de test de la pochette en aluminium avant de l'utiliser. Le placer sur une surface plane, horizontale et propre.
3. Tenez le flacon de tampon verticalement et remplissez le tube d'extraction de fluide tampon jusqu'à ce qu'il s'écoule jusqu'à la ligne de remplissage du tube d'extraction (300 µl).

⚠ **Attention :** Si la quantité de tampon est excessive ou insuffisante, un résultat de test incorrect peut se produire.

4. Placez le tube d'extraction dans le support de tubes.

Prélèvement et extraction des échantillons

1. Inclinez légèrement la tête du patient vers l'arrière d'environ 45 ° - 70 ° pour redresser le passage de l'avant du nez.
2. Insérez l'écouvillon avec une tige flexible dans la narine parallèlement au palais.

⚠ **Attention :** utilisez un écouvillon nasopharyngé dédié pour le prélèvement des échantillons.

3. L'écouvillon doit atteindre une profondeur égale à la distance entre les narines et l'ouverture externe de l'oreille.

⚠ **Attention :** en cas de résistance lors de l'insertion de l'écouvillon, retirez-le et essayez de l'insérer dans la narine opposée.

4. Frottez et roulez doucement l'écouvillon, 3 à 4 fois. Laisser

l'écouvillon en place pendant plusieurs secondes pour absorber les sécrétions.
5. Retirez lentement l'écouvillon tout en le faisant tourner et insérez-le dans le tube d'extraction.
6. Faites tourbillonner la pointe de l'écouvillon dans le fluide tampon à l'intérieur du tube d'extraction, en poussant dans la paroi du tube d'extraction au moins cinq fois, puis faites sortir l'écouvillon en pressant le tube d'extraction avec vos doigts.
7. Cassez l'écouvillon au point de rupture et fermez le capuchon du tube d'extraction.

Réaction avec le dispositif de test

1. Ouvrez le capuchon de la buse de descente au bas du tube d'extraction.
2. Distribuer verticalement 5 gouttes d'échantillons extraits dans le puits d'échantillon (S) de l'appareil. Ne pas manipuler ni déplacer le dispositif de test tant que le test n'est pas terminé et prêt pour la lecture.

⚠ **Attention :** les bulles qui se produisent dans le tube d'extraction peuvent conduire à des résultats inexacts. Si vous ne parvenez pas à créer suffisamment de gouttes, cela peut être dû à un colmatage de la buse de distribution. Secouez doucement le tube pour libérer le blocage jusqu'à ce que vous observiez la formation de gouttes libres.

3. Fermez la buse et jetez le tube d'extraction contenant l'écouvillon usagé conformément à vos réglementations locales et au protocole d'élimination des déchets biologiques
4. Démarrer le minuteur, lire le résultat à 15 minutes. Ne lisez pas les résultats après 20 minutes.
5. Éliminez l'appareil usagé conformément aux réglementations locales et au protocole d'élimination des déchets biologiques.

Ecouvillons de contrôle Positif et Négatif

Remarque: veuillez consulter la section Contrôle de qualité externe de ce mode d'emploi pour la fréquence de test des écouvillons de contrôle de qualité externe.

1. Tenez le flacon de tampon verticalement et remplissez le tube d'extraction de liquide tampon jusqu'à la ligne de remplissage du tube d'extraction (300 µl).

⚠ **Attention :** Si la quantité de tampon est excessive ou insuffisante, un résultat de test incorrect peut se produire.

2. Placez le tube d'extraction dans le support de tubes.
3. Insérez l'écouvillon de contrôle positif ou négatif dans le liquide tampon à l'intérieur du tube d'extraction et faites tremper l'écouvillon

pendant 1 minute. Faites tourbillonner la pointe de l'écouvillon de contrôle dans le liquide tampon à l'intérieur du tube d'extraction, en poussant dans la paroi du tube d'extraction au moins cinq fois, puis faites sortir l'écouvillon en pressant le tube d'extraction avec vos doigts.
4. Éliminez l'écouvillon de contrôle utilisé conformément à votre protocole d'élimination des déchets biologiques dangereux.
5. Fermez le bouchon du tube d'extraction.
6. Suivez la procédure de test ci-dessus [Réaction avec le dispositif de test].

Interprétation du test (voir la figure)

1. Résultat négatif : La présence de seulement la ligne de contrôle (C) et aucune ligne de test (T) dans la fenêtre de résultat indique un résultat négatif.
2. Résultat positif : la présence de la ligne de test (T) et de la ligne de contrôle (C) dans la fenêtre de résultat, quelle que soit la ligne qui apparaît en premier, indique un résultat positif.

⚠ **Attention :** la présence d'une ligne de test (T), aussi faible soit-elle, indique un résultat positif.

3. Résultat invalide : si la ligne de contrôle (C) n'est pas visible dans la fenêtre de résultats après avoir effectué le test, le résultat est considéré comme invalide.

Limitations du test

1. Le contenu de ce kit doit être utilisé pour la détection professionnelle et qualitative de l'antigène SARS-CoV-2 à partir d'un écouvillon nasopharyngé. D'autres types d'échantillons peuvent conduire à des résultats incorrects et ne doivent pas être utilisés.
2. Le non-respect des instructions relatives à la procédure de test et à l'interprétation des résultats du test peut affecter les performances du test et / ou produire des résultats invalides.
3. Un résultat de test négatif peut survenir si l'échantillon a été collecté, extrait ou transporté de manière incorrecte. Un résultat de test négatif n'élimine pas la possibilité d'une infection par le SARS-CoV-2 et doit être confirmé par une culture virale ou un test moléculaire.
4. Des résultats de test positifs n'excluent pas la possibilité de co-infections avec d'autres agents pathogènes.
5. Les résultats des tests doivent être évalués conjointement avec d'autres données cliniques disponibles pour le médecin.
6. La lecture des résultats du test avant 15 minutes ou après 20 minutes peut donner des résultats incorrects.

7. Panbio™ COVID-19 Ag Rapid Test n'est pas destiné à détecter les virus défectueux (non infectieux) au cours des dernières étapes de l'excrétion virale qui pourraient être détectés par des tests moléculaires PCR.[8]
8. Des résultats positifs peuvent survenir en cas d'infection par le SARS-CoV.

Contrôle de qualité

1. Contrôle de qualité interne :

le dispositif de test a une ligne de test (T) et une ligne de contrôle (C) sur la surface du dispositif de test. Ni la ligne de test ni la ligne de contrôle ne sont visibles dans la fenêtre de résultat avant l'application d'un échantillon. La ligne de contrôle est utilisée pour le contrôle de la procédure et doit toujours apparaître si la procédure de test est effectuée correctement et que les réactifs de test de la ligne de contrôle fonctionnent.

2. Contrôle de qualité externe :

Les contrôles sont spécifiquement formulés et fabriqués pour garantir les performances du Panbio™ COVID-19 Ag Rapid Test Device et sont utilisés pour vérifier la capacité de l'utilisateur à effectuer correctement le test et à interpréter les résultats. Le contrôle positif produira un résultat de test positif et a été fabriqué pour produire une ligne de test visible (T). Le contrôle négatif produira un résultat de test négatif.

Les bonnes pratiques de laboratoire suggèrent l'utilisation de contrôles positifs et négatifs pour veiller à ce que :

- Les réactifs de test fonctionnent et
- Que le test soit correctement effectué.

Des contrôles externes peuvent être réalisés dans l'une des circonstances suivantes :

- Par un nouvel opérateur avant d'effectuer des tests sur des échantillons de patients,
- Lors de la réception d'un nouvel envoi de tests,
- À intervalles réguliers, selon les exigences locales et / ou selon les procédures de contrôle qualité de l'utilisateur.

Caractéristiques de performance

1. Évaluation externe du Panbio™ COVID-19 Ag Rapid Test Device

Les performances cliniques du Panbio™ COVID-19 Ag Rapid Test Device ont été déterminées en testant des échantillons 140 positifs et 445 négatifs pour l'antigène SARS-CoV-2 (Ag) pour avoir une sensibilité de 91,4% (95% CI: 85,5-95,5%) et une spécificité de 99,8% (95% CI: 98,8-100%). Les échantillons cliniques ont été

jugés positifs ou négatifs en utilisant une méthode de référence FDA EUA RT-PCR

Panbio™ COVID-19 Ag Rapid Test Device Resultats

		Resultats Tests PCR		
		Positif	**Negatif**	**Total**
Panbio™ COVID-19 Ag Rapid Test Device Resultats	**Positif**	128	1	129
	Negatif	12	444	456
	Total	140	445	585
		Sensibilité	Spécificité	Pourcentage de concordance Global
		91,4% [85,5%;95,5%]	**99,8%** [98,8%;100%]	**97,8%** [96,2%;98,8%]

- Les données de performance ont été calculées à partir d'une étude sur des personnes soupçonnées d'avoir été exposées au COVID-19 ou qui ont présenté des symptômes au cours des 7 derniers jours.
- La stratification des échantillons positifs après l'apparition des symptômes ou une exposition suspectée entre 0-3 jours a une sensibilité de 94,9% (n=39) et 4-7 jours a une sensibilité de 90,1% (n=101).
- La concordance positive du Panbio™ COVID-19 Ag Rapid Test Device est plus élevée avec des échantillons ayant des valeurs de Ct ≤ 33 avec une sensibilité de 98,2%. Comme suggéré dans les références 8 et 9, les patients avec une valeur de Ct > 33 ne sont plus contagieux.[8, 9]

2. Limite de détection

Il a été confirmé que le Panbio™ COVID-19 Ag Rapid Test Device détecte 2,5 x $10^{1,8}$ $TCID_{50}$ / ml de SARS-CoV-2 qui a été isolé à partir d'un patient confirmé COVID-19 en Corée.

3. Effet de crochet

Il n'y a pas d'effet crochet à 1,0x$10^{5,8}$ $TCID_{50}$ / ml de SARS-CoV-2 qui a été isolé d'un patient confirmé COVID-19 en Corée.

4. Réactivité croisée

La réactivité croisée du Panbio™ COVID-19 Ag Rapid Test Device a été évaluée en testant 25 virus et 14 autres micro-organismes. Les concentrations d'essai finales de virus et d'autres micro-organismes sont documentées dans le tableau ci-dessous. Les virus et autres micro-organismes suivants, à l'exception de la nucléoprotéine

du coronavirus humain SARS, n'ont aucun effet sur les résultats des tests du Panbio™ COVID-19 Ag Rapid Test Device. Le test rapide Panbio™ COVID-19 Ag Rapid Test Device a une réactivité croisée avec la nucléoprotéine du SARS-coronavirus humain à une concentration de 25 ng / ml ou plus car le SARS-CoV a une forte homologie (79,6%) avec le SARS-CoV-2.

No,	Types d' échantillons	Substance de réaction croisée	Concentration finale du test	Résultat du Test
1	Virus	Adenovirus Type3	2,0 X $10^{6,5}$ $TCID_{50}$/ml	Pas de réaction croisée
2		Adenovirus Type7	2,0 X $10^{4,75}$ $TCID_{50}$/ml	Pas de réaction croisée
3		Echovirus2	1,0 X $10^{6,5}$ $TCID_{50}$/ml	Pas de réaction croisée
4		Echovirus11	2,0 X $10^{5,25}$ $TCID_{50}$/ml	Pas de réaction croisée
5		Virus Herpès simplex humain (VHS) 1	2,0 X $10^{6,25}$ $TCID_{50}$/ml	Pas de réaction croisée
6		Virus Herpès simplex humain (VHS) 2	2,0 X $10^{4,75}$ $TCID_{50}$/ml	Pas de réaction croisée
7		Virus Measles Ag	2,0 X $10^{3,5}$ $TCID_{50}$/ml	Pas de réaction croisée
8		Influenza virus A (H1N1) Strain (A/Virginia/ ATCC1/2009)	2,6 X $10^{5,0}$ PFU/ml	Pas de réaction croisée
9		Influenza virus A (H1N1) Strain (A/WS/33)	5,0 X $10^{7,25}$ $TCID_{50}$/ml	Pas de réaction croisée
10		Influenza virus A(H3N2) Strain (A/Hong Kong/8/68)	N/A*	Pas de réaction croisée
11		Influenza virus B Strain (B/ Lee/40)	2,0 X $10^{5,25}$ $TCID_{50}$/ml	Pas de réaction croisée

No,	Types d' échantillons	Substance de réaction croisée	Concentration finale du test	Résultat du Test
12-14	Virus	Parainfluenza Type 1, Parainfluenza Type 2, Parainfluenza Type 3	N/A*	Pas de réaction croisée
15		Parainfluenza Type 4A	$1,97 \times 10^{7,0}$ PFU/ml	Pas de réaction croisée
16		Virus Respiratoire Syncitial (VRS) type A	$4,22 \times 10^{5,0}$ $TCID_{50}$/ml	Pas de réaction croisée
17		Virus Respiratoire Syncitial (RSV) type B	$5,62 \times 10^{5,0}$ $TCID_{50}$/ml	Pas de réaction croisée
18		HCoV-HKU1	10 µg/ml	Pas de réaction croisée
19		Rhinovirus A16	$8,8 \times 10^{5,0}$ PFU/ml	Pas de réaction croisée
20		HCoV-NL63	$1,7 \times 10^{5,0}$ $TCID_{50}$/ml	Pas de réaction croisée
21		HCoV-OC43	$8,9 \times 10^{5,0}$ $TCID_{50}$/ml	Pas de réaction croisée
22		HCoV-229E	$1,51 \times 10^{6,0}$ $TCID_{50}$/ml	Pas de réaction croisée
23		Nucléoprotéine du SARS-coronavirus humain	25 ng/ml	Réaction croisée
24		Nucleoproteine du MERS-CoV	0,25 mg/ml	Pas de réaction croisée
25		Metapneumovirus humain (hMPV) 16 Type A1	$1,06 \times 10^{6,0}$ PFU/ml	Pas de réaction croisée

No,	Types d' échantillons	Substance de réaction croisée	Concentration finale du test	Résultat du Test
1	Autre Microorganisme	*Staphylococcus aureus*	$1,0 \times 10^{6,0}$ CFU/ml	Pas de réaction croisée
2		*Staphylococcus saprophyticus*	$1,0 \times 10^{6,0}$ CFU/ml	Pas de réaction croisée
3		*Neisseria sp.(Neisseria lactamica)*	$1,0 \times 10^{6,0}$ CFU/ml	Pas de réaction croisée
4		*Escherichia coli*	$1,0 \times 10^{6,0}$ CFU/ml	Pas de réaction croisée
5		*Staphylococcus haemolyticus*	$1,0 \times 10^{6,0}$ CFU/ml	Pas de réaction croisée

No,	Types d' échantillons	Substance de réaction croisée	Concentration finale du test	Résultat du Test
6	Autre Microorganisme	*Streptococcus pyogenes*	1,0 X $10^{6,0}$ CFU/ml	Pas de réaction croisée
7		*Streptococcus salivarius*	1,0 X $10^{6,0}$ CFU/ml	Pas de réaction croisée
8		*Hemophilus parahaemolyticus*	1,0 X $10^{6,0}$ CFU/ml	Pas de réaction croisée
9		*Proteus vulgaris*	1,0 X $10^{6,0}$ CFU/ml	Pas de réaction croisée
10		*Moraxella catarrhalis*	1,0 X $10^{6,0}$ CFU/ml	Pas de réaction croisée
11		*Klebsiella pneumoniae*	1,0 X $10^{6,0}$ CFU/ml	Pas de réaction croisée
12		*Fusobacterium necrophorum*	1,0 X $10^{6,0}$ CFU/ml	Pas de réaction croisée
13		*Mycobacterium tuberculosis*	10 mg/ml	Pas de réaction croisée
14		*Pool de lavages nasaux humains*	N/A*	Pas de réaction croisée

** Aucune concentration fournie par le fournisseur. La solution mère non diluée a été testée.*

5. Substances interférentes

Les 42 substances potentiellement interférentes suivantes n'ont aucun impact sur le Panbio™ COVID-19 Ag Rapid Test Device. Les concentrations d'essai finales des substances interférentes sont documentées dans le tableau ci-dessous.

No,	Types d' échantillons	Substances interférentes	Concentration finale du test	Résultat du Test
1	Substance Endogène	Mucine	0,5%	Pas d'interférence
2		Hémoglobine	100 mg/L	Pas d'interférence
3		Triglycérides	1,5 mg/L	Pas d'interférence
4		Ictère (Bilirubine)	40 mg/dL	Pas d'interférence
5		Facteur Rhumatoïde	200 IU/ml	Pas d'interférence
6		Anticorps anti-nucléaire	>1:40	Pas d'interférence
7		Enceinte	Dilution au dixième	Pas d'interférence

No,	Types d' échantillons	Substances interférentes	Concentration finale du test	Résultat du Test
8		Éther glycérylique de guaiacol	1 µg/ml	Pas d'interférence
9		Albuterol	0,005 mg/dL	Pas d'interférence
10		Ephedrine	0,1 mg/ml	Pas d'interférence
11		Chlorpheniramine	0,08 mg/dL	Pas d'interférence
12		Diphenhydramine	0,08 mg/dL	Pas d'interférence
13		Ribavirin	26,7 µg /ml	Pas d'interférence
14		Oseltamivir	0,04 mg/dL	Pas d'interférence
15		Zanamivir	17,3 µg /ml	Pas d'interférence
16		Chlorhydrate de phényléphrine	15% v/v	Pas d'interférence
17		Chlorhydrate d'oxymétazoline	15% v/v	Pas d'interférence
18		Amoxicilline	5,4 mg/dL	Pas d'interférence
19		Acide acétylsalicylique	3 mg/dL	Pas d'interférence
20		Ibuprofène	21,9 mg/dL	Pas d'interférence
21		Chlorothiazide	2,7 mg/dL	Pas d'interférence
22	Substance Exogène	Indapamide	140 ng/ml	Pas d'interférence
23		Glimépiride (sulfonylurées)	0,164 mg/dL	Pas d'interférence
24		Acarbose	0,03 mg/dL	Pas d'interférence
25		Ivermectine	4,4 mg/L	Pas d'interférence
26		Lopinavir	16,4 µg/L	Pas d'interférence
27		Ritonavir	16,4 µg/L	Pas d'interférence
28		Phosphate de chloroquine	0,99 mg/L	Pas d'interférence
29		Chlorure de sodium chloride avec conservateurs	4,44 mg/ml	Pas d'interférence
30		Beclomethasone	4,79 ng/ml	Pas d'interférence
31		Dexamethasone	0,6 µg/ml	Pas d'interférence
32		Flunisolide	0,61 µg/ml	Pas d'interférence
33		Triamcinolone	1,18 ng/ml	Pas d'interférence
34		Budesonide	2,76 ng/ml	Pas d'interférence
35		Mometasone	1,28 ng/ml	Pas d'interférence
36		Fluticasone	2,31 ng/ml	Pas d'interférence

No,	Types d' échantillons	Substances interférentes	Concentration finale du test	Résultat du Test
37	Substance Exogène	Sulfure	9,23 µg/ml	Pas d'interférence
38		Benzocaine	0,13 mg/ml	Pas d'interférence
39		Menthol	0,15 mg/ml	Pas d'interférence
40		Mupirocine	10 µg/ml	Pas d'interférence
41		Tobramycine	24,03 µg/ml	Pas d'interférence
42		Biotine	1,2 µg/ml	Pas d'interférence

6. Répétabilité et reproductibilité

La répétabilité et la reproductibilité du Panbio™ COVID-19 Ag Rapid Test Device ont été établies à l'aide de panels de référence internes contenant des échantillons négatifs et une gamme d'échantillons positifs.. Aucune différence n'a été observée à l'intérieur des séries, entre les séries, entre les lots, entre les sites et entre les jours.

PREPARATION

1 Laissez tous les composants du kit atteindre une température comprise entre 15 et 30 ° C avant de procéder au test pendant 30 minutes.
Remarque: le professionnel de santé doit se conformer aux directives de sécurité personnelle, y compris l'utilisation d'équipements de protection individuelle.

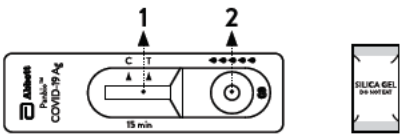
2 **Ouvrez la boite et recherchez les éléments suivants**
1. Testeur avec déshydratant dans un sachet individuel en aluminium
2. Solution tampon
3. Tube d'extraction
4. Bouchon pour les tubes d'extraction
5. Écouvillon de contrôle positif
6. Écouvillon de contrôle négatif
7. Écouvillons nasopharyngés stérilisés pour le prélèvement d'échantillons
8. Porte tubes
9. Guide de référence rapide (nasopharyngé)
10. Notice d'utilisation

3 Lisez attentivement ces instructions avant d'utiliser le kit de Panbio™ COVID-19 Ag Rapid Test Device.

4 Regardez la date d'expiration de la boîte du kit. Si la date d'expiration est dépassée, utilisez un autre kit.

5 **Ouvrez la pochette en aluminium et recherchez les éléments suivants:**
1. Fenêtre de résultats
2. Échantillon bien

Ensuite, étiquetez l'appareil avec l'identifiant du patient.



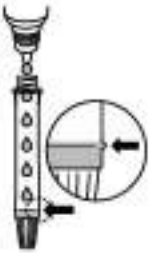
●●●●● : 5 gouttes de l'échantillon extrait

FRENCH

PROCEDURE

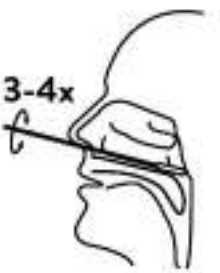
1 Tenez le flacon de tampon verticalement et remplissez le tube d'extraction avec du liquide tampon jusqu'à ce qu'il s'écoule jusqu'à la ligne de remplissage du tube d'extraction (300 µl).

⚠ **Attention:** Si la quantité de tampon est excessive ou insuffisante, un résultat de test incorrect peut se produire.

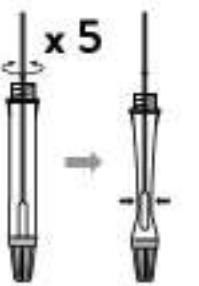


2 Placez le tube d'extraction dans le support de tubes.

3 Inclinez la tête du patient en arrière. Insérez l'écouvillon dans la narine. Frottez et roulez doucement l'écouvillon, 3 à 4 fois. Laissez l'écouvillon en place pendant plusieurs secondes. Retirez lentement l'écouvillon.

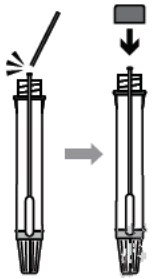


4 Insérez l'échantillon sur écouvillon dans le tube d'extraction. Faites tourbillonner la pointe de l'écouvillon dans le fluide tampon à l'intérieur du tube d'extraction, en poussant dans la paroi du tube d'extraction au moins cinq fois, puis faites sortir l'écouvillon en pressant le tube d'extraction avec vos doigts.



PROCEDURE

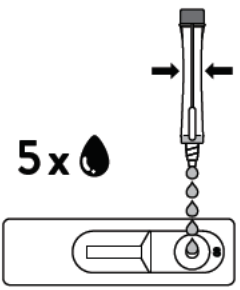
5 Cassez l'écouvillon au point de rupture et fermez le capuchon du tube d'extraction.



6 Ouvrez le capuchon de la buse à goutte au bas du tube d'extraction.

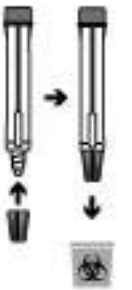
7 Distribuer verticalement 5 gouttes d'échantillons extraits dans le puits d'échantillon (S) de l'appareil. Ne pas manipuler ni déplacer le dispositif de test tant que le test n'est pas terminé et prêt pour la lecture.

⚠ **Attention:** les bulles qui se produisent dans le tube d'extraction peuvent conduire à des résultats inexacts. Si vous ne parvenez pas à créer suffisamment de gouttes, cela peut être dû à un colmatage de la buse de distribution. Secouez doucement le tube pour libérer le blocage jusqu'à ce que vous observiez la formation de gouttes libres.



PROCEDURE

8 Fermez la buse et jetez le tube d'extraction avec l'écouvillon usagé conformément à vos réglementations locales et au protocole d'élimination des déchets biologiques.



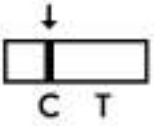
9 Démarrer le minuteur, lire le résultat à 15 minutes. Ne pas lire le résultat après 20 minutes.

10 L'Elimination des appareils usagés se fait conformément à la réglementation locale en vigueur et selon le protocole d'élimination des déchets dangereux.

INTERPRETATION DU TEST

NEGATIF

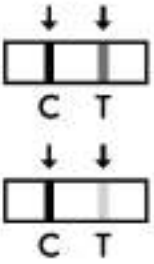
La présence seule de la ligne de contrôle (C) et aucune ligne de test (T) dans la fenêtre de résultat indique un résultat négatif.



POSITIF

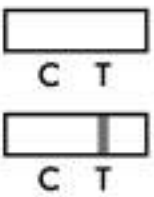
La présence de la ligne de test (T) et de la ligne de contrôle (C) dans la fenêtre de résultat, quelle que soit la ligne qui apparaît en premier, indique un résultat positif.

⚠ **Attention:** la présence d'une ligne de test (T), aussi faible soit-elle, indique un résultat positif.



INVALIDE

Si la ligne de contrôle (C) n'est pas visible dans la fenêtre de résultat après l'exécution du test, le résultat est considéré comme invalide. Les instructions peuvent ne pas avoir été suivies correctement. Il est recommandé de relire la notice d'utilisation avant de tester à nouveau l'échantillon avec un nouveau dispositif de test.



FRENCH

A proposito del test

IT

Introduzione

La patologia provocata da Coronavirus (COVID-19) è una malattia infettiva causata da un coronavirus appena scoperto, la sindrome respiratoria acuta grave coronavirus 2 (SARS-CoV-2)[1]. Il SARS-CoV-2 è un β-coronavirus, che è un virus a RNA a filamento positivo, incapsulato e non segmentato[2]. Si diffonde per trasmissione da uomo a uomo tramite goccioline o contatto diretto, ed è stato stimato che l'infezione ha un periodo medio di incubazione di 6,4 giorni e un numero di riproduzione di base di 2,24-3,58. Tra i pazienti con polmonite causata dalla SARS-CoV-2, la febbre era il sintomo più comune, seguita dalla tosse[3]. I principali test IVD utilizzati per COVID-19 utilizzano la real-time reverse transcriptase-polymerase chain reaction (RT-PCR) che richiede alcune ore[4]. La disponibilità di un test diagnostico point-of-care rapido ed economico è fondamentale per supportare gli operatori sanitari nella diagnosi dei pazienti e prevenire un'ulteriore diffusione del virus[5]. I test antigenici avranno un ruolo fondamentale nella lotta contro il COVID-19[6].

Principio del test

Il dispositivo Panbio™ COVID-19 Ag Rapid Test Device contiene una striscia di membrana che è pre-rivestita con anticorpo anti-SARS-CoV-2 immobilizzato sulla linea di test e un anticorpo monoclonale di topo anti-IgY di pollo sulla linea di controllo. Due tipi di coniugati (IgG umane specifiche per SARS-CoV-2 Ag coniugate con oro e IgY di pollo coniugate con oro) migrano cromatograficamente verso l'alto sulla membrana e reagiscono rispettivamente con l'anticorpo anti-SARS-CoV-2 e con l'anticorpo monoclonale di topo anti-IgY di pollo pre-rivestito. Per un risultato positivo, le IgG umane specifiche per SARS-CoV-2 Ag coniugate con oro e l'anticorpo anti-SARS-CoV-2 formeranno una linea di test nella finestra dei risultati. Né la linea del test né la linea di controllo sono visibili nella finestra dei risultati prima dell'applicazione del campione del paziente. Una linea di controllo visibile è necessaria per indicare che il risultato del test è valido.

Uso previsto

Panbio™ COVID-19 Ag Rapid Test Device è un test rapido diagnostico *in vitro* per la ricerca qualitativa dell'antigene SARS-CoV-2 (Ag) in campioni umani da tampone nasofaringeo provenienti da individui che soddisfano criteri clinici e/o epidemiologici COVID-19. Il dispositivo Panbio™ COVID-19 Ag Rapid Test Device è solo per uso professionale ed è destinato ad essere utilizzato come ausilio nella diagnosi dell'infezione da SARS-CoV-2. Il prodotto può essere utilizzato in qualsiasi ambiente, di laboratorio e non, che soddisfi i requisiti specificati nelle Istruzioni per

l'uso e nella normativa locale.
Il test fornisce risultati preliminari. I risultati negativi non precludono l'infezione da SARS-CoV-2 e non possono essere utilizzati come unica base per il trattamento o per altre decisioni di gestione. I risultati negativi devono essere combinati con le osservazioni cliniche, l'anamnesi del paziente e le informazioni epidemiologiche. Il test non è destinato ad essere utilizzato come test di screening per SARS-CoV-2 sui donatori.

Materiali forniti
- 25 Dispositivi di test confezionati singolarmente in buste di alluminio con essiccante
- Buffer (1 x 9 ml/flacone)
- 25 Provette di estrazione
- 25 Tappi per provette di estrazione
- 1 Tampone di controllo positivo
- 1 Tampone di controllo negativo
- 25 Tamponi sterili nasofaringei per la raccolta del campione
- 1 Rack portaprovette
- 1 Guida rapida di riferimento (Nasofaringeo)
- 1 Istruzioni per l'uso

Materiali richiesti ma non forniti
- Dispositivi di protezioni individuali in base alle raccomandazioni locali (ad esempio abito/protezione da laboratorio, maschera facciale, scudo facciale/occhialini e guanti), Timer, Contenitore per rifiuti a rischio biologico

Principi attivi dei componenti principali
- **1 Dispositivo di test** Coniugato d'oro: IgG umane specifiche verso SARS-CoV-2 Ag oro colloidale e IgY di pollo – oro colloidale. Linea di test: monoclonale di topo anti-SARS-CoV-2 Linea di controllo: monoclonale di topo anti- IgY di pollo
- **Buffer** Tricina , Cloruro di sodio, Tween 20 , Azoturo di sodio (<0,1%), Proclin 300

Conservazione e Stabilità
1. Il kit deve essere conservato a una temperatura compresa tra 2 e 30 °C. Non congelare il kit o i suoi componenti.
   Nota: Se conservato in frigorifero, tutti i componenti del kit devono essere portati a temperatura ambiente (15-30 °C) per almeno 30 minuti prima di eseguire il test. Non aprire il sacchetto mentre i componenti vengono portati a temperatura ambiente.

2. Il flacone del Buffer può essere aperto e richiuso ad ogni test. Il tappo del Buffer deve essere chiuso saldamente dopo ogni utilizzo. Il Buffer è stabile fino alla data di scadenza se conservato a 2-30 °C.
3. Eseguire l'analisi immediatamente dopo aver rimosso il dispositivo di test dalla busta di alluminio.
4. Non utilizzare il kit oltre la data di scadenza.
5. La durata di conservazione del kit è quella indicata sulla confezione esterna.
6. Non utilizzare il kit se la confezione è danneggiata o il sigillo è rotto.
7. I campioni con tampone diretto devono essere testati immediatamente dopo il prelievo. Se non è possibile effettuare il test immediatamente, il tampone di raccolta può essere conservato in una provetta di estrazione riempita con Buffer (300 µl) a temperatura ambiente (15-30 °C) per un massimo di due ore prima del test.

Avvertenze

1. Solo per uso diagnostico *in vitro*. Non riutilizzare il dispositivo di test e i componenti del kit.
2. Queste istruzioni devono essere rigorosamente seguite da un professionista sanitario qualificato per ottenere risultati accurati. Tutti gli utenti devono leggere le istruzioni prima di eseguire un test.
3. Non mangiare o fumare mentre si maneggiano i campioni.
4. Indossare guanti protettivi durante la manipolazione dei campioni e lavarsi accuratamente le mani dopo averli maneggiati.
5. Evitare spruzzi o la formazione di aerosol di campione e di Buffer.
6. Pulire accuratamente le fuoriuscite utilizzando un disinfettante appropriato.
7. Decontaminare e smaltire tutti i campioni, i kit di reazione e i materiali potenzialmente contaminati (ad es. tampone di prelievo, provetta di estrazione, dispositivo di test) in un contenitore a rischio biologico come se fossero rifiuti infettivi e smaltirli secondo le normative locali vigenti.
8. Non mescolare o scambiare campioni diversi.
9. Non mescolare reagenti di lotti diversi o di altri prodotti.
10. Non conservare il kit alla luce diretta del sole.
11. Per evitare la contaminazione, quando si apre la busta non toccare la testa del tampone di raccolta in dotazione.
12. I tamponi sterili forniti nella confezione devono essere usati solo per la raccolta di campioni nasofaringei.
13. Per evitare la contaminazione incrociata, non riutilizzare i tamponi sterili per la raccolta dei campioni.
14. Non diluire il tampone raccolto con nessuna soluzione eccetto il Buffer di estrazione fornito.

15. Il tampone contiene <0,1% di azoturo di sodio come conservante che può essere tossico se ingerito. Se smaltito attraverso un lavandino, sciacquare con abbondante acqua.[7]

Procedura del test (Fare riferimento alla Figura)

Campioni da Tampone Nasofaringeo

Nota: Il personale sanitario deve rispettare le linee guida di sicurezza personali, tra cui l'uso di dispositivi di protezione personale.

Preparazione del test

1. Lasciare che tutti i componenti del kit raggiungano una temperatura tra i 15 e i 30 °C per 30 minuti prima del test.
2. Rimuovere il dispositivo di test dal sacchetto di alluminio prima dell'uso. Posizionarlo su una superficie piana, orizzontale e pulita.
3. Tenere il flacone del Buffer in posizione verticale e riempire la provetta di estrazione con il liquido fino al raggiungimento della linea di riempimento della provetta di estrazione (300 µl).

⚠ **Attenzione:** Se la quantità di tampone è eccessiva o insufficiente, può verificarsi un risultato del test non corretto.

4. Posizionare la provetta di estrazione nel portaprovette.

Raccolta del campione ed Estrazione

1. Inclinare leggermente indietro la testa del paziente di circa 45°-70° per agevolare il passaggio dalla parte anteriore del naso.
2. Inserire il tampone con asta flessibile attraverso la narice parallelamente al palato.

⚠ **Attenzione:** Utilizzare un tampone nasofaringeo dedicato per la raccolta dei campioni.

3. Il tampone deve raggiungere una profondità pari alla distanza tra le narici e l'apertura esterna dell'orecchio.

⚠ **Attenzione:** Se si incontra resistenza durante l'inserimento del tampone, rimuoverlo e tentare l'inserimento nella narice opposta.

4. Strofinare e ruotare delicatamente il tampone 3-4 volte. Lasciare il tampone in posizione per alcuni secondi per assorbire le secrezioni.
5. Estrarre lentamente il tampone ruotandolo e inserirlo nella provetta di estrazione.
6. Ruotare la punta del tampone nel liquido all'interno della provetta di estrazione, premendolo sulla parete della provetta di estrazione almeno cinque volte e poi spremere il tampone strizzando la provetta di estrazione con le dita.
7. Spezzare il tampone nel punto di rottura e chiudere il tappo della provetta di estrazione.

Reazione con dispositivo di test

1. Aprire il tappo dell'ugello posizionato nella parte inferiore della provetta di estrazione.
2. Dispensare 5 gocce di campione estratto verticalmente nel pozzetto del campione (S) sul dispositivo. Non maneggiare o spostare il dispositivo fino a quando il test non è completo e pronto per la lettura.

⚠ **Attenzione:** La comparsa di bolle nella provetta di estrazione può portare a risultati imprecisi. Se non si riuscisse ad ottenere un numero di gocce sufficienti, ciò potrebbe essere causato dall'intasamento dell'ugello di erogazione. Agitare delicatamente la provetta per rimuovere l'ostruzione fino a osservare la formazione di goccia libera.

3. Chiudere l'ugello e smaltire la provetta di estrazione contenente il tampone usato secondo le normative locali e il protocollo di smaltimento dei rifiuti biologici.
4. Avviare il timer. Leggere il risultato a 15 minuti. Non leggere i risultati dopo 20 minuti.
5. Smaltire il dispositivo usato in base alle normative locali e al protocollo di smaltimento dei rifiuti per rischio biologico.

Tampone di controllo positivo / negativo

Nota: fare riferimento alla sezione Controllo Qualità Esterno di queste Istruzioni per l'utilizzo e per la frequenza di test di tamponi di controllo qualità esterno.

1. Tenere il flacone di buffer verticalmente e riempire la provetta di estrazione con il liquido fino alla linea di riempimento della provetta di estrazione (300 µl).

⚠ **Attenzione:** Se la quantità di buffer è eccessiva o insufficiente, potrebbe verificarsi un risultato del test errato.

2. Posizionare la provetta di estrazione nel rack portaprovette.
3. Inserire il tampone di controllo positivo o negativo nel liquido all'interno della provetta di estrazione e immergere il tampone per 1 minuto. Ruotare la punta del tampone di controllo nel liquido all'interno della provetta di estrazione, spingendo nella parete della provetta di estrazione almeno cinque volte e poi premere il tampone strizzando la provetta di estrazione con le dita.
4. Smaltire il tampone di controllo usato in conformità con il protocollo di smaltimento dei rifiuti per rischio biologico.
5. Chiudere il tappo della provetta di estrazione.
6. Seguire la procedura di cui sopra [Reazione con dispositivo di test].

Interpretazione del test (Fare riferimento alla figura)

1. Risultato negativo: la presenza della sola linea di controllo (C) e

nessuna linea di test (T) all'interno della finestra del risultato indica un risultato negativo.

2. Risultato positivo: la presenza della linea di test (T) e della linea di controllo (C) all'interno della finestra dei risultati, indipendentemente dalla linea visualizzata per prima, indica un risultato positivo.

⚠ **Attenzione:** la presenza di qualsiasi linea di test (T), non importa quanto debole, indica un risultato positivo.

3. Risultato non valido: se la linea di controllo (C) non è visibile all'interno della finestra dei risultati dopo l'esecuzione del test, il risultato viene considerato non valido.

Limitazioni del test

1. Il contenuto di questo kit deve essere utilizzato per la ricerca professionale e qualitativo dell'antigene SARS CoV-2 da tampone nasofaringeo. Altri tipi di campioni possono portare a risultati non corretti e non devono essere utilizzati.
2. Il mancato rispetto delle istruzioni per la procedura di test e dell'interpretazione dei risultati possono influire negativamente sulle prestazioni del test e/o produrre risultati non validi.
3. Un risultato negativo può verificarsi se il campione è stato raccolto, estratto o trasportato in modo improprio. Un risultato negativo del test non esclude la possibilità di infezione da SARS-CoV-2 e deve essere confermato dalla coltura virale o da un saggio molecolare.
4. I risultati positivi dei test non escludono le co-infezioni con altri agenti patogeni.
5. I risultati dei test devono essere valutati in concomitanza con altri dati clinici a disposizione del medico.
6. Leggere i risultati del test prima di 15 minuti o dopo 20 minuti può dare risultati errati.
7. Panbio™ COVID-19 Ag Rapid Test Device non è destinato a rilevare virus difettoso (non infettivo) durante le fasi successive di mutazione virale che potrebbero essere rilevate dai test molecolari PCR.[8]
8. Risultati positivi possono verificarsi in caso di infezione da SARS-CoV.

Controllo qualità

1. Controllo di qualità interno:

Il dispositivo di test ha una linea di test (T) e una linea di controllo (C) sulla superficie del dispositivo di test. Né la linea di test né la linea di controllo sono visibili nella finestra dei risultati prima di applicare un campione. La linea di controllo viene utilizzata per il controllo procedurale e deve sempre apparire se la procedura di test viene eseguita correttamente e se i reagenti del test della linea di controllo funzionano.

2. Controllo esterno di qualità:

I controlli sono formulati e fabbricati in modo specifico per garantire le prestazioni di Panbio™ COVID-19 Ag Rapid Test Device e vengono utilizzati per verificare la capacità dell'utente di eseguire correttamente il test e interpretare i risultati. Il Controllo Positivo produrrà un risultato positivo del test ed è stato fabbricato per produrre una linea di test visibile (T). Il controllo negativo produrrà un risultato negativo del test. Una buona pratica di laboratorio suggerisce l'uso di controlli positivi e negativi per assicurarsi che:

- I reagenti del test stanno funzionando e
- Il test viene eseguito correttamente.

I controlli esterni di qualità possono essere eseguiti in una delle seguenti circostanze:

- Da un nuovo operatore prima di eseguire test su campioni di pazienti,
- Quando si riceve una nuova spedizione di test,
- A intervalli periodici come dettato dai requisiti locali, e/o dalle procedure di Controllo Qualità dell'utente.

Caratteristiche delle performance

1. Valutazione esterna di Panbio™ COVID-19 Ag Rapid Test Device

Le prestazioni cliniche di Panbio™ COVID-19 Ag Rapid Test Device sono state determinate testando campioni 140 positivi e 445 negativi per l'antigene SARS-CoV-2 (Ag). Sono state evidenziate una sensibilità di 91,4% (95% CI: 85,5-95,5%) e una specificità di 99,8% (95% CI: 98,8-100%). I campioni clinici sono stati determinati come positivi o negativi utilizzando un metodo di riferimento FDA EUA RT-PCR.

Risultati di Panbio™ COVID-19 Ag Rapid Test Device

		Risultato del test PCR		
		Positivo	**Negativo**	**Totale**
Risultati di Panbio™ COVID-19 Ag Rapid Test Device	**Positivo**	128	1	129
	Negativo	12	444	456
	Totale	140	445	585
		Sensibilità	Specificità	Percentuale di concordanza complessiva
		91,4% [85,5%;95,5%]	**99,8%** [98,8%;100%]	**97,8%** [96,2%;98,8%]

- I dati di performance sono stati calcolati tramite uno studio su individui sospettati di esposizione al COVID-19 o che hanno presentato sintomi negli ultimi 7 giorni.
- La stratificazione dei campioni positivi post insorgenza di sintomi o sospetta esposizione tra 0-3 giorni ha una sensibilità del 94,9% (n=39) e a 4-7 giorni ha una sensibilità di 90,1% (n=101).
- La concordanza positiva di Panbio™ COVID-19 Ag Rapid Test Device è più alta con campioni con "valori Ct ≤ 33 con una sensibilità del 98,2%. Come suggerito nei riferimenti 8 e 9, i pazienti con valori Ct >33 non sono più contagiosi.[8, 9]

2. Limite di rilevamento

Panbio™ COVID-19 Ag Rapid Test Device è in grado di rilevare 2,5X10[1,8] $TCID_{50}$/ml di SARS-CoV-2 che è stato isolato da un paziente confermato COVID-19 in Corea.

3. Effetto gancio

Non vi è alcun effetto gancio a 1,0x10[5,8] $TCID_{50}$/ml di SARS- CoV-2 che è stato isolato da un paziente confermato COVID-19 in Corea.

4. Reattività crociata

La reattività crociata di Panbio™ COVID-19 Ag Rapid Test Device è stata valutata testando 25 virus e altri 14 microrganismi. Le concentrazioni di test finali di virus e altri microrganismi sono documentate nella tabella seguente. I seguenti virus e altri microrganismi, ad eccezione della Nucleoproteina SARS-coronavirus umana, non hanno alcun effetto sui risultati dei test di Panbio™ COVID-19 Ag Rapid Test Device. Panbio™ COVID-19 Ag Rapid Test Device ha reattività crociata con Nucleoproteina SARS-coronavirus umana ad una concentrazione di 25 ng/ml o più perché SARS-CoV ha un'omologia elevata (79,6%) al SARS-CoV-2.

No,	Tipi di campione	Sostanza di cross-reazione	Concentrazione dei test finali	Risultato del test
1	Virus	Adenovirus Type3	2,0 X $10^{6,5}$ $TCID_{50}$/ml	Nessuna cross reazione
2		Adenovirus Type7	2,0 X $10^{4,75}$ $TCID_{50}$/ml	Nessuna cross reazione
3		Echovirus2	1,0 X $10^{6,5}$ $TCID_{50}$/ml	Nessuna cross reazione
4		Echovirus11	2,0 X$10^{5,25}$ $TCID_{50}$/ml	Nessuna cross reazione
5		Human herpesvirus (HSV) 1	2,0 X $10^{6,25}$ $TCID_{50}$/ml	Nessuna cross reazione
6		Human herpesvirus (HSV) 2	2,0 X $10^{4,75}$ $TCID_{50}$/ml	Nessuna cross reazione
7		Mumps Virus Ag	2,0 X $10^{3,5}$ $TCID_{50}$/ml	Nessuna cross reazione
8		Influenza virus A (H1N1) Strain (A/Virginia/ATCC1/2009)	2,6 X $10^{5,0}$ PFU/ml	Nessuna cross reazione
9		Influenza virus A (H1N1) Strain (A/WS/33)	5,0 X $10^{7,25}$ $TCID_{50}$/ml	Nessuna cross reazione
10		Influenza virus A(H3N2) Strain (A/Hong Kong/8/68)	N/A*	Nessuna cross reazione
11		Influenza virus B Strain (B/Lee/40)	2,0 X $10^{5,25}$ $TCID_{50}$/ml	Nessuna cross reazione
12-14		Parainfluenza Type 1, Parainfluenza Type 2, Parainfluenza Type 3	N/A*	Nessuna cross reazione
15		Parainfluenza Tipo 4A	1,97 X $10^{7,0}$ PFU/ml	Nessuna cross reazione
16		Respiratory syncytial virus (RSV) type A	4,22 X $10^{5,0}$ $TCID_{50}$/ml	Nessuna cross reazione
17		Respiratory syncytial virus (RSV) type B	5,62 X $10^{5,0}$ $TCID_{50}$/ml	Nessuna cross reazione
18		HCoV-HKU1	10 µg/ml	Nessuna cross reazione
19		Rinovirus A16	8,8 X $10^{5,0}$ PFU/ml	Nessuna cross reazione
20		HCoV-NL63	1,7 X $10^{5,0}$ $TCID_{50}$/ml	Nessuna cross reazione

No,	Tipi di campione	Sostanza di cross-reazione	Concentrazione dei test finali	Risultato del test
21	Virus	HCoV-OC43	8,9 X $10^{5,0}$ $TCID_{50}$/ml	Nessuna cross reazione
22		HCoV-229E	1,51 X $10^{6,0}$ $TCID_{50}$/ml	Nessuna cross reazione
23		Nucleoproteina SARS-coronavirus umana	25 ng/ml	Cross reazione
24		Nucleoproteina MERS-CoV	0,25 mg/ml	Nessuna cross reazione
25		Metapneumovirus umano (hMPV) 16 Tipo A1	1,06 X $10^{6,0}$ PFU/ml	Nessuna cross reazione

No,	Tipi di campione	Sostanza di cross-reazione	Concentrazione dei test finali	Risultato del test
1	Altro Microorganismo	*Staphylococcus aureus*	1,0 X $10^{6,0}$ CFU/ml	Nessuna cross reazione
2		*Staphylococcus saprophyticus*	1,0 X $10^{6,0}$ CFU/ml	Nessuna cross reazione
3		*Neisseria sp,(Neisseria lactamica)*	1,0 X $10^{6,0}$ CFU/ml	Nessuna cross reazione
4		*Escherichia coli*	1,0 X $10^{6,0}$ CFU/ml	Nessuna cross reazione
5		*Staphylococcus haemolyticus*	1,0 X $10^{6,0}$ CFU/ml	Nessuna cross reazione
6		*Streptococcus pyogenes*	1,0 X $10^{6,0}$ CFU/ml	Nessuna cross reazione
7		*Streptococcus salivarius*	1,0 X $10^{6,0}$ CFU/ml	Nessuna cross reazione
8		*Hemophilus parahaemolyticus*	1,0 X $10^{6,0}$ CFU/ml	Nessuna cross reazione
9		*Proteus vulgaris*	1,0 X $10^{6,0}$ CFU/ml	Nessuna cross reazione
10		*Moraxella catarrhalis*	1,0 X $10^{6,0}$ CFU/ml	Nessuna cross reazione
11		*Klebsiella pneumoniae*	1,0 X $10^{6,0}$ CFU/ml	Nessuna cross reazione
12		*Fusobacterium necrophorum*	1,0 X $10^{6,0}$ CFU/ml	Nessuna cross reazione

No,	Tipi di campione	Sostanza di cross-reazione	Concentrazione dei test finali	Risultato del test
13	Altro Microorganismo	*Mycobacterum tuberculosis*	10 mg/ml	Nessuna cross reazione
14		*Lavaggio nasale umano in pool*	N/A*	Nessuna cross reazione

** Nessuna concentrazione fornita dal fornitore. È stata testata una soluzione di stock non diluito.*

5. Sostanze interferenti

Le seguenti 42 sostanze potenzialmente interferenti non hanno alcun impatto su Panbio™ COVID-19 Ag Rapid Test Device. La concentrazione finale di test delle sostanze interferenti è documentata nella tabella sotto.

No,	Tipi di campione	Sostanze interferenti	Concentrazione dei test finali	Risultato del test
1	Sostanza endogena	Mucin	0,5%	Nessuna interferenza
2		Hemoglobin	100 mg/L	Nessuna interferenza
3		Triglycerides	1,5 mg/L	Nessuna interferenza
4		Icteric (Bilirubin)	40 mg/dL	Nessuna interferenza
5		Rheumatoid factor	200 IU/ml	Nessuna interferenza
6		Anti-nuclear antibody	>1:40	Nessuna interferenza
7		Pregnant	Diluizione 1:10	Nessuna interferenza
8	Sostanza esogena	Guaiacol glyceryl ether	1 µg/ml	Nessuna interferenza
9		Albuterol	0,005 mg/dL	Nessuna interferenza
10		Ephedrine	0,1 mg/ml	Nessuna interferenza
11		Chlorpheniramine	0,08 mg/dL	Nessuna interferenza
12		Diphenhydramine	0,08 mg/dL	Nessuna interferenza
13		Ribavirin	26,7 µg /ml	Nessuna interferenza
14		Oseltamivir	0,04 mg/dL	Nessuna interferenza
15		Zanamivir	17,3 µg /ml	Nessuna interferenza
16		Phenylephrine hydrochloride	15% v/v	Nessuna interferenza
17		Oxymetazolin hydrochloride	15% v/v	Nessuna interferenza
18		Amoxicillin	5,4 mg/dL	Nessuna interferenza
19		Acetylsalicylic acid	3 mg/dL	Nessuna interferenza
20		Ibuprofen	21,9 mg/dL	Nessuna interferenza
21		Chlorothiazide	2,7 mg/dL	Nessuna interferenza

No,	Tipi di campione	Sostanze interferenti	Concentrazione dei test finali	Risultato del test
22	Sostanza esogena	Indapamide	140 ng/ml	Nessuna interferenza
23		Glimepiride (Sulfonylureas)	0,164 mg/dL	Nessuna interferenza
24		Acarbose	0,03 mg/dL	Nessuna interferenza
25		Ivermectin	4,4 mg/L	Nessuna interferenza
26		Lopinavir	16,4 µg/L	Nessuna interferenza
27		Ritonavir	16,4 µg/L	Nessuna interferenza
28		Chloroquine phosphate	0,99 mg/L	Nessuna interferenza
29		Cloruro di sodio con conservanti	4,44 mg/ml	Nessuna interferenza
30		Beclometasone	4,79 ng/ml	Nessuna interferenza
31		Desametasone	0,6 µg/ml	Nessuna interferenza
32		Flunisolide	0,61 µg/ml	Nessuna interferenza
33		Triamcinolone	1,18 ng/ml	Nessuna interferenza
34		Budesonide	2,76 ng/ml	Nessuna interferenza
35		Mometasone	1,28 ng/ml	Nessuna interferenza
36		Fluticasone	2,31 ng/ml	Nessuna interferenza
37		Zolfo	9,23 µg/ml	Nessuna interferenza
38		Benzocaina	0,13 mg/ml	Nessuna interferenza
39		Mentolo	0,15 mg/ml	Nessuna interferenza
40		Mupirocina	10 µg/ml	Nessuna interferenza
41		Tobramicina	24,03 µg/ml	Nessuna interferenza
42		Biotina	1,2 µg/ml	Nessuna interferenza

6. Ripetibilità e riproducibilità

La ripetibilità e la riproducibilità di Panbio™ COVID-19 Ag Rapid Test Device sono state stabilite utilizzando pannelli di riferimento interni contenenti campioni positivi alti, positivi medi, positivi deboli e negativi. Non sono state osservate differenze all'interno della serie, tra le serie, tra i lotti, tra i siti e tra i giorni.

PREPARAZIONE

1 Consentire a tutti i componenti del kit di raggiungere una temperatura tra 15-30°C per 30 minuti prima dell'esecuzione del test.
Nota: Gli operatori sanitari devono rispettare le linee guida per la sicurezza personale, incluso l'uso di dispositivi di protezione personale.

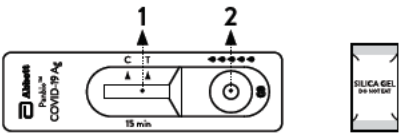
2 **Aprire la confezione e cercare quanto segue:**
1. Dispositivo di test confezionato singolarmente in busta di alluminio con essiccante
2. Buffer
3. Provetta di estrazione
4. Tappo della provetta di estrazione
5. Tampone di controllo positivo
6. Tampone di controllo negativo
7. Tamponi sterili nasofaringei per la raccolta del campione
8. Rack portaprovette
9. Guida rapida di riferimento (Nasofaringeo)
10. Istruzioni per l'uso

3 Leggere attentamente queste istruzioni prima di utilizzare il kit Panbio™ COVID-19 Ag Rapid Test Device.

4 Guarda la data di scadenza della scatola del kit. Se la data di scadenza è trascorsa, usa un altro kit.

5 **Aprire la busta di alluminio e cercare quanto segue:**
1. Finestra dei risultati
2. Pozzetto del campione

Quindi, etichettare il dispositivo con l'identificatore del paziente.

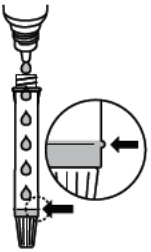


●●●●● : 5 gocce del campione estratto

PROCEDURA DEL TEST

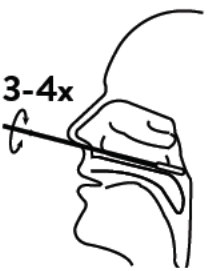
1 Tenere il flacone del buffer verticalmente e riempire la provetta di estrazione fino alla linea di riempimento della provetta di estrazione (300 µl).

⚠ **Attenzione:** Se la quantità di buffer è eccessiva o insufficiente, potrebbe verificarsi un risultato di test errato.

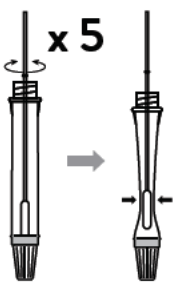


2 Posizionare la provetta di estrazione nel rack portaprovette.

3 Inclinare la testa del paziente all'indietro. Inserire il tampone attraverso la narice. Strofinare e ruotare delicatamente il tampone 3-4 volte. Lasciare il tampone in posizione per alcuni secondi. Rimuovere lentamente il tampone.



4 Inserire il tampone di campionamento nella provetta di estrazione. Ruotare la punta del tampone nel liquido all'interno della provetta di estrazione, spingendo sulla parete della provetta di estrazione almeno cinque volte e poi premere il tampone strizzando la provetta di estrazione con le dita.



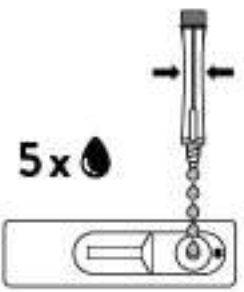
PROCEDURA DEL TEST

5 Spezzare il tampone nel punto di rottura e chiudere il tappo della provetta di estrazione.

6 Aprire il tappo dell'ugello posizionato nella parte inferiore della provetta di estrazione.

7 Dispensare 5 gocce di campione estratto verticalmente nel pozzetto del test (S) sul dispositivo. Non maneggiare o spostare il dispositivo fino a quando il test non è completo e pronto per la lettura.

⚠ **Attenzione:** La comparsa di bolle nella provetta di estrazione può portare a risultati imprecisi. Se non si riuscisse ad ottenere un numero di gocce sufficienti, ciò potrebbe essere causato dall'intasamento dell'ugello di erogazione. Agitare delicatamente la provetta per rimuovere l'ostruzione fino a osservare la formazione di goccia libera.



PROCEDURA DEL TEST

8 Chiudere l'ugello e smaltire la provetta di estrazione contenente il tampone usato in base alle normative locali e al protocollo di smaltimento dei rifiuti biologici.

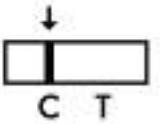
9 Avviare il timer. Leggere il risultato a 15 minuti. Non leggere i risultati dopo 20 minuti.

10 Smaltire il dispositivo usato in base alle normative locali e al protocollo di smaltimento dei rifiuti biologici.

INTERPRETAZIONE DEL TEST

NEGATIVO

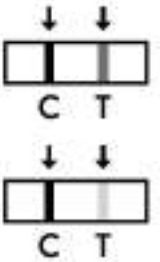
La presenza della sola linea di controllo (C) e nessuna linea di test (T) all'interno della finestra dei risultati indica un risultato negativo.



POSITIVO

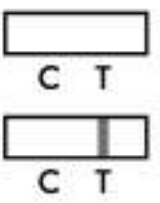
La presenza della linea di test (T) e della linea di controllo (C) all'interno della finestra dei risultati, indipendentemente dalla linea visualizzata per prima, indica un risultato positivo.

⚠ **Attenzione:** La presenza di qualsiasi linea di test (T), non importa quanto debole, indica un risultato positivo.



INVALIDO

Se la linea di controllo (C) non è visibile all'interno della finestra dei risultati dopo l'esecuzione del test, il risultato viene considerato non valido. Le istruzioni potrebbero non essere state seguite correttamente. Si consiglia di leggere nuovamente il foglietto illustrativo prima di testare nuovamente il campione con un nuovo dispositivo di test.



Sobre o Teste

PT

Introdução

A doença do Coronavírus (COVID-19) é uma doença infecciosa causada por um coronavírus recém-descoberto, coronavírus da síndrome respiratória aguda grave 2 (SARS-CoV-2)[1]. O SARS-CoV-2 é um β-coronavírus, que é um vírus de RNA com envelope de sentido positivo não segmentado[2]. É disseminado por transmissão de humano para humano através de gotículas ou contato direto, e estima-se que a infecção tenha um período médio de incubação de 6,4 dias e um número básico de reprodução de 2,24–3,58. Entre os pacientes com pneumonia causada por SARS-CoV-2, a febre foi o sintoma mais comum, seguido pela tosse[3]. Os principais ensaios IVD utilizados para COVID-19 empregam a reação em cadeia da polimerase-transcriptase reversa em tempo real (RT-PCR) que leva algumas horas[4]. A disponibilidade de um teste de diagnóstico rápido e econômico é fundamental para permitir que profissionais de saúde ajudem no diagnóstico de pacientes e previna a disseminação do vírus[5]. Os testes de antígenos desempenharão um papel crítico na luta contra a COVID-19[6].

Princípio do Teste

O Panbio™ COVID-19 Ag Rapid Test Device contém uma tira de membrana, que é pré-revestida com anticorpo antiSARS-CoV-2 imobilizado na linha de teste e IgY monoclonal de camundongo antigalinha na linha de controle. Dois tipos de conjugados (IgG humana específica para conjugado de ouro SARS-CoV-2 Ag e conjugado de ouro IgY de galinha) movem-se para cima na membrana cromatograficamente e reagem com o anticorpo antiSARS-CoV-2 e IgY monoclonal de camundongo antigalinha pré-revestido respectivamente. Para um resultado positivo, a IgG humana específica para o conjugado de ouro SARS-CoV-2 Ag e o anticorpo antiSARS-CoV-2 formarão uma linha de teste na janela de resultados. Nem a linha de teste nem a linha de controle são visíveis na janela de resultados antes de aplicar a amostra do paciente. Uma linha de controle visível é necessária para indicar que um resultado de teste é válido.

Uso Pretendido

O Panbio™ COVID-19 Ag Rapid Test Device é um teste rápido de diagnóstico *in vitro* para a detecção qualitativa do antígeno SARS-CoV-2 (Ag) em amostras de esfregaço nasofaríngeo humano de indivíduos que atendem aos critérios clínicos e/ou epidemiológicos da COVID-19. O Panbio™ COVID-19 Ag Rapid Test Device destina-se apenas a uso profissional e deve ser usado como auxiliar no diagnóstico da infecção por SARS-CoV-2. O produto pode ser usado em qualquer ambiente

laboratorial e não laboratorial que atenda aos requisitos especificados nas Instruções de Uso e na regulamentação local.
O teste fornece resultados preliminares. Resultados negativos não excluem a infecção por SARS-CoV-2 e não podem ser usados como única base para o tratamento ou outras decisões. Os resultados negativos devem ser combinados com observações clínicas, histórico do paciente e informações epidemiológicas. O teste não se destina a ser usado como teste de triagem de doadores para SARS-CoV-2.

Materiais Fornecidos

- 25 dispositivos de teste com dessecante em bolsa individual
- Tampão (1 x 9 ml/frasco)
- 25 tubos de extração
- 25 tampas de tubo de extração
- 1 swab controle positivo
- 1 swab controle negativo
- 25 swabs nasofaríngeos esterilizados para coleta de amostra
- 1 suporte para tubos
- 1 guia de referência rápida (nasofaríngea)
- 1 Instrução de uso

Material Necessário, Mas Não Fornecido

- Equipamento de proteção individual de acordo com a recomendações locais (exemplo: jaleco/roupa de proteção, máscara facial, protetor facial/óculos e luvas), cronômetro, recipiente para risco biológico

Ingredientes Ativos dos Componentes Principais

- **1 Dispositivo de teste** Conjugado de ouro: IgG humana específica para coloide de ouro SARS-CoV-2 Ag e IgY de galinha - coloide de ouro, linha de teste: antiSARS-CoV-2 monoclonal de camundongo Linha de controle: IgY monoclonal de camundongo antigalinha
- **Tampão** Tricina, Cloreto de Sódio, Tween 20, Azida de Sódio (<0,1%), Proclin 300

Armazenamento e Estabilidade

1. O kit de teste deve ser armazenado a uma temperatura entre 2 e 30°C. Não congele o kit ou seus componentes.
   Observação: Quando armazenados em um refrigerador, todos os componentes do kit devem estar em temperatura ambiente (15-30°C) por no mínimo 30 minutos antes de realizar o teste. Não abra a bolsa enquanto os componentes atingem a temperatura ambiente.

2. O frasco de tampão pode ser aberto e selado novamente para cada ensaio. A tampa do frasco tampão deve ser firmemente selada entre cada uso. O tampão é estável até a data de validade se mantido entre 2 e 30°C.
3. Realize o teste imediatamente após remover o dispositivo de teste da embalagem.
4. Não use o kit de teste após o prazo de validade.
5. O prazo de validade do kit está indicado na embalagem externa.
6. Não use se o kit de teste se a bolsa estiver danificada ou se a vedação estiver violada.
7. As amostras diretas de esfregaço devem ser testadas imediatamente após a coleta. Se o teste imediato não for possível, a amostra do esfregaço pode ser mantida em um tubo de extração cheio de tampão de extração (300 µl) em temperatura ambiente (15-30°C) por até duas horas antes do teste.

Advertências

1. Somente para uso para diagnóstico *in vitro*. Não reutilize o dispositivo de teste e os componentes do kit.
2. Essas instruções devem ser estritamente seguidas por profissionais de saúde treinados, para obtenção de resultados precisos. Todos os usuários devem ler as instruções antes de realizar um teste.
3. Não coma ou fume durante o manuseio de amostras.
4. Use luvas de proteção ao manusear as amostras e lave bem as mãos em seguida.
5. Evite respingos ou formação de aerossol na amostra e no tampão.
6. Limpe bem os derramamentos usando um desinfetante apropriado.
7. Descontamine e descarte todas as amostras, kits de reação e materiais potencialmente contaminados (ou seja, swab, tubo de extração, dispositivo de teste) em um recipiente de risco biológico como se fossem resíduos infecciosos e descarte de acordo com os regulamentos locais aplicáveis.
8. Não misture ou troque amostras diferentes.
9. Não misture reagentes de lotes diferentes ou de outros produtos.
10. Não guarde o kit com exposição à luz solar direta.
11. Para evitar contaminação, não toque na ponta do swab fornecido ao abrir a bolsa do swab.
12. Os swabs esterilizados fornecidos na embalagem devem ser utilizados apenas para coleta de amostras nasofaríngeas.
13. Para evitar contaminação cruzada, não reutilize os swabs esterilizados para a coleta de amostras.
14. Não dilua o swab coletado com qualquer solução, exceto o tampão de extração fornecido.

15. O tampão contém azida de sódio a <0,1% como conservante e pode ser tóxico se ingerido. Quando descartado em uma pia, lave com bastante água.[7]

Procedimento de Teste (consulte a figura)

Amostras de Esfregaço Nasofaríngeo

Nota: o profissional de saúde deve cumprir as diretrizes de segurança pessoal, incluindo o uso de equipamento de proteção individual.

Preparação de Teste

1. Deixe todos os componentes do kit atingirem uma temperatura entre 15-30°C antes do teste por 30 minutos.
2. Remova o dispositivo de teste da bolsa de alumínio antes de usar. Coloque sobre uma superfície plana, horizontal e limpa.
3. Segure o frasco de tampão verticalmente e encha o tubo de extração com fluido de tampão até que ele flua até a linha de enchimento do tubo de extração (300 µl).

⚠ **Cuidado:** Se a quantidade de tampão for excessiva ou insuficiente, um resultado de teste impróprio pode ocorrer.

4. Coloque o tubo de extração no suporte de tubos.

Coleta e Extração de Amostras

1. Incline a cabeça do paciente ligeiramente para trás cerca de 45°-70° para endireitar a passagem da frente do nariz.
2. Insira o swab com uma haste flexível através da narina paralela ao palato.

⚠ **Cuidado:** Use o swab nasofaríngeo dedicado para a coleta de amostras.

3. O swab deve atingir uma profundidade igual à distância das narinas até a abertura externa da orelha.

⚠ **Cuidado:** Se houver resistência durante a inserção do swab, remova-o e tente inseri-lo na narina oposta.

4. Esfregue e role suavemente o swab, 3-4 vezes. Deixe o swab no local por alguns segundos para absorver as secreções.
5. Remova lentamente o swab enquanto o gira e o insira no tubo de extração.
6. Gire a ponta do swab no fluido tampão dentro do tubo de extração, empurrando na parede do tubo de extração pelo menos cinco vezes e, em seguida, aperte o swab apertando o tubo de extração com os dedos.
7. Quebre o swab no ponto de quebra e feche a tampa do tubo de extração.

Reação com Dispositivo de Teste

1. Abra a tampa do bico de gotejamento na parte inferior do tubo de extração.

2. Dispense 5 gotas das amostras extraídas verticalmente na cavidade da amostra (S) do dispositivo. Não manuseie ou mova o dispositivo de teste até que o teste esteja concluído e pronto para leitura.

⚠ **Cuidado:** As bolhas que ocorrem no tubo de extração podem levar a resultados imprecisos. Se você não conseguir criar gotas suficientes, isso pode ser causado por entupimento no bico dispensador. Agite o tubo suavemente para liberar o bloqueio até observar a formação livre de gotas.

3. Feche o bico e descarte o tubo de extração contendo o swab usado de acordo com os regulamentos locais e o protocolo de descarte de resíduos de risco biológico.
4. Inicie o cronômetro. Leia o resultado do teste em 15 minutos. Não leia os resultados após 20 minutos.
5. Descarte o dispositivo usado de acordo com os regulamentos locais e o protocolo de descarte de resíduos de risco biológico.

Swab de Controle Positivo / Negativo

Nota: Por favor consulte a seção Controle de Qualidade Externo desta instrução de uso para saber a frequência de testagem externa da qualidade dos swabs de controle.

1. Segure o frasco de tampão verticalmente e encha o tubo de extração com fluido de tampão até que ele flua até a linha de enchimento do tubo de extração (300 µl).

⚠ **Cuidado:** Se a quantidade de tampão for excessiva ou insuficiente, um resultado de teste impróprio pode ocorrer.

2. Coloque o tubo de extração no suporte de tubos.
3. Insira o swab de controle positivo ou negativo no fluido tampão dentro do tubo de extração e mergulhe o swab por 1 minuto. Gire a ponta do swab de controle no fluido tampão dentro do tubo de extração, empurrando na parede do tubo de extração pelo menos cinco vezes e, em seguida, aperte o swab apertando o tubo de extração com os dedos.
4. Descarte o swab de controle usado de acordo com seu protocolo de descarte de resíduos de risco biológico.
5. Feche a tampa do tubo de extração.
6. Siga o procedimento de teste acima [Reação com Dispositivo de Teste].

Interpretação do Teste (consulte a figura)

1. Resultado negativo: A presença apenas da linha de controle (C) e nenhuma linha de teste (T) dentro da janela de resultado indica um resultado negativo.

2. Resultado positivo: A presença da linha de teste (T) e da linha de controle (C) dentro da janela de resultados, independentemente de qual linha apareça primeiro, indica um resultado positivo.

⚠ **Cuidado:** A presença de qualquer linha de teste (T), não importa o quão tênue, indica um resultado positivo.

3. Resultado inválido: Se a linha de controle (C) não estiver visível na janela de resultados após a realização do teste, o resultado é considerado inválido.

Limitações de Teste

1. O conteúdo deste kit deve ser usado para a detecção profissional e qualitativa do antígeno SARS-CoV-2 em esfregaço nasofaríngeo. Outros tipos de amostra podem levar a resultados incorretos e não devem ser usados.
2. O não cumprimento das instruções para o procedimento de teste e a interpretação dos resultados do teste pode afetar adversamente o desempenho do teste e/ou produzir resultados inválidos.
3. Um resultado de teste negativo pode ocorrer se a amostra foi coletada, extraída ou transportada de forma inadequada. Um resultado de teste negativo não elimina a possibilidade de infecção por SARS-CoV-2 e deve ser confirmado por cultura viral ou um ensaio molecular.
4. Os resultados positivos dos testes não descartam coinfecções com outros patógenos.
5. Os resultados do teste devem ser avaliados em conjunto com outros dados clínicos disponíveis para o médico.
6. Ler os resultados do teste antes de 15 minutos ou depois de 20 minutos pode gerar resultados incorretos.
7. O Panbio™ COVID-19 Ag Rapid Test Device não se destina a detectar vírus defeituosos (não infecciosos) durante as fases posteriores da eliminação viral, que devem ser detectados por testes moleculares de PCR .[8]
8. Resultados positivos podem ocorrer em caso de infecção com o SARS-CoV.

Controle de Qualidade

1. Controle de Qualidade Interno:

O dispositivo de teste tem uma linha de teste (T) e uma linha de controle (C) na superfície do dispositivo de teste. Nem a linha de teste nem a linha de controle são visíveis na janela de resultados antes de aplicar uma amostra. A linha de controle é usada para o controle do procedimento e deve sempre aparecer se o procedimento do teste for realizado

corretamente e os reagentes do teste da linha de controle estiverem funcionando.

2. Controle de Qualidade Externo:

Os controles são especificamente formulados e fabricados para garantir o desempenho do Panbio™ COVID-19 Ag Rapid Test Device e são usados para verificar a capacidade do usuário de realizar o teste de maneira adequada e interpretar os resultados. O Controle Positivo produzirá um resultado de teste positivo e foi fabricado para produzir uma linha de teste visível (T). O Controle Negativo produzirá um resultado de teste negativo.

As boas práticas de laboratório sugerem o uso de controles positivos e negativos para garantir que:

- Os reagentes de teste estão funcionando; e
- O teste foi executado corretamente.

Controles externos podem ser testados em qualquer uma das circunstâncias a seguir:

- Por um novo operador antes de realizar o teste em amostras de pacientes,
- Ao receber uma nova remessa de teste,
- Em intervalos periódicos, conforme ditado pelos requisitos locais e/ou pelos procedimentos de Controle de Qualidade do usuário.

Características de Desempenho

1. Avaliação Externa do Panbio™ COVID-19 Ag Rapid Test Device

A performance clínica do Panbio™ COVID-19 Ag Rapid Test Device foi determinada pela testagem de 140 amostras positivas e 445 amostras negativas para o antígeno (Ag) SARS-CoV-2 para ter a sensibilidade de 91,4% (95% CI: 85,5-95,5%) e a especificidade de 99,8% (95% CI: 98,8-100%). As amostras clínicas foram determinadas como sendo positivas ou negativas usando um teste RT-PCR aprovado pelo FDA EUA como método de referência.

Resultados do Panbio™ COVID-19 Ag Rapid Test Device

		Resultado do teste de PCR		
		Positivo	**Negativo**	**Total**
Resultados do Panbio™ COVID-19 Ag Rapid Test Device	**Positivo**	128	1	129
	Negativo	12	444	456
	Total	140	445	585
		Sensibilidade	Especificidade	Percentual de concordância Total
		91,4% [85,5%;95,5%]	**99,8%** [98,8%;100%]	**97,8%** [96,2%;98,8%]

- Os dados de performance foram calculados a partir de um estudo de indivíduos suspeitos de exposição a COVID-19 ou quem apresentou sintomas nos últimos 7 dias.
- Estratificação das amostras positivas após o início dos sintomas ou que tenham suspeita de exposição entre 0-3 dias tiveram uma sensibilidade de 94,9% (n=39) e entre 4-7 dias tiveram uma sensibilidade de 90,1% (n=101).
- A concordância positiva do Panbio™ COVID-19 Ag Rapid Test Device é maior com valor de Ct ≤33 com uma sensibilidade de 98,2%. Como sugerido nas referências 8 e 9, pacientes com valor de Ct> 33 não são mais contagiosos. [8, 9]

2. Limite de Detecção

O Panbio™ COVID-19 Ag Rapid Test Device confirmou detectar $2,5X10^{1,8}$ $TCID_{50}$/ml de SARS-CoV-2 que foi isolado de um paciente confirmado com COVID-19 na Coreia.

3. Efeito Gancho

Não há efeito gancho em $1,0x10^{5,8}$ $TCID_{50}$/ml de SARS-CoV-2 que foi isolado de um paciente confirmado com COVID-19 na Coreia.

4. Reatividade Cruzada

A reatividade cruzada do Panbio ™ COVID-19 Ag Rapid Test Device foi avaliada testando 25 tipos de vírus e outros 14 tipos de microrganismos. As concentrações finais de vírus e outros microrganismos testados estão documentadas na Tabela abaixo. Os seguintes vírus e outros microrganismos, exceto a Nucleoproteína Humana do SARS-coronavírus, não têm efeito nos resultados de teste do Panbio ™ COVID-19 Ag Rapid Test Device. O Panbio ™ COVID-19 Ag Rapid Test Device tem reatividade cruzada com a Nucleoproteína Humana do SARS-coronavírus a uma concentração

de 25 ng/ml ou mais, porque o SARS-CoV tem alta homologia (79,6%) para o SARS-CoV-2.

Nº	Tipos de Espécime	Substância com potencial reação cruzada	Concentração Final Testada	Resultado do Teste
1	Vírus	Adenovírus Tipo 3	$2,0 \times 10^{6,5}$ $TCID_{50}$/ml	Sem reação cruzada
2		Adenovírus Tipo 7	$2,0 \times 10^{4,75}$ $TCID_{50}$/ml	Sem reação cruzada
3		Echovirus2	$1,0 \times 10^{6,5}$ $TCID_{50}$/ml	Sem reação cruzada
4		Echovirus11	$2,0 \times 10^{5,25}$ $TCID_{50}$/ml	Sem reação cruzada
5		Herpesvírus humano (HSV) 1	$2,0 \times 10^{6,25}$ $TCID_{50}$/ml	Sem reação cruzada
6		Herpesvírus humano (HSV) 2	$2,0 \times 10^{4,75}$ $TCID_{50}$/ml	Sem reação cruzada
7		Vírus da caxumba Ag	$2,0 \times 10^{3,5}$ $TCID_{50}$/ml	Sem reação cruzada
8		Vírus influenza A (H1N1) Estirpe (A/Virginia/ATCC1/2009)	$2,6 \times 10^{5,0}$ PFU/ml	Sem reação cruzada
9		Vírus da gripe A (H1N1) Estirpe (A/WS/33)	$5,0 \times 10^{7,25}$ $TCID_{50}$/ml	Sem reação cruzada
10		Vírus influenza A (H3N2) Estirpe (A/Hong Kong/8/68)	N/A*	Sem reação cruzada
11		Vírus da gripe Estirpe (B/Lee/40)	$2,0 \times 10^{5,25}$ $TCID_{50}$/ml	Sem reação cruzada
12-14		Parainfluenza Tipo 1, Parainfluenza tipo 2, Parainfluenza tipo 3	N/A*	Sem reação cruzada
15		Parainfluenza Tipo 4A	$1,97 \times 10^{7,0}$ PFU/ml	Sem reação cruzada
16		Vírus sincicial respiratório (RSV) tipo A	$4,22 \times 10^{5,0}$ $TCID_{50}$/ml	Sem reação cruzada
17		Vírus sincicial respiratório (RSV) tipo B	$5,62 \times 10^{5,0}$ $TCID_{50}$/ml	Sem reação cruzada
18		HCoV-HKU1	10 µg/ml	Sem reação cruzada
19		Rhinovirus A16	$8,8 \times 10^{5,0}$ PFU/ml	Sem reação cruzada

Nº	Tipos de Espécime	Substância com potencial reação cruzada	Concentração Final Testada	Resultado do Teste
20	Vírus	HCoV-NL63	$1,7 \times 10^{5,0}$ $TCID_{50}$/ml	Sem reação cruzada
21		HCoV-OC43	$8,9 \times 10^{5,0}$ $TCID_{50}$/ml	Sem reação cruzada
22		HCoV-229E	$1,51 \times 10^{6,0}$ $TCID_{50}$/ml	Sem reação cruzada
23		Nucleoproteína Humana do SARS-coronavirus	25 ng/ml	Reação cruzada
24		Nucleoproteína do MERS-CoV	0,25 mg/ml	Sem reação cruzada
25		Metapneumovirus Humano(hMPV) 16 Tipo A1	$1,06 \times 10^{6,0}$ PFU/ml	Sem reação cruzada

Nº	Tipos de Espécime	Substância com potencial reação cruzada	Concentração Final Testada	Resultado do Teste
1	Outro Microrganismo	*Staphylococcus aureus*	$1,0 \times 10^{6,0}$ CFU/ml	Sem reação cruzada
2		*Staphylococcus saprophyticus*	$1,0 \times 10^{6,0}$ CFU/ml	Sem reação cruzada
3		*Neisseria sp,(Neisseria lactamica)*	$1,0 \times 10^{6,0}$ CFU/ml	Sem reação cruzada
4		*Escherichia coli*	$1,0 \times 10^{6,0}$ CFU/ml	Sem reação cruzada
5		*Staphylococcus haemolyticus*	$1,0 \times 10^{6,0}$ CFU/ml	Sem reação cruzada
6		*Streptococcus pyogenes*	$1,0 \times 10^{6,0}$ CFU/ml	Sem reação cruzada
7		*Streptococcus salivarius*	$1,0 \times 10^{6,0}$ CFU/ml	Sem reação cruzada
8		*Hemophilus parahaemolyticus*	$1,0 \times 10^{6,0}$ CFU/ml	Sem reação cruzada
9		*Proteus vulgaris*	$1,0 \times 10^{6,0}$ CFU/ml	Sem reação cruzada
10		*Moraxella catarrhalis*	$1,0 \times 10^{6,0}$ CFU/ml	Sem reação cruzada
11		*Klebsiella pneumoniae*	$1,0 \times 10^{6,0}$ CFU/ml	Sem reação cruzada

Nº	Tipos de Espécime	Substância com potencial reação cruzada	Concentração Final Testada	Resultado do Teste
12	Outro Microrganismo	*Fusobacterium necrophorum*	1,0 X $10^{6,0}$ CFU/ml	Sem reação cruzada
13		*Mycobacterum tuberculosis*	10 mg/ml	Sem reação cruzada
14		*Lavado nasal humano agrupado*	N/A*	Sem reação cruzada

**Nenhuma concentração fornecida pelo fornecedor. A solução estoque não diluída foi testada.*

5. Substâncias Interferentes

As seguintes 42 substâncias potencialmente interferentes não têm impacto no Panbio™ COVID-19 Ag Rapid Test Device. As concentrações de teste finais das substâncias interferentes estão documentadas na Tabela abaixo.

Nº	Tipos de Espécime	Substâncias Interferentes	Concentração Final Testada	Resultado do Teste
1	Substância Endógena	Mucina	0,5%	Sem Interferência
2		Hemoglobina	100 mg/L	Sem Interferência
3		Triglicerídeos	1,5 mg/L	Sem Interferência
4		Icterícia (bilirrubina)	40 mg/dL	Sem Interferência
5		Fatores reumatoides	200 IU/ml	Sem Interferência
6		Anticorpo antinuclear	>1:40	Sem Interferência
7		Grávida	Diluição de 10 vezes	Sem Interferência
8	Substância Exógena	Guaiacol gliceril éter	1 µg/ml	Sem Interferência
9		Albuterol	0,005 mg/dL	Sem Interferência
10		Efedrina	0,1 mg/ml	Sem Interferência
11		Clorfeniramina	0,08 mg/dL	Sem Interferência
12		Difenidramina	0,08 mg/dL	Sem Interferência
13		Ribavirina	26,7 µg /ml	Sem Interferência
14		Oseltamivir	0,04 mg/dL	Sem Interferência
15		Zanamivir	17,3 µg /ml	Sem Interferência
16		Cloridrato de fenilefrina	15% v/v	Sem Interferência
17		Cloridrato de oximetazolina	15% v/v	Sem Interferência
18		Amoxicilina	5,4 mg/dL	Sem Interferência
19		Ácido acetilsalicílico	3 mg/dL	Sem Interferência

Nº	Tipos de Espécime	Substâncias Interferentes	Concentração Final Testada	Resultado do Teste
20	Substância Exógena	Ibuprofeno	21,9 mg/dL	Sem Interferência
21		Clorotiazida	2,7 mg/dL	Sem Interferência
22		Indapamida	140 ng/ml	Sem Interferência
23		Glimepirida (Sulfonilureias)	0,164 mg/dL	Sem Interferência
24		Acarbose	0,03 mg/dL	Sem Interferência
25		Ivermectina	4,4 mg/L	Sem Interferência
26		Lopinavir	16,4 µg/L	Sem Interferência
27		Ritonavir	16,4 µg/L	Sem Interferência
28		Fosfato de cloroquina	0,99 mg/L	Sem Interferência
29		Cloreto de Sódio com conservantes	4,44 mg/ml	Sem Interferência
30		Beclometasona	4,79 ng/ml	Sem Interferência
31		Dexametasona	0,6 µg/ml	Sem Interferência
32		Flunisolida	0,61 µg/ml	Sem Interferência
33		Triancinolona	1,18 ng/ml	Sem Interferência
34		Budesonida	2,76 ng/ml	Sem Interferência
35		Mometasona	1,28 ng/ml	Sem Interferência
36		Fluticasona	2,31 ng/ml	Sem Interferência
37		Enxofre	9,23 µg/ml	Sem Interferência
38		Benzocaína	0,13 mg/ml	Sem Interferência
39		Mentol	0,15 mg/ml	Sem Interferência
40		Mupirocina	10 µg/ml	Sem Interferência
41		Tobramicina	24,03 µg/ml	Sem Interferência
42		Biotina	1,2 µg/ml	Sem Interferência

6. Repetibilidade e Reprodutibilidade

Repetibilidade e reprodutibilidade do Panbio™ COVID-19 Ag Rapid Test Device foram estabelecidas usando painéis de referência internos contendo amostras negativas e uma gama de amostras positivas. Não houve diferenças observadas dentro da execução, entre execuções, entre lotes, entre locais e entre dias.

PREPARAÇÃO

1 Deixe todos os componentes do kit atingirem uma temperatura entre 15-30°C antes do teste por 30 minutos.
Nota: Profissionais de saúde devem cumprir as diretrizes de segurança pessoal, incluindo o uso de equipamento de proteção individual.

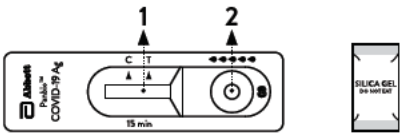
2 **Abra o pacote e observe o seguinte:**
1. Dispositivo de teste com dessecante em bolsa individual
2. Tampão
3. Tubo de extração
4. Tampa de tubos de extração
5. Swab controle positivo
6. Swab controle negativo
7. Swabs nasofaríngeos esterilizados para coleta de amostra
8. Suporte para tubos
9. Guia de referência rápida (nasofaríngea)
10. Instruções de uso

3 Leia atentamente estas instruções antes de usar o kit Panbio™ COVID-19 Ag Rapid Test Device.

4 Observe a data de validade da caixa do kit. Se a data de validade já passou, use outro kit.

5 **Abra a bolsa de alumínio e observe o seguinte:**
1. Janela de resultados
2. Cavidade de amostra

Em seguida, rotule o dispositivo com o identificador do paciente.

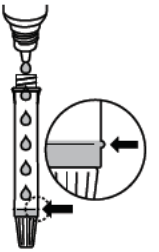


●●●●●: 5 gotas da amostra extraída

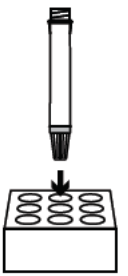
PROCEDIMENTO DE TESTE

1 Segure o frasco de tampão verticalmente e encha o tubo de extração com fluido de tampão até que ele flua até a linha de enchimento do tubo de extração (300µl).

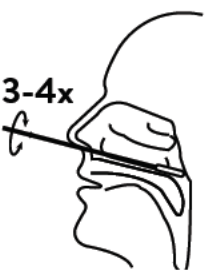
⚠ **Cuidado:** Se a quantidade de tampão for excessiva ou insuficiente, um resultado de teste impróprio pode ocorrer.



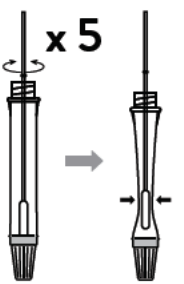
2 Coloque o tubo de extração no suporte de tubos.



3 Incline a cabeça do paciente para trás. Insira o swab pela narina. Esfregue e role suavemente o swab, 3-4 vezes. Deixe o swab no lugar por alguns segundos. Remova o swab lentamente.



4 Insira a amostra de esfregaço no tubo de extração. Gire a ponta do swab no fluido tampão dentro do tubo de extração, empurrando na parede do tubo de extração pelo menos cinco vezes e, em seguida, aperte o swab apertando o tubo de extração com os dedos.



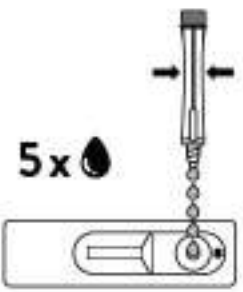
PROCEDIMENTO DE TESTE

5 Quebre o swab no ponto de quebra e feche a tampa do tubo de extração.

6 Abra a tampa do bico de gotejamento na parte inferior do tubo de extração.

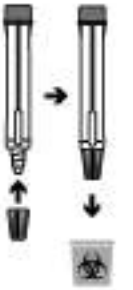
7 Dispense 5 gotas das amostras extraídas verticalmente na cavidade da amostra (S) do dispositivo. Não manuseie ou mova o dispositivo de teste até que o teste esteja concluído e pronto para leitura.

⚠ **Cuidado:** As bolhas que ocorrem no tubo de extração podem levar a resultados imprecisos. Se você não conseguir criar gotas suficientes, isso pode ser causado por entupimento no bico dispensador. Agite o tubo suavemente para liberar o bloqueio até observar a formação livre de gotas.



PROCEDIMENTO DE TESTE

8 Feche o bico e descarte o tubo de extração contendo o swab usado de acordo com os regulamentos locais e o protocolo de descarte de resíduos de risco biológico.



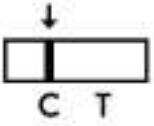
9 Inicie o cronômetro. Leia o resultado do teste em 15 minutos. Não leia os resultados após 20 minutos.

10 Descarte o dispositivo usado de acordo com os regulamentos locais e o protocolo de descarte de resíduos de risco biológico.

INTERPRETAÇÃO DE TESTE

NEGATIVO

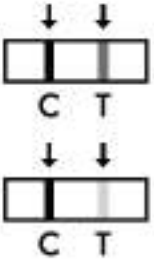
A presença apenas da linha de controle (C) e nenhuma linha de teste (T) dentro da janela de resultado indica um resultado negativo.



POSITIVO

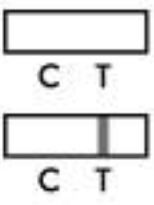
A presença da linha de teste (T) e da linha de controle (C) dentro da janela de resultados, independentemente de qual linha apareça primeiro, indica um resultado positivo.

⚠ **Cuidado:** A presença de qualquer linha de teste (T), não importa o quão tênue, indica um resultado positivo.



INVÁLIDO

Se a linha de controle (C) não estiver visível na janela de resultados após a realização do teste, o resultado é considerado inválido. As instruções podem não ter sido seguidas corretamente. É recomendável ler o a instrução de uso novamente antes de testar novamente a amostra com um novo dispositivo de teste.



PORTUGUÊS

О тесте

RU

Введение

Болезнь, вызванная коронавирусом (COVID-19), является инфекционным заболеванием, вызываемым недавно обнаруженным коронавирусом 2 группы (SARS-CoV-2)[1], связанным с тяжелым синдромом острой дыхательной недостаточности. SARS-CoV-2 — это β-коронавирус, который представляет собой оболочечный вирус с несегментированной положительно-полярной нитью РНК[2]. Он распространяется путем передачи от человека человеку воздушно-капельным путем или при прямом контакте; по оценкам, инкубационный период инфекции составляет в среднем 6,4 дня, а базовое репродуктивное число — 2,24-3,58. Среди пациентов с пневмонией, вызванной SARS-CoV-2, лихорадка была наиболее распространенным симптомом, после которого следует кашель[3]. В основных анализах, используемых для *in vitro* диагностики инфекции COVID-19, используется полимеразная цепная реакция с обратной транскриптазой (ОТ-ПЦР; RT-PCR) в реальном времени, которая занимает несколько часов[4]. Наличие экономичного и быстрого диагностического теста в месте оказания медицинской помощи имеет решающее значение для того, чтобы медицинские работники могли помочь в диагностике пациентов и предотвратить дальнейшее распространение вируса[5]. Тесты на антигены будут играть важнейшую роль в борьбе с COVID-19[6].

Принцип теста

Экспресс-тест Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) содержит мембранную полоску, предварительно покрытую иммобилизованным анти-SARS-CoV-2 антителом на тестовой линии, и мышиным моноклональным анти-куриным IgY на контрольной линии. Два типа конъюгатов (человеческий IgG, специфичный для конъюгата антигена SARS-CoV-2 на золотой подложке, и конъюгат куриного IgY на золотой подложке) движутся вверх по мембране хроматографически и реагируют с анти-SARS-CoV-2 антителом и с предварительно покрытым мышиным моноклональным анти-куриным IgY, соответственно. Для получения положительного результата человеческий IgG, специфичный к конъюгату антигена SARS-CoV-2 на золотой подложке и анти-SARS-CoV-2 антитела, образуют в окне результата тестовую линию. Ни тестовая, ни контрольная линии в окне результата до нанесения образца, полученного у пациента, не видны. Видимая контрольная линия необходима, чтобы показать, что результат анализа действителен.

Назначение

Экспресс-тест Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) - это экспресс-тест *in vitro* для качественного определения антигена SARS-CoV-2 (Ag) в образцах мазков из носоглотки, полученных у пациентов, соответствующих клиническим и / или эпидемиологическим критериям COVID-19. Экспресс-тест Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) предназначен только для профессионального применения в качестве помощи при диагностике инфекции, вызванной вирусом SARS-CoV-2. Медицинское изделие может использоваться в любой лабораторной и не лабораторной среде, которая соответствует требованиям, указанным в инструкции по применению и местным нормам.

Тестирование представляет предварительные результаты тестирования. Отрицательные результаты не исключают инфицирование SARS-CoV-2, и их нельзя использовать в качестве единственного основания для лечения или принятия другого решения в рамках ведения пациента. Отрицательные результаты должны соответствовать клиническим наблюдениям, данным анамнеза заболевания и эпидемиологической информации. Тест не предназначен для использования в качестве скринингового теста доноров на SARS-CoV-2.

Предоставляемые материалы

- 25 тест-кассет в индивидуальной вакуумной упаковке с осушителем
- Буфер (1 x 9 мл / флакон)
- 25 пробирок экстракционные
- 25 колпачков для пробирок экстракционных
- 1 Положительный контрольный образец
- 1 Отрицательный контрольный образец
- 25 Стерильных назофарингеальных тампонов (тупферов) для сбора образцов
- 1 Штатив
- 1 Краткое руководство (назофарингеальный тампон)
- 1 Инструкция по применению

Необходимые, но не предоставляемые материалы

- Средства индивидуальной защиты в соответствии с местными рекомендациями (халат / лабораторный халат, маска для лица, защитный экран для лица / очки и перчатки), таймер, контейнер для биологических опасных отходов

Активные ингредиенты основных компонентов

- **Тест-кассета** Конъюгат на золотой подложке: человеческий IgG, специфичный к коллоиду антигена SARS-CoV-2 на золотой подложке и коллоиду куриного IgY на золотой подложке; Тестовая линия: Моноклональные мышиные анти-SARS-CoV-2 антитела ; Контрольная линия: Мышиные моноклональные анти-куриные IgY
- **Буфер** Трицин, хлорид натрия , Твин 20 , Азид натрия (<0,1%), Проклин 300

Хранение и стабильность

1. Набор следует хранить при температуре от 2 до 30 °C. Не замораживайте набор или его компоненты.
   Примечание: При хранении в холодильнике все компоненты набора должны быть приведены к комнатной температуре (15-30 °C) минимум за 30 минут до проведения теста. Не открывайте тест-кассету, пока компоненты не дойдут до комнатной температуры.
2. Флакон с буфером флакон можно открывать и запечатывать заново для каждого анализа. Крышка флакона с буфером должна быть плотно закрыта между использованиями. Буфер стабилен до истечения срока годности, если хранится при температуре 2-30 °C.
3. Выполните тест сразу же после извлечения тест-кассеты из индивидуальной упаковки.
4. Не используйте набор после истечения срока годности.
5. Срок годности набора указан на наружной упаковке.
6. Не используйте набор, если индивидуальная упаковка повреждена или ее герметичность нарушена.
7. Тампоны (тупферы) с образцами должны быть протестированы сразу же после взятия. Если немедленное тестирование невозможно, тампон (тупфер) с образцом можно хранить в экстракционной пробирке, заполненной экстракционным буфером (300 мкл), при комнатной температуре (15-30 °C) в течение двух часов до начала анализа.

Меры предосторожности

1. Предназначен только для диагностики *in vitro*. Не используйте повторно тест-кассету и компоненты набора.
2. Эти инструкции должны строго соблюдаться обученным медицинским работником для достижения точных

результатов. Все пользователи должны перед выполнением анализа прочитать инструкцию.
3. Не принимайте пищу и не курите при обращении с образцами.
4. При работе с образцами наденьте защитные перчатки, а после - тщательно вымойте руки.
5. Избегайте разбрызгивания или образования аэрозолей образцов и буфера.
6. Тщательно удалите пролитую жидкость с помощью соответствующего дезинфицирующего средства.
7. Необходимо обеззараживать и утилизировать все образцы, наборы и потенциально загрязненные материалы (тампон, экстракционная пробирка, тест-кассета) в контейнере для биологически опасных отходов, по правилам для инфицированных отходов, в соответствии с местным законодательством.
8. Различные образцы не должны смешиваться или взаимозаменяться.
9. Не смешивайте реагенты различных серий или реагенты для других медицинских изделий.
10. Не храните набор под прямыми солнечными лучами.
11. Во избежание загрязнения не прикасайтесь к головке прилагаемого тампона (тупфера) при открывании упаковки тампона (тупфера).
12. Прилагаемые стерильные тампоны (тупферы) в упаковке следует использовать только для получения мазков из носоглотки.
13. Во избежание перекрестного загрязнения не следует повторно использовать стерильные тампоны для получения мазков.
14. Не смешивайте тампон с образцом с какими-либо растворами, кроме поставляемого экстракционного буфера.
15. Буфер содержит <0,1% азида натрия в качестве консерванта, который может быть токсичным при проглатывании. При утилизации в водопровод промойте его большим количеством воды.[7]

Процедура проведения теста (см. рисунок)

Образцы мазков из носоглотки

Примечание: Медицинский работник должен соблюдать правила техники безопасности, включая использование средств индивидуальной защиты.

Подготовка

1. Перед тестированием выдержите все компоненты набора в течение 30 минут при температуре 15-30 °C.
2. Извлеките тест-кассету из индивидуальной упаковки перед использованием. Поместите ее на ровную, горизонтальную и чистую поверхность.
3. Держа флакон с буфером вертикально наполните экстракционную пробирку буферным раствором, пока она не дойдет до линии заполнения экстракционной пробирки (300 мкл).

⚠ **Предупреждение:** Если объем буфера чрезмерен или недостаточен, результат теста может быть неправильным.

4. Установите экстракционную пробирку в штатив.

Сбор образцов и экстракция

1. Слегка наклоните голову пациента назад примерно на 45°-70°, чтобы выпрямить проход передних отделов носа.
2. Введите тампон с гибким стержнем через ноздрю параллельно небу.

⚠ **Предупреждение:** Используйте специальный назофаринтгеальный тампон для получения образцов.

3. Тампон следует вводить на глубину, равную расстоянию от ноздрей до наружного отверстия уха.

⚠ **Предупреждение:** Если во время введения тампона возникает сопротивление, извлеките его и попытайтесь ввести в противоположную ноздрю.

4. Аккуратно потрите поверхность тампоном и поверните его 3-4 раза. Оставьте тампон на месте на несколько секунд, чтобы он впитал выделения.
5. Медленно извлеките тампон, вращая его, и вставьте в экстракционную пробирку.
6. Наконечник тампона проворачивают в буферном растворе внутри экстракционной пробирки, вдавливая его в стенку экстракционной пробирки не менее пяти раз, а затем тампон выжимают, сдавливая экстракционную пробирку пальцами.
7. Тампон разламывают в точке разлома, и колпачок для пробирки экстракционной закрывают.

Реакция с тест-кассетой

1. Откройте крышку колпачка - капельницы в нижней части экстракционной пробирки.
2. Внесите 5 капель раствора из экстракционной пробирки вертикально в ячейку для образца (S) на тест-кассете. Не

трогайте и не перемещайте тест-кассету, пока тест не будет завершен и готов к считыванию.

⚠ **Предупреждение:** Пузырьки, возникающие в экстракционной пробирке, могут привести к неточным результатам. Если отмерить достаточное количество капель не удается, это может быть вызвано засорением колпачка-капельницы. Осторожно встряхните пробирку, чтобы устранить обструкцию, пока не образуются свободные капли.

3. Закройте колпачок -капельницу, и утилизируйте экстракционную пробирку, содержащую использованный тампон в соответствии с местными правилами и протоколом утилизации биологически опасных отходов.
4. Запустите таймер. Результат можно считывать через 15 минут. Не считывайте результаты, если прошло 20 минут и больше.
5. Использованную тест-кассету утилизируют в соответствии с местными правилами и протоколом утилизации биологически опасных отходов.

Положительный / Отрицательный контрольные образцы

Примечание: См. Раздел «Внешний контроль качества» данной инструкции, чтобы узнать, как часто использовать контрольные образцы для внешнего контроля качества.

1. Держа флакон с буфером вертикально наполните экстракционную пробирку буферным раствором, пока она не дойдет до линии заполнения экстракционной пробирки (300 мкл).

⚠ **Предупреждение:** Если объем буфера чрезмерен или недостаточен, результат теста может быть неправильным.

2. Установите экстракционную пробирку в штатив.
3. Поместите положительный или отрицательный контрольный образец в буферный раствор внутри экстракционной пробирки и замочите образец на 1 минуту. Наконечник контрольного образца проворачивают в буферном растворе внутри экстракционной пробирки, вдавливая его в стенку экстракционной пробирки не менее пяти раз, а затем образец выжимают, сдавливая экстракционную пробирку пальцами.
4. Использованный контрольный образец утилизируют в соответствии с местными правилами и протоколом утилизации биологически опасных отходов.
5. Закройте колпачок экстракционной пробирки.
6. Выполните описанную выше процедуру испытания [Реакция с тест-кассетой].

Интерпретация теста (см. рисунок)

1. Отрицательный результат: Наличие только контрольной линии (C) и отсутствие тестовой линии (T) в окошке для считывания указывает на отрицательный результат теста.
2. Положительный результат: Наличие тестовой (T) и контрольной (C) линии в окне результата, независимо от того, какая линия появляется первой, указывает на положительный результат.

⚠ **Предупреждение:** Наличие тестовой линии (T), какой бы слабой она ни была, свидетельствует о положительном результате.

3. Неверный результат: Если контрольная линия (C) не видна в окне результатов после выполнения теста, результат считается неверным.

Ограничения теста

1. Содержимое этого набора должно использоваться для профессионального и качественного определения антигена SARS-CoV-2 в мазке из носоглотки. Другие типы образцов могут привести к неправильным результатам и не должны использоваться.
2. Несоблюдение инструкций по проведению анализа и интерпретации его результатов может отрицательно повлиять на проведение анализа и/или привести к неверным результатам.
3. Отрицательный результат теста может быть получен, если образец был собран, экстрагирован или транспортирован неправильно. Отрицательный результат теста не исключает возможности заражения SARS-CoV-2 и должен быть подтвержден посевом на вирус или молекулярным анализом.
4. Положительные результаты теста не исключают коинфекций другими возбудителями.
5. Результаты анализа должны оцениваться в сочетании с другими клиническими данными, доступными врачу.
6. Считывание результатов теста раньше, чем через 15 минут или позже, чем через 20 минут, может привести к получению неверных результатов.
7. Экспресс-тест Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) не предназначено для обнаружения дефектного (неинфекционного) вируса на более поздних стадиях выделения вируса, которое может быть обнаружено с помощью молекулярных тестов ПЦР.[8]

8. Положительный результат может быть получен в случае инфицирования SARS-CoV.

Контроль качества

1. Внутренний контроль качества:

На поверхности тест-кассеты имеются тестовая линия (T) и контрольная линия (C). Ни тестовая, ни контрольная линии не видны в окне результатов до нанесения образца. Контрольная линия используется для контроля проведения процедуры и должна появляться всегда, если процедура испытания проводится должным образом, а реагенты контрольной линии работают.

2. Внешний контроль качества:

Контрольные линии специально разработаны и изготовлены для обеспечения работы Экспресс-теста Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) и используются для проверки способности пользователя правильно проводить анализ и интерпретировать результаты. Положительный контроль дает положительный результат теста и был изготовлен для получения видимой тестовой линии (T). Отрицательный контроль приведет к отрицательному результату теста.

Согласно требованиям Надлежащей лабораторной практики, предполагается использование положительного и отрицательного контролей, чтобы убедиться в том, что:

- Реагенты для анализа работают, и
- Анализ выполнен правильно.

Внешний контроль может быть проведен при любых следующих обстоятельствах:

- Новым оператором перед проведением анализа образцов от пациентов,
- При получении новой партии набора,
- Периодически, в соответствии с местными требованиями и/или процедурами контроля качества, применяемыми пользователем.

Эксплуатационные характеристики

1. **Внешняя оценка Экспресс-теста Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device)**
   Клиническая эффективность Экспресс-тест Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) была определена путем тестирования 140 положительных и 445 отрицательных образцов на антиген SARS-CoV-2 (Ag) с чувствительностью 91,4% (95% CI: 85,5-95,5%) и специфичностью 99,8% (95% CI: 98,8-100%). Клинические образцы были определены как положительные или отрицательные с использованием эталонного метода ОТ-ПЦР, разрешеннный FDA на использование в чрезвычайных ситуациях.

Результаты для Экспресс-тест Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device)

		Результаты теста ПЦР		
		Положительный результат	**Отрицательный результат**	**Итого**
Результаты для Экспресс-тест Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device)	**Положительный результат**	128	1	129
	Отрицательный результат	12	444	456
	Итого	140	445	585
		Чувствительностью	Специфичностью	Общая процентная согласованность
		91,4% [85,5%;95,5%]	**99,8%** [98,8%;100%]	**97,8%** [96,2%;98,8%]

- Данные о производительности были рассчитаны на основе исследования лиц, подозреваемых в контакте с COVID-19 или у которых в течение последних 7 дней проявлялись симптомы.
- Стратификация положительных образцов после появления симптомов или подозрения на контакт между 0–3 днями имеет чувствительность 94,9% (n=39), а 4–7 дней - чувствительность 90,1% (n=101).

- Положительный отклик Panbio™ COVID-19 Ag Rapid Test Device выше для образцов с кп ≤33 ед. с чувствительностью 98,2%. Как указано в рекомендациях 8 и 9, пациенты со значением кп >33 ед. больше не являются вирулентными.[8, 9]

2. Предел обнаружения

Подтверждено, что Экспресс-тест Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) обеспечивает обнаружение 2,5X$10^{1,8}$ $ТЦД_{50}$/мл SARS-CoV-2, выделенного у пациента с подтвержденной инфекцией COVID-19 в Корее.

3. Эффект высокой дозы (Hook Effect)

При дозе 1,0x$10^{5,8}$ $ТЦД_{50}$/мл SARS- CoV-2, выделенного у пациента с подтвержденной инфекцией COVID-19 в Корее, эффект высокой дозы отсутствует.

4. Перекрестная реактивность

Перекрестную реактивность Экспресс-теста Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) оценивали путем тестирования 25 вирусов и 14 других микроорганизмов. Окончательные тестовые концентрации вирусов и других микроорганизмов приведены в таблице ниже. Следующие вирусы и другие микроорганизмы, кроме Нуклеопротеина человеческого SARS-коронавирус, не влияют на результаты анализа с помощью Экспресс-теста Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device). Существует перекрестная реактивность Экспресс-теста Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) с Нуклеопротеином человеческим SARS-коронавирус в концентрации 25 нг / мл или более, поскольку SARS-CoV имеет высокую гомологичность (79,6%) с SARS-CoV-2.

№	Типы образцов	Вещество, вызывающее перекрестную реакцию	Окончательная тестовая концентрация	Результаты теста
1	Вирус	Аденовирус тип 3	2,0 X $10^{6,5}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
2		Аденовирус тип 7	2,0 X $10^{4,75}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
3		Эховирус 2	1,0 X $10^{6,5}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
4		Эховирус 11	2,0 X $10^{5,25}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
5		Герпесвирус человека (HSV) 1	2,0 X $10^{6,25}$ $ТЦД_{50}$/мл	Нет перекрестной реакции

№	Типы образцов	Вещество, вызывающее перекрестную реакцию	Окончательная тестовая концентрация	Результаты теста
6	Вирус	Герпесвирус человека (HSV) 2	$2,0 \times 10^{4,75}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
7		Антиген парамиксофируса	$2,0 \times 10^{3,5}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
8		Штамм вируса гриппа A (H1N1) (A/Virginia/ ATCC1/2009)	$2,6 \times 10^{5,0}$ PFU/мл	Нет перекрестной реакции
9		Штамм вируса гриппа A (H1N1) (A/WS/33)	$5,0 \times 10^{7,25}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
10		Штамм вируса гриппа A (H3N2) (A/Hong Kong/8/68)	Н/П*	Нет перекрестной реакции
11		Штамм вируса гриппа B (B/Lee/40)	$2,0 \times 10^{5,25}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
12-14		Вирус парагриппа типа 1, Вирус парагриппа типа 2, Вирус парагриппа типа 3	Н/П*	Нет перекрестной реакции
15		Вирус парагриппа типа 4A	$1,97 \times 10^{7,0}$ PFU/мл	Нет перекрестной реакции
16		Респираторно-синцитиальный вирус (RSV) типа A	$4,22 \times 10^{5,0}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
17		Респираторно-синцитиальный вирус (RSV) типа B	$5,62 \times 10^{5,0}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
18		HCoV-HKU1	10 мкг/мл	Нет перекрестной реакции
19		Риновирус A16	$8,8 \times 10^{5,0}$ PFU/мл	Нет перекрестной реакции
20		HCoV-NL63	$1,7 \times 10^{5,0}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
21		HCoV-OC43	$8,9 \times 10^{5,0}$ $ТЦД_{50}$/мл	Нет перекрестной реакции
22		HCoV-229E	$1,51 \times 10^{6,0}$ $ТЦД_{50}$/мл	Нет перекрестной реакции

№	Типы образцов	Вещество, вызывающее перекрестную реакцию	Окончательная тестовая концентрация	Результаты теста
23	Вирус	Нуклеопротеин человеческий SARS-коронавирус	25 нг/мл	Перекрестная реакция
24		Нуклеопротеин коронавируса БВРС	0,25 мг/мл	Нет перекрестной реакции
25		Метапневмовирус человека (hMPV) 16 Тип A1	1,06 X $10^{6,0}$ PFU/мл	Нет перекрестной реакции

№	Типы образцов	Вещество, вызывающее перекрестную реакцию	Окончательная тестовая концентрация	Результаты теста
1	Другой микроорганизм	*Staphylococcus aureus*	1,0 X $10^{6,0}$ КОЕ/мл	Нет перекрестной реакции
2		*Staphylococcus saprophyticus*	1,0 X $10^{6,0}$ КОЕ/мл	Нет перекрестной реакции
3		*Neisseria sp.(Neisseria lactamica)*	1,0 X $10^{6,0}$ КОЕ/мл	Нет перекрестной реакции
4		*Escherichia coli*	1,0 X $10^{6,0}$ КОЕ/мл	Нет перекрестной реакции
5		*Staphylococcus haemolyticus*	1,0 X $10^{6,0}$ КОЕ/мл	Нет перекрестной реакции
6		*Streptococcus pyogenes*	1,0 X $10^{6,0}$ КОЕ/мл	Нет перекрестной реакции
7		*Streptococcus salivarius*	1,0 X $10^{6,0}$ КОЕ/мл	Нет перекрестной реакции
8		*Hemophilus parahaemolyticus*	1,0 X $10^{6,0}$ КОЕ/мл	Нет перекрестной реакции
9		*Proteus vulgaris*	1,0 X $10^{6,0}$ КОЕ/мл	Нет перекрестной реакции
10		*Moraxella catarrhalis*	1,0 X $10^{6,0}$ КОЕ/мл	Нет перекрестной реакции
11		*Klebsiella pneumoniae*	1,0 X $10^{6,0}$ КОЕ/мл	Нет перекрестной реакции
12		*Fusobacterium necrophorum*	1,0 X $10^{6,0}$ КОЕ/мл	Нет перекрестной реакции

№	Типы образцов	Вещество, вызывающее перекрестную реакцию	Окончательная тестовая концентрация	Результаты теста
13	Другой микроорганизм	*Микобактерии туберкулеза*	10 мг/мл	Нет перекрестной реакции
14		*Пул образцов жидкости, собранных при промывании носа*	Н/П*	Нет перекрестной реакции

*Поставщик не предоставил концентрации. Был протестирован неразбавленный исходный раствор.

5. Интерферирующие вещества

Следующие 42 потенциально интерферирующих веществ не оказывают никакого влияния на Экспресс-тест Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device). Окончательные тестовые концентрации интерферирующих веществ задокументированы в нижеприведенной таблице.

№	Типы образцов	Интерферирующие вещества	Окончательная тестовая концентрация	Результаты теста
1	Эндогенная субстанция	Муцин	0,5%	Нет влияния
2		Гемоглобин	100 мг/л	Нет влияния
3		Триглицериды	1,5 мг/л	Нет влияния
4		Билирубин	40 мг/дл	Нет влияния
5		Ревматоидный фактор	200 МЕ/мл	Нет влияния
6		Антиядерное антитело	>1:40	Нет влияния
7		Беременность	10-кратное разведение	Нет влияния
8	Экзогенная субстанция	Глицериловый эфир гваякола	1 мкг/мл	Нет влияния
9		Альбутерол	0,005 мг/дл	Нет влияния
10		Эфедрин	0,1 мг/мл	Нет влияния
11		Хлорфенирамин	0,08 мг/дл	Нет влияния
12		Дифенгидрамин	0,08 мг/дл	Нет влияния
13		Рибавирин	26,7 мкг/мл	Нет влияния
14		Осельтамивир	0,04 мг/дл	Нет влияния
15		Занамивир	17,3 мкг/мл	Нет влияния
16		Фенилэфрина гидрохлорид	15% об,/об,	Нет влияния

№	Типы образцов	Интерферирующие вещества	Окончательная тестовая концентрация	Результаты теста
17	Экзогенная субстанция	Оксиметазолина гидрохлорид	15% об,/об,	Нет влияния
18		Амоксициллин	5,4 мг/дл	Нет влияния
19		Ацетилсалициловая кислота	3 мг/дл	Нет влияния
20		Ибупрофен	21,9 мг/дл	Нет влияния
21		Хлортиазид	2,7 мг/дл	Нет влияния
22		Индапамид	140 нг/мл	Нет влияния
23		Глимепирид (Сульфонилмочевина)	0,164 мг/дл	Нет влияния
24		Акарбоза	0,03 мг/дл	Нет влияния
25		Ивермектин	4,4 мг/л	Нет влияния
26		Лопинавир	16,4 мкг/л	Нет влияния
27		Ритонавир	16,4 мкг/л	Нет влияния
28		Хлорохина фосфат	0,99 мг/л	Нет влияния
29		Хлорид натрия с консервантами	4,44 мг/мл	Нет влияния
30		Беклометазон	4,79 нг/мл	Нет влияния
31		Дексаметазон	0,6 мкг/мл	Нет влияния
32		Флунизолид	0,61 мкг/мл	Нет влияния
33		Триамцинолон	1,18 нг/мл	Нет влияния
34		Будесонид	2,76 нг/мл	Нет влияния
35		Мометазон	1,28 нг/мл	Нет влияния
36		Флутиказон	2,31 нг/мл	Нет влияния
37		Сера	9,23 мкг/мл	Нет влияния
38		Бензокаин	0,13 мг/мл	Нет влияния
39		Ментол	0,15 мг/мл	Нет влияния
40		Мупироцин	10 мкг/мл	Нет влияния
41		Тобрамицин	24,03мкг/мл	Нет влияния
42		Биотин	1,2 мкг/мл	Нет влияния

6. Повторяемость и воспроизводимость

Повторяемость и воспроизводимость Экспресс-тест Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) была определена с использованием собственных эталонных панелей, содержащих отрицательные образцы и ряд положительных образцов. Различий в внутри одной серии, между сериями, между центрами и между днями не наблюдали.

ПОДГОТОВКА

1 Перед тестированием выдержите все компоненты набора в течение 30 минут при температуре 15-30 °C
Примечание: Медицинский работник должен соблюдать правила техники безопасности, включая использование средств индивидуальной защиты.

2 **Откройте упаковку и проверьте комплектность:**

1. Тест-кассета в индивидуальной вакуумной упаковке с осушителем
2. Буфер
3. Пробирка экстракционная
4. Колпачок для пробирки экстракционной
5. Положительный контрольный образец
6. Отрицательный контрольный образец
7. Стерильные назофарингеальные тампоны (тупферов) для сбора образцов
8. Штатив
9. Краткое руководство (назофарингеальный тампон)
10. Инструкция по применению

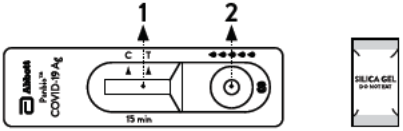
3 Перед использованием Экспресс-теста Panbio™ COVID-19 Ag (Panbio™ COVID-19 Ag Rapid Test Device) внимательно прочитайте данные инструкции.

4 Проверьте срок годности набора. Если срок годности прошел, используйте другой набор.

5 **Откройте индивидуальную упаковку тест-кассеты и проверьте комплектность:**

1. Окно результата
2. Ячейка для образца

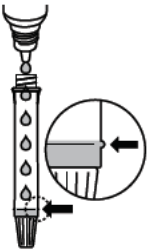
Затем наклейте на тест-кассету идентификатор пациента.



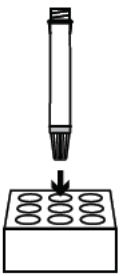
●●●●●: 5 капель раствора из экстракционной пробирки

ПРОЦЕДУРА ТЕСТИРОВАНИЯ

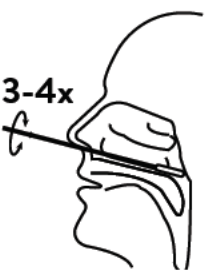
1 Держа флакон с буфером вертикально наполните экстракционную пробирку буферным раствором, пока она не дойдет до линии заполнения экстракционной пробирки (300 мкл).
⚠ **Предупреждение:** Если объем буфера чрезмерен или недостаточен, результат теста может быть неправильным.



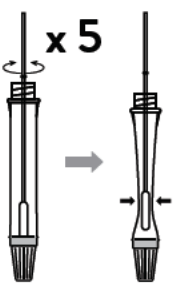
2 Установите экстракционную пробирку в штатив.



3 Наклоняют голову пациента назад. Вставляют тампон через. Аккуратно потрите поверхность тампоном и поверните его 3-4 раза.Оставляют тампон на несколько секунд. Медленно извлекают тампон.



4 Вставьте тампон с образцом в экстракционную пробирку. Наконечник тампона проворачивают в буферном растворе внутри экстракционной пробирки, вдавливая его в стенку экстракционной пробирки не менее пяти раз, а затем тампон выжимают, сдавливая экстракционную пробирку пальцами.

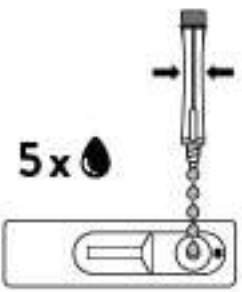


ПРОЦЕДУРА ТЕСТИРОВАНИЯ

5 Тампон разламывают в точке разлома, и колпачок для пробирки экстракционной закрывают.

6 Откройте крышку колпачка - капельницы в нижней части экстракционной пробирки.

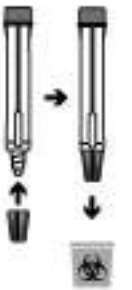
7 Внесите 5 капель раствора из экстракционной пробирки вертикально в ячейку для образца (S) на тест-кассете. Не трогайте и не перемещайте тест-кассету, пока тест не будет завершен и готов к считыванию.



⚠ **Предупреждение:** Пузырьки, возникающие в экстракционной пробирке, могут привести к неточным результатам. Если отмерить достаточное количество капель не удается, это может быть вызвано засорением колпачка-капельницы. Осторожно встряхните пробирку, чтобы устранить обструкцию, пока не образуются свободные капли.

ПРОЦЕДУРА ТЕСТИРОВАНИЯ

8 Закройте колпачок-капельницу, и утилизируйте экстракционную пробирку, содержащую использованный тампон в соответствии с местными правилами и протоколом утилизации биологически опасных отходов.



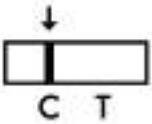
9 Запустите таймер. Результат можно считывать через 15 минут. Не считывайте результаты, если прошло 20 минут и больше.

10 Использованную тест-кассету утилизируют в соответствии с местными правилами и протоколом утилизации биологически опасных отходов.

ИНТЕРПРЕТАЦИЯ ТЕСТА

ОТРИЦАТЕЛЬНЫЙ

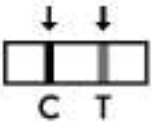
Наличие только контрольной линии (C) и отсутствие тестовой линии (T) в окошке для считывания указывает на отрицательный результат теста.

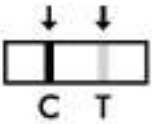


ПОЛОЖИТЕЛЬНЫЙ

Положительный результат: Наличие тестовой (T) и контрольной (C) линии в окне результата, независимо от того, какая линия появляется первой, указывает на положительный результат.

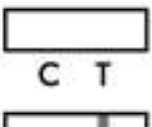
⚠ **Предупреждение:** Наличие тестовой линии (T), какой бы слабой она ни была, свидетельствует о положительном результате.

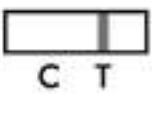




НЕВЕРНЫЙ РЕЗУЛЬТАТ

Если контрольная линия (C) не видна в окне результатов после выполнения теста, результат считается неверным. Инструкции могли быть выполнены неправильно. В этом случае рекомендуется снова прочитать инструкцию по применению перед повторным тестированием образца с использованием новой тест-кассетой.





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GLOSSARY OF SYMBOLS / SYMBOLVERZEICHNIS / GLOSARIO DE SÍMBOLOS / GLOSSAIRE DES SYMBOLES / GLOSSARIO DEI SIMBOLI / GLOSSÁRIO DE SÍMBOLOS / ГЛОССАРИЙ ОБОЗНАЧЕНИЙ

	Temperature limitation Temperaturbegrenzung Limitación de temperatura Limitation de température Limitazione di temperatura Limitação de temperatura Температурный диапазон
IVD	For *in vitro* diagnostic use only Medizinprodukt für *in-vitro* Diagnostik Sólo para uso diagnóstico *in vitro* Pour un usage de diagnostic *in vitro* uniquement Ad uso esclusivo diagnostico *in vitro* Somente para uso para diagnóstico *in vitro* Медицинское изделие для диагностики *In Vitro*
	Do not reuse Nicht wiederverwenden No reutilizar Ne pas réutiliser Non riutilizzare Não reutilizar Не использовать повторно
	Do not use if package is damaged Bei beschädigter Verpackung nicht verwenden No lo use si el paquete está dañado Ne pas utiliser si le colis est endommagé Non utilizzare se la confezione è danneggiata Não use se o pacote estiver danificado Не используйте, если упаковка повреждена

LOT	Lot Number Chargencode Número de lote Numéro de lot Numero di lotto Número de Lote Номер серии
REF	Catalog Number Artikelnummer Número de catalogo Numéro de catalogue Numero di catalogo Número no Catálogo Каталожный номер
	Consult instructions for use Gebrauchsanleitung beachten Consultar instrucciones de uso Consulter les instructions d'utilisation Consultare le istruzioni per l'uso Consulte as instruções de uso См. Инструкцию по применению
	Keep dry Trocken aufbewahren Mantener seco Garder au sec Mantenere asciutto Manter seco Хранить в сухом месте
	Biological Risks Biologisches Risiko Riesgos biológicos Risques biologiques Rischi biologici Riscos Biológicos Биологическая опасность
	Use By Verwendbar bis Usar por Utiliser par Utilizzare per Usar até Использовать до

	Manufacturer Hersteller Fabricante Fabricant Produttore Fabricante Производитель
	Date of manufacture Herstellungsdatum Fecha de manufactura Date de fabrication Data di produzione Data de fabricação Дата производства
	Keep away from sunlight Von Sonnenlicht fernhalten Mantener alejado de la luz solar Tenir à l'écart de la lumière du soleil Tenere lontano dalla luce solare Manter longe da luz solar Беречь от попадания солнечных лучей
	CE mark CE Zeichen Marca CE Marquage CE Marcatura CE Marca CE Знак соответствия продукции техническим регламентам ЕС
	Contains sufficient for X tests Ausreichend für X Prüfungen Contiene suficiente para X pruebas Contient suffisamment pour les tests X Contenuto sufficiente per X test Contém suficiente para X testes Содержит материалы, достаточные для выполнения X тестов

	Caution Achtung Precaución Attention Attenzione Cuidado Предупреждение
STERILE EO	Sterilized using ethylene oxide Sterilisiert mit Ethylenoxid Esterilizado con óxido de etileno. Stérilisé à l'oxyde d'éthylène Sterilizzato con ossido di etilene Esterilizado com óxido de etileno Стерилизовано окисидом этилена
STERILE R	Sterilized using irradiation Sterilisiert durch Bestrahlung Esterilizado mediante irradiación. Stérilisé par irradiation Sterilizzato con irradiazione Esterilizado por irradiação Стерилизовано с использованием облучения
	Do not re-sterilize Nicht sterilisieren No volver a esterilizar Ne pas re-stériliser Non risterilizzare Não reesterilize Не стерилизуйте повторно

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Date Issued : 2020.10
41FK10-07-A2

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IDENTIFY COVID-19 CONTAGIOUS PATIENTS **IN 15 MINUTES**

With Patient-friendly Nasal Sample Collection

PANBIO™ COVID-19 Ag RAPID TEST DEVICE

FOR PEOPLE SUSPECTED OF **COVID-19 EXPOSURE**

HIGH PERFORMANCE COMPARED TO NASAL PCR

- Panbio™ vs. Nasal PCR: Sensitivity 98.1%, Specificity 99.8%

PATIENT-FRIENDLY NASAL SAMPLE COLLECTION

- ~ 2 cm insertion depth minimizes undesirable reflexes like coughing or sneezing[1]

FAST IDENTIFICATION OF CONTAGIOUS INDIVIDUALS

- Test results in 15 minutes

ACCESSIBLE, LARGE-SCALE TESTING HELPS CONTAIN THE VIRUS SPREAD

- Enables immediate treatment or isolation measures to minimize transmission

HIGH PERFORMANCE
COMPARED TO NASAL PCR

		NASAL PCR TEST RESULT		
		POSITIVE	**NEGATIVE**	**TOTAL**
PANBIO™ COVID-19 Ag TEST RESULT	**POSITIVE**	102	1	103
	NEGATIVE	2	403	405
	TOTAL	104	404	508

SENSITIVITY	**SPECIFICITY**	**OPA**
98.1% [93.2%; 99.8%]	**99.8%** [98.6%; 100.0%]	**99.4%** [98.3%; 99.9%]

Performance data was calculated from a study of individuals suspected of exposure to COVID-19 or who have presented with symptoms in the last 7 days.

The clinical performance data was also calculated vs nasopharyngeal swab specimens using an FDA EUA RT-PCR reference and has a sensitivity of 91.1% (95% CI: 84.2-95.6%) and specificity of 99.7% (95% CI: 98.6-100.0%).

Positive agreement is higher with samples of Ct values ≤33 with a sensitivity of 99.0%. Patients with Ct value >33 are no longer contagious.[2]

PCR = polymerase chain reaction
OPA = overall percent agreement

PATIENT-FRIENDLY NASAL SAMPLE COLLECTION **ENABLES SCALE-UP** IN NONTRADITIONAL SETTINGS

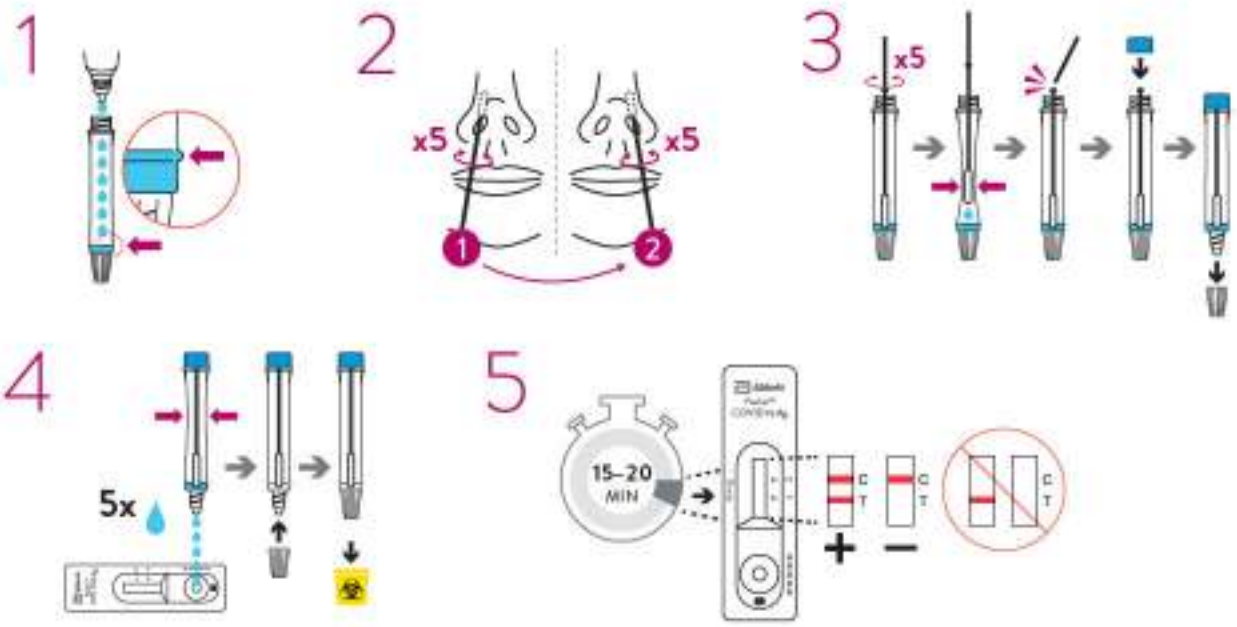
~ 2 CM NASAL SWAB INSERTION DEPTH

- Minimize undesirable reflexes like coughing or sneezing[1]
- Reduce risk of infecting healthcare workers by reducing the duration of the procedure[3]
- Less invasive and less patient discomfort[3] helps overcome patient resistance to procedure
- Lower technical complexity[3]; easier training for staff

LARGE SCALE DEPLOYMENT AT THE POINT OF CARE

- Mass production and deployment capability
- Can be used in a wide variety of non-laboratory settings
- Run multiple tests in parallel for high throughput
- No special/additional instruments required

SIMPLE TEST PROCEDURE



Consult Instructions for Use for complete procedure.

BIOHAZARD RISK-REDUCTION FEATURES

Reduce the risk of facility contamination and healthcare worker exposure.

SPECIFICATIONS

- **TEST TIME:** 15 MINUTES
- **STORAGE:** 2°C–30°C
- **CE MARK, WHO EUL**
- **SAMPLE TYPE:** NASAL SWAB

INTENDED USE: Panbio™ COVID-19 Ag Rapid Test Device is an *in vitro* diagnostic rapid test for the qualitative detection of SARS-CoV-2 antigen (Ag) in human nasal swab specimens from individuals who meet COVID-19 clinical and/or epidemiological criteria. Panbio™ COVID-19 Ag Rapid Test Device is for professional use only and is intended to be used as an aid in the diagnosis of SARS-CoV-2 infection. The product may be used in any laboratory and non-laboratory environment that meets the requirements specified in the Instructions for Use and local regulation. The test provides preliminary test results. Negative results don't preclude SARS-CoV-2 infection and they cannot be used as the sole basis for treatment or other management decisions. Negative results must be combined with clinical observations, patient history and epidemiological information. The test is not intended to be used as a donor screening test for SARS-CoV-2.

ORDER INFORMATION

PANBIO™ COVID-19 Ag RAPID TEST DEVICE (NASAL)

CATALOG NUMBER: 41FK11 (CE, WHO EUL), 41FK21 (CE/WHO/2D)

CONTENTS:

- 25 Test Devices
- 1 Buffer (9 mL/bottle)
- 25 Extraction Tubes
- 25 Extraction Tube Caps
- 1 Positive Control Swab
- 1 Negative Control Swab
- 25 Sterilized Nasal Swabs for Sample Collection
- 1 Tube Rack
- 1 Quick Reference Guide
- 1 Instructions for Use

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WWW.POC-COVID.ABBOTT

Product not available in all countries. Not approved for sale in the USA.

1. Poudaves-Letourmy S, et al. *European Annals of Otorhinolaryngology, Head and Neck Diseases.* 2020.
2. La Scola B, et al. Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards. *Eur J Clin Microbiol Infect Dis.* 2020;39:1059-1061. doi:10.1007/s10096-020-03913-9.
3. Office of the Assistant Secretary for Health. COVID-19 Fact Sheet. Nasal Specimen Collection for SARS-CoV-2 Diagnostic Testing 2020.

120007018-04-05/21

Abbott

Privacy Office; Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

August 23, 2021

Sent via e-mail

Re: Partial Access – OUR FILE# NSHA-2021-065

On May 20, 2021 Nova Scotia Health (NSH) received your request under the *Freedom of Information and Protection of Privacy Act* (*FOIPOP Act*).

We understand your application to be for a copy of the following:
All documents, emails, and correspondence (including texts) within the Dept. of Health and Wellness, and within/ between the NS Health Authority, including with/ from voting and non-voting members of the Therapeutics and Prophylactics Advisory Group relating to AbCellera's monoclonal antibody (bamlanivimab) a federally authorized treatment for COVID-19. (Date Range for Record Search: from 02/20/2020 to 05/12/2021).

Please find a copy of the records located in response to your request. We have withheld advice and recommendations developed a minister under section 14(1) and personal information under sections 20(1) and 20(3)(a)of the *FOIPOP Act*. We have marked discussions about other COVID drugs as "unrelated".

We are currently involved in a consultation with the federal government, however, they have indicated that they will not be able to complete the consultation for another few months. We have marked all discussions with or about the federal government as "third party".

Should you have any questions, please do not hesitate to contact me.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review.

Sincerely,
Katie Smith
Freedom of Information Officer
Nova Scotia Health Authority
Halifax, Nova Scotia

To:	NS Health COVID Network
Date:	22 December 2020
From:	Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group
Subject:	Bamlanivimab, unrelated [redacted] interim recommendation

Bamlanivimab Recommendation: use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units.

Rationale:

- **Health Canada indication**:
  - Bamlanivimab is authorized for use under an interim order for patients ≥ 12 years of age (≥40 kg) with mild to moderate COVID-19 at high risk of progressing to severe COVID-19 illness and/or hospitalization
- **Evidence**: BLAZE-1 (interim analysis of a Phase II trial)
  - Non-hospitalized patients (≥ 18 years of age) with recently diagnosed mild to moderate COVID-19. Approximately 69% of patients had risk factors for severe COVID-19.
  - **Efficacy:** Numerically reduced hospital admissions (signal of increased benefit in those >/= 65 and BMI >/= 35), however statistical analysis of this clinical outcome not provided
  - **Safety**: No signal of serious harm
- **Role in therapy**: **Pragmatic research**
  - Bamlanivimab cannot be endorsed for use in routine care based on the published evidence to date
  - Until further efficacy and safety data are published to support bamlanivimab in routine care, the advisory group recommends use in the context of pragmatic research to evaluate real-world clinical safety and effectiveness in NS Health
- **Population:**
  - **Non-severe COVID-19 aged 65 and older**
  - Bamlanivimab is a neutralizing monoclonal antibody and is ideal for early disease in non-severe patients as it targets pre-cellular viral entry
  - Blaze-1 supports use in non-severe COVID-19 population, however evidence from BLAZE-1 is not clear in terms of which patients with risk factors benefit most. There was increased benefit for those aged 65 and greater and BMI greater than 35.
  - Individuals 65 years of age and up are at highest risk for progression to severe disease and death and mount less of an immune response
- **Setting:**
  - **Regional care units (RCU)**
  - Health Canada approved a relatively broad indication that is not feasible to implement in the context of pragmatic research using our existing NS Health infrastructure
  - One NS Health affiliated setting that may be able to incorporate bamlanivimab administration in non-severe outpatients are the RCUs
  - Use of RCUs would allow patients who are very vulnerable to COVID-19 to receive bamlanivimab and allow data collection in individuals at high risk of disease progression
  - Other settings to be considered after initial roll out in NS Health affiliated RCUs
- **Public health/IPAC considerations**:
  - Advisory group discussed inherent infection-control issues if community-based COVID-19 positive patients were directed to existing healthcare facilities or infusion centers. RCUs were suggested as a practical setting to administer bamlanivimab without having to introduce COVID-19 positive patients into a new healthcare environment, and aligns with the pragmatic research method of using existing systems. Would not require an infusion center and would administer to patients in their RCU bed. An order set, IV monograph, pre medications, anaphylaxis kit, and nurse to infuse bamlanivimab and monitor for infusion reactions will be needed.

unrelated [redacted]

[redacted]

Note: Recommendations will be reviewed on a monthly basis by the NS Therapeutics and Prophylactics Advisory Group (review date: January 21, 2021)

nova scotia health

Agenda / Action Items

MEETING DETAILS			
Meeting Title	COVID-19 Network Meeting		
Location	Zoom		
Meeting Date	Tuesday, April 6, 2021	**Meeting Time**	4:30 to 6:30 p.m.
Purpose	A bi-weekly update meeting that provides an opportunity for clinical and medical leaders to discuss current pandemic strategies.		

PARTICIPANTS			
Co-chairs	Shelly McNeil	Alyson Lamb	
Participants	Marika Warren	Brett MacDougall	Angela Keenan
	Kimberley Anderson	Andrew Heighton	Cynthia Stockman
	Lisa Barrett	s.20(1)	Vickie Sullivan
	Darlene Davis	Lynn Johnston	Wanda Matthews
	Kate Mercer	Tamara Gilley	Heather Wolfe
	Tasha Ramsey	Maria Alexiadis	Ryan Sommers
	Tammy MacDonald	Christine Short	Jeannette Comeau
	Debbie Burris	s.20(1)	Melanie DiQuinzio
	Lynn Edwards	Janice Chisholm	Cheryl Pugh
	Tanya Munroe	Tania Sullivan	Todd Howlett
	Sam Hodder	Andrew Harris	Lois Bowden
	Todd Hatchette	Tara Sampalli	Christy Bussey
	Dylana Arsenault	Amy MacDonald	Glenn Patriquin
	Lorianne MacLean	Kirk McGee	Gary O'Toole
	Leah MacDonald	Annette Elliot Rose	Noella Whelan
	Nancy MacConnell-Maxner	Jennifer MacDougall	Cathy Ann Casault
	Carla MacDonald	Michelle DePodesta	
Guest(s)			
Regrets	Susan Stevens	Aaron Smith	Paul Hernandez
	Cindy MacQuarrie	Nicki Doyle	Ian Davis
	Katie MacLeod	Deborah Purvis	Scott Mawdsley
	Chris Lata	Cheryl Tschupruk	Tanya Penney
	Tony O'Leary	David Henderson	Greg Hirsch
	Doris Grant	Kris Srivatsa	Cindy Connolly

Item	Description	Lead
1.0	unrelated	unrelated
2.0	unrelated unrelated	unrelated

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Agenda / Action Items

Item	Description	Lead
	unrelated unrelated	unrelated

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Agenda / Action Items

Item	Description	Lead
3.0	unrelated	unrelated
4.0	unrelated	unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
	unrelated	unrelated
5.0	unrelated	unrelated
6.0	unrelated	• unrelated
7.0	unrelated	unrelated

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Agenda / Action Items

Item	Description	Lead
	unrelated	unrelated

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Agenda / Action Items

Item	Description	Lead

	unrelated	unrelated
		• Key anti-COVID monoclonal antibodies:
		  ○ Goal – prevent progression of mild COVID disease in high risk individuals.
		  ○ Top monoclonal candidates:
		  ▪ Bamlanivumab (has a recommendation in NS)
		  ▪ Bamlanivumab/Etesevimab
		unrelated

8.0	unrelated	unrelated
9.0	unrelated	unrelated
10.0	unrelated	unrelated
11.0	unrelated	unrelated

Agenda / Action Items

MEETING DETAILS			
Meeting Title	COVID-19 Network Meeting		
Location	Zoom		
Meeting Date	Tuesday, April 27, 2021	**Meeting Time**	4:30 to 6:30 p.m.
Purpose	A bi-weekly update meeting that provides an opportunity for clinical and medical leaders to discuss current pandemic strategies.		

PARTICIPANTS			
Co-chairs	Shelly McNeil	Alyson Lamb	Cindy MacQuarrie
Participants	Marika Warren	Steve Button	Angela Keenan
	Kimberley Anderson	Andrew Heighton	Cynthia Stockman
	Paul Hernandez	s.20(1)	Ian Davis
	Darlene Davis	Lynn Johnston	Katie MacLeod
	Kate Mercer	Theresa Hawkesworth	Heather Wolfe
	Tasha Ramsey	Anita Muise	Andre Bernard
	Tammy MacDonald	s.20(1)	Jeannette Comeau
	Scott Mawdsley	s.20(1)	Melanie DiQuinzio
	Chris Lata	Natalie Cheng	Maria Alexiadis
	Lynn Edwards	Janice Chisholm	Cheryl Tschupruk
	Leah MacDonald	Tania Sullivan	Tony O'Leary
	Sam Hodder	Kirk McGee	Gary O'Toole
	Todd Hatchette	Tara Sampalli	Greg Hirsch
	Doris Grant	Amy MacDonald	Glenn Patriquin
	Cindy Connolly	Annette Elliot Rose	Noella Whelan
	Nancy MacConnell-Maxner	Jennifer MacDougall	Cathy Ann Casault
	Carla MacDonald	Michelle DePodesta	Vickie Sullivan
	Lorianne MacLean	Dylana Arsenault	Lois Bowden
	Tanya Munroe	Todd Howlett	Cheryl Pugh
	Debbie Burris	Brett MacDougall	
Regrets	Susan Stevens	Tamara Gilley	Lisa Barrett
	Ryan Sommers	Robert Zwicker	David Henderson
	Andrew Harris	Kris Srivatsa	Christy Bussey
	Nicki Doyle		

Item	Description	Lead
1.0	unrelated	unrelated
2.0	unrelated	unrelated

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Agenda / Action Items

Item	Description	Lead
	unrelated	• unrelated
3.0	unrelated	unrelated
4.0	unrelated	unrelated
5.0	unrelated	unrelated
6.0	unrelated	unrelated

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Agenda / Action Items

Item	Description	Lead
	[redacted]	unrelated
7.0	unrelated	unrelated
8.0	unrelated	unrelated

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Agenda / Action Items

Item	Description	Lead
9.0	unrelated	unrelated
10.0	unrelated	unrelated
11.0	unrelated	unrelated

Agenda / Action Items

Item	Description	Lead

12.0	**Therapeutics Update**
	(Tasha Ramsey)
		Recommendation:
		Bamlanivimab – Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19:
		• 65 years of age and older in NS Health affiliated Regional Care Units **OR**
		• 18 years of age and older hospitalized for other reasons at high risk for progression (e.g.: early transplant).
		
		Rationale:
		• Bamlanivimab is approved by Health Canada under an Interim Order for those with mild to moderate COVID-19 at high risk of progressing to severe COVID-19.
		• Health Canada examples of factors that are high risk for progression to severe disease include:
		  ○ ≥ 65 years of age
		  ○ BMI ≥ 35
		  ○ Chronic kidney disease
		  ○ Diabetes
		  ○ Immunosuppressive disease or receiving immunosuppressive treatment
		  ○ ≥ 55 years old AND any of: cardiovascular disease, hypertension, or chronic respiratory disease
		• NS Health affiliated RCUs initially selected as a study location for administration convenience.
		• Individuals with non-severe COVID-19 hospitalized for another reason represent a second setting that is convenient to infuse bamlanivimab.
		
		unrelated
		
		Key Decision: Network members support and approve both recommendations.

13.0	unrelated	unrelated
14.0	unrelated	unrelated

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Agenda / Action Items

Item	Description	Lead
	unrelated	unrelated
15.0	unrelated	• unrelated

Agenda / Action Items

MEETING DETAILS			
Meeting Title	COVID Network Meeting		
Location	Skype		
Meeting Date	Tuesday, December 8, 2020	**Meeting Time**	4:00 to 6:00 p.m.
Purpose	A weekly update meeting that provides an opportunity for clinical and medical leaders to discuss current pandemic strategies.		

PARTICIPANTS			
Co-chairs	Shelly McNeil	Alyson Lamb	Lois Bowden
Participants	Christy Bussey	Nicki Doyle	Dylana Arsenault
	Kimberley Anderson	Andrew Heighton	Cynthia Stockman
	Lisa Barrett	s.20(1)	Ian Davis
	Darlene Davis	Lynn Johnston	Katie MacLeod
	Andrew Harris	Gary O'Toole	Heather Wolfe
	Tasha Ramsey	Cheryl Pugh	Ryan Sommers
	Tammy MacDonald	Carmel Turpin	Jeannette Comeau
	Bethany McCormick	Shauna Thompson	Melanie DiQuinzio
	Chris Lata	Maria Alexiadis	Rick Gibson
	Lynn Edwards	Janice Chisholm	Cheryl Tschupruk
	Tanya Penney	Tania Sullivan	Tanya Munroe
	Sam Hodder	Sandy Cantwell Kerr	David Henderson
	Todd Hatchette	Tara Sampalli	s.20(1)
	Paul Hernandez	Sally Loring	Glen Patriquin
	Aaron Smith	Kirk McGee	Christine Short
	Cindy Connolly	Annette Elliot Rose	Noella Whelan
	Nancy MacConnell-Maxner	Wendy McVeigh	Cathy Ann Casault
	Carla MacDonald	Jason LeBlanc	
Regrets	Cindy MacQuarrie	Angela Keenan	Kate Mercer
	Tony O'Leary	Susan Stevens	Kris Srivatsa
	Jennifer MacDougall	Michelle DePodesta	Lorianne MacLean
	Todd Howlett	Greg Hirsch	Marika Warren
	Deborah Purvis		
Guest	Doris Grant	Lewis Bedford	Susan Dunn
	Andrea Rose		

Item	Description	Lead
1.0	unrelated	unrelated
2.0	unrelated	unrelated

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Agenda / Action Items

Item	Description	Lead
	unrelated	unrelated
3.0	unrelated	unrelated
4.0	unrelated	unrelated

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Agenda / Action Items

Item	Description	Lead
5.0	unrelated	unrelated
6.0	**Therapeutics Update (Tasha Ramsey/Lisa Barrett)**	• [redacted] Bamlanivimab [redacted] may be used in the context of pragmatic research. • Several monoclonal antibodies have just come out (or are about to come out) that require infusion. Monoclonal antibodies require infusion and monitoring for infusion reactions. This is typically done in infusion centers. However, infusion clinics in Nova Scotia are usually booked well in advance and often to capacity with patients that are immunocompromised. Use of these agents will depend on the level of disease (non-severe vs. severe) and those with non-severe disease will require infusion on an outpatient basis. Administration logistics for the wave of monoclonal antibodies that are about to come out will require careful consideration. unrelated • Tasha will provide the network with information unrelated and suggestions of how bamlanivimab could potentially be implemented. **Further discussion will occur at next week's meeting.**

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Agenda / Action Items

Item	Description	Lead
7.0	unrelated	unrelated
8.0	unrelated	unrelated

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Agenda / Action Items

Item	Description	Lead
	unrelated	unrelated
9.0	unrelated	unrelated
10.0	unrelated	unrelated
11.0	unrelated	• unrelated
12.0	unrelated	• unrelated

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MEETING DETAILS			
Meeting Title	COVID Network Meeting		
Location	Skype		
Meeting Date	Tuesday, December 22, 2020	**Meeting Time**	4:30 to 6:30 p.m.
Purpose	A weekly update meeting that provides an opportunity for clinical and medical leaders to discuss current pandemic strategies.		

PARTICIPANTS			
Co-chairs	Shelly McNeil	Alyson Lamb	
Participants	Marika Warren	Noella Whelan	Angela Keenan
	Kimberley Anderson	Andrew Heighton	Christine Short
	Lisa Barrett	s.20(1)	Kirk McGee
	Darlene Davis	Lynn Johnston	Susan Stevens
	Kate Mercer	Gary O'Toole	Heather Wolfe
	Tasha Ramsey	Deborah Purvis	Ryan Sommers
	Tammy MacDonald	Carmel Turpin	Jeannette Comeau
	Cheryl Pugh	Shauna Thompson	Melanie DiQuinzio
	Todd Howlett	Maria Alexiadis	Rick Gibson
	Lynn Edwards	Janice Chisholm	Cheryl Tschupruk
	Ruth Harding	Michelle DePodesta	Christy Bussey
	Carla MacDonald	Andrew Harris	David Henderson
	Todd Hatchette	Nancy MacConnell-Maxner	s.20(1)
	Dylana Arsenault	Annette Elliot Rose	Glen Patriquin
	Doris Grant	Greg Hirsch	
Regrets	Ian Davis	Nicki Doyle	Cynthia Stockman
	Sally Loring	Cathy Ann Casault	Kris Srivatsa
	Paul Hernandez	Tara Sampalli	Lois Bowden
	Cindy MacQuarrie	Lorianne MacLean	Tanya Munroe
	Aaron Smith	Bethany McCormick	Chris Lata
	Cindy Connolly	Tanya Penney	Katie MacLeod
	Jennifer MacDougall	Tania Sullivan	Tony O'Leary
	Sam Hodder		

Item	Description	Lead
1.0	unrelated	• unrelated
2.0	unrelated	unrelated

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Agenda / Action Items

Item	Description	Lead
3.0	unrelated	unrelated
4.0	unrelated	unrelated unrelated

Agenda / Action Items

Item	Description	Lead
5.0	**Therapeutics Update (Tasha Ramsey/Lisa Barrett)**	unrelated • Bamlanivimab ○ Clinical Trial or Pragmatic Research ○ Health Canada approval with conditions and distribtuted free of charge. ○ Neutralizing monoclonal antibody ○ Second Health Canada authorized treatment for COVID-19. Authorized on the interim for treatment of patients ≥ 12 years of age (≥40 kg) with mild to moderate COVID-19 illness at high risk for progressing to severe COVID-19 illness and/or hospitalization. ○ High Risk meets one of the following criteria: ▪ ≥ 65 years old ▪ BMI ≥ 35 for adults ▪ Chronic kidney disease ▪ Diabetes ▪ Immunosuppressive disease or receiving immunosuppressive treatment ▪ ≥ 55 years old AND any of: cardiovascular disease, hypertension, or chronic respiratory disease ▪ 12-17 years of age AND have any of: BMI ≥ 85th percentile for age/gender, sickle cell disease, congenital or acquired heart disease, neurodevelopmental disorders, a medical-related technological dependence, asthma or other chronic respiratory disease. ○ Targets SARS-CoV-2 spike protein preventing viral attachment and cell entry, decreasing viral replication and reducing severity of illness. unrelated

Agenda / Action Items

Item	Description	Lead
	Therapeutics Update Cont'd	• Interim Recommendations: will be reviewed on a monthly basis by the NS Therapeutics and Prophylactics Advisory Group (review date: January 21, 2021)

Bamlanivimab:

- Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 who are 65 years of age and older in NS Health-affiliated Regional Care Units.
- Rationale for 65 years of age:
  - **Health Canada Indication**: Authorized for use under an interim order for patients ≥ 12 years of age (≥ 40 kg) with mild to moderate COVID-19 at high risk of progressing to severe COVID-19 illness and/or hospitalization.
  - **Evidence:** BLAZE-1 (interim analysis of a Phase II trial)
    - Non-hospitalized patients (≥ 18 years of age) with recently diagnosed mild to moderate COVID-19. Approximately 69% of patients had risk factors for severe COVID-19.
    - Efficacy: Numerically reduced hospital admissions (signal of increased benefit in those >/=65 and BMI >/=35, however statistical analysis of this clinical outcome not provided.
    - Safety: NO signal of serious harm.
  - **Role in therapy:** Pragmatic research:
    - Cannot be endorsed for use in routine care based on the published evidence to date.
    - Until further efficacy and safety data are published to support bamlanivimab in routine care, the advisory group recommends use in the context of pragmatic research to evaluate real-world clinical safety and effectiveness in NS Health.
  - **Population:** Non-severe COVID-19 aged 65 and older
    - Bamlanivimab is a monoclonal antibody and is ideal for early disease in non-severe patients as it targets pre-cellular viral entry.
    - BLAZE-1 supports use in non-severe COVID-19 population, however evidence from BLASE-1 is not clear in terms of which patients with risk factors benefit most. There was increased benefit for those aged 65 and greater and BMI greater than 35.
    - Individuals 65 years of age and up are at highest risk for progression to severe disease and death and less of an immune response.

Agenda / Action Items

Item	Description	Lead

	Therapeutics Update Cont'd	• **Setting: Regional Care Units**
		  • Health Canada approved a relatively broad indication that is not feasible to implement in the context of pragmatic research using our existing NS Health infrastructure.
		  • One NS Health affiliated setting that may be able to incorporate bamlanivimab administration in non-severe outpatients are the RCUs.
		  • Use of RCUs would allow patients who are very vulnerable to COVID-19 to receive bamlanivimab and allow data collection in individuals at high risk of disesase progression.
		  • Other settings to be considered after initial roll out in NS Health affiliated RCUs.
		• CATCO is the Canadian Arm of the WHO's international SOLIDARITY Trial (only treatment arm is Remdesivir)
		unrelated
		• COVID VICTORY STUDY – https://co-vic.ca/

6.0	unrelated	unrelated

Agenda / Action Items

Item	Description	Lead
7.0	unrelated	unrelated
8.0	unrelated	unrelated

Agenda / Action Items

MEETING DETAILS			
Meeting Title	COVID-19 Network Meeting		
Location	Zoom		
Meeting Date	Tuesday, February 16, 2021	**Meeting Time**	4:30 to 6:30 p.m.
Purpose	A weekly update meeting that provides an opportunity for clinical and medical leaders to discuss current pandemic strategies.		

PARTICIPANTS			
Co-chairs	Shelly McNeil	Cindy MacQuarrie	Alyson Lamb
Participants	Carla MacDonald	Kate Mercer	Angela Keenan
	Kimberley Anderson	Andrew Heighton	Cynthia Stockman
	Lisa Barrett	s.20(1)	Ian Davis
	Darlene Davis	Lynn Johnston	Katie MacLeod
	Theresa Hawkesworth	Vivian Tan	Heather Wolfe
	Tasha Ramsey	Marika Warren	Ryan Sommers
	Tammy MacDonald	Michelle DePodesta	Jeannette Comeau
	Tanya Munroe	Shauna Thompson	Vickie Sullivan
	Todd Howlett	Maria Alexiadis	Dylana Arsenault
	Lynn Edwards	Janice Chisholm	Debbie Burris
	Tanya Penney	Tania Sullivan	Christy Bussey
	Sam Hodder	Andrew Harris	Amy MacDonald
	Todd Hatchette	Doris Grant	Greg Hirsch
	Paul Hernandez	Sally Loring	Glenn Patriquin
	s.20(1)	Kirk McGee	Cheryl Pugh
	Cindy Connolly	Annette Elliot Rose	Wanda Matthews
	Nancy MacConnell-Maxner	Brett MacDougall	Cathy Ann Casault
Guest			
Regrets	Susan Stevens	Christine Short	Deborah Purvis
	Chris Lata	Tara Sampalli	David Henderson
	Aaron Smith	Kris Srivatsa	Lorianne MacLean
	Lois Bowden	Jennifer MacDougall	Noella Whelan
	Gary O'Toole	Tony O'Leary	Cheryl Tschupruk
	Scott Mawdsley	Melanie DiQuinzio	Nicki Doyle
	Tamara Gilley		

Item	Description	Lead
1.0	unrelated	unrelated
2.0		

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Agenda / Action Items

Item	Description	Lead
	unrelated	unrelated
3.0	unrelated	unrelated

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Agenda / Action Items

Item	Description	Lead
	unrelated	unrelated
4.0	unrelated	unrelated
5.0	unrelated	unrelated
6.0	unrelated	unrelated

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Agenda / Action Items

Item	Description	Lead
7.0	**Therapeutics Recommendations** (Tasha Ramsey/Lisa Barrett)	unrelated

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Agenda / Action Items

Item	Description	Lead
	Therapeutics Recommendations Cont'd	unrelated

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Agenda / Action Items

Item	Description	Lead
8.0	unrelated	unrelated
9.0	unrelated	unrelated
10.0	unrelated	unrelated

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Agenda / Action Items

MEETING DETAILS			
Meeting Title	COVID-19 Network Meeting		
Location	Zoom		
Meeting Date	Tuesday, March 23, 2021	**Meeting Time**	4:30 to 6:30 p.m.
Purpose	A bi-weekly update meeting that provides an opportunity for clinical and medical leaders to discuss current pandemic strategies.		

PARTICIPANTS			
Co-chairs	Shelly McNeil	Cindy MacQuarrie	Alyson Lamb
Participants	Marika Warren	Amy MacDonald	Angela Keenan
	Kimberley Anderson	Andrew Heighton	Cynthia Stockman
	Lisa Barrett	s.20(1)	Ian Davis
	Debbie Burris	Vickie Sullivan	Theresa Hawkesworth
	Kate Mercer	Cheryl Pugh	Heather Wolfe
	Tasha Ramsey	Todd Howlett	Maureen Carew
	Tammy MacDonald	Christine Short	Jeannette Comeau
	Andre Bernard	Maria Alexiadis	Melanie DiQuinzio
	Michelle DePodesta	Tanya Munroe	Christy Bussey
	Carla MacDonald	Janice Chisholm	Cathy Ann Casault
	Dylana Arsenault	Tania Sullivan	Nancy MacConnell-Maxner
	Sam Hodder	Andrew Harris	David Henderson
	Todd Hatchette	Annette Elliot Rose	Greg Hirsch
	Paul Hernandez	Noella Whelan	Glenn Patriquin
	Cindy Connolly	Kirk McGee	Gary O'Toole
	Yossry Hussein		
Guest(s)	Barbara Goodall		
Regrets	Susan Stevens	Tamara Gilley	s.20(1)
	Ryan Sommers	Shauna Thompson	Jennifer MacDougall
	Scott Mawdsley	Nicki Doyle	Doris Grant
	Darlene Davis	Lynn Johnston	Katie MacLeod
	Deborah Purvis	Chris Lata	Cheryl Tschupruk
	Lynn Edwards	Tanya Penney	Tony O'Leary
	Tara Sampalli	Sally Loring	Wanda Matthews
	Kris Srivatsa	Brett MacDougall	Lois Bowden
	Aaron Smith	Lorianne MacLean	

Item	Description	Lead
1.0	unrelated	unrelated
2.0	unrelated	unrelated

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Agenda / Action Items

Item	Description	Lead
	unrelated	unrelated

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Agenda / Action Items

Item	Description	Lead
		unrelated
3.0	unrelated	unrelated
4.0	unrelated	

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Agenda / Action Items

Item	Description	Lead
	unrelated	unrelated
5.0	unrelated	
6.0	unrelated	

Agenda / Action Items

Item	Description	Lead
7.0	**Therapeutics Update** (Lisa Barrett/Tasha Ramsey/Barbara Goodall)	unrelated • Current Recommendations: ○ unrelated ○ Bamlanivimab (Neutralizing monoclonal antibody) – Used in the context of pragmatic research (e.g. the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units. ▪ 150 vials available (150 patients that could be treated). unrelated • 3 COVID Investigational Therapeutic Studies: unrelated ○ CATCO NOS (Bamlanivimab) ○ unrelated • Pharamcy One-pagers and other resourceswill be uploaded to the COVID Hub. unrelated unrelated • Important to follow appropriate order sets. • Important for staff to obtain permission from the patient for ID to have conversations with them so that they can gather information and determine if any of the available agents may benefit them now or in their future care.
8.0	unrelated	
9.0		
10.0		

To:	NS Health COVID Network
Date:	9 February 2021
From:	Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group
Subject:	Recommendations

The Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group has the following new recommendations for the COVID Network to consider for approval:

The following recommendations were approved by the COVID Network on December 22, 2020. The Advisory Group reviewed them as part of our monthly review of previous recommendations. We have no revisions to the recommendations at this time.

Bamlanivimab: Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units.

Note: Recommendations will be reviewed on a monthly basis by the NS Therapeutics and Prophylactics Advisory Group

To:	NS Health COVID Network
Date:	26 April 2021
From:	Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group
Subject:	Bamlanivimab and unrelated : Revised Recommendations

The Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group has the following revised recommendations for the COVID Network to consider for approval:

1. Bamlanivimab: use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19:

- **65 years of age and older in NS Health affiliated Regional Care Units OR**
- **18 years of age and older hospitalized for other reasons at high risk for progression (e.g.: early transplant)**

The current NS Health bamlanivimab recommendation is: use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units.

Bamlanivimab is approved by Health Canada under an Interim Order for those with mild to moderate COVID-19 at high risk of progressing to severe COVID-19. Heath Canada examples of factors that are high risk for progression to severe disease include:

- ≥ 65 years of age
- BMI ≥ 35
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or receiving immunosuppressive treatment
- ≥ 55 years old AND any of: cardiovascular disease, hypertension, or chronic respiratory disease

NS Health affiliated Regional Care Units were initially selected as a study location for administration convenience. Individuals with non-severe COVID-19 hospitalized for another reason represent a second setting that is convenient to infuse bamlanivimab.

unrelated [redacted]

[redacted]

[redacted]

[redacted].

Note: Recommendations will be reviewed on a monthly basis by the NS Therapeutics and Prophylactics Advisory Group

From: Tracey, Angela
To: Ramsey, Tasha
Cc: Covid Network
Subject: RE: Therapeutics Update to COVID Network
Date: Thursday, December 3, 2020 12:34:16 PM
Attachments: image002.jpg
image003.jpg

Thank you Tasha.
Copying Cindy, Shelly, and Alyson so that they are aware.
Can we confirm your start time for 4:45 p.m.?

Regards,
Angela

Angela Tracey
Administrative Assistant to Cindy MacQuarrie
Senior Director for Interprofessional Practice and Learning
Nova Scotia Health
716 King Street
New Waterford, NS B1H 3Z5
Office: 902-592-3421
Fax: 902-592-3344
Email: Angela.Tracey@nshealth.ca

From: Ramsey, Tasha
Sent: Thursday, December 03, 2020 12:11 PM
To: Tracey, Angela <Angela.Tracey@nshealth.ca>
Subject: Re: Therapeutics Update to COVID Network

Yes- I am happy to. I can go over the unrelated [redacted] we plan to use in the context of pragmatic research.

I would also like to ask the network for their thoughts on the implementation of these agents. Several that have just come out (or are about to come out) require infusion. Some will require infusion on an outpatient basis (in non-severe patients).

We may have to put some thought into the creation of something along the lines of a NS Health affiliated infusion clinic specifically for COVID patients.

unrelated [redacted] it looks like NS Health is going to be provided with bamlanivimab for free from the federal government. We have to determine how to get it to non-severe patients.

It would be helpful to at least introduce the problem to the COVID network and initiate the process of determining who the key people will be to create a solution.

Tasha

From: "Tracey, Angela" <Angela.Tracey@nshealth.ca>
Date: Thursday, December 3, 2020 at 10:10 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: Therapeutics Update to COVID Network

Good Morning Tasha,

Cindy has asked me to reach out to see if you would be able to provide a quick (15 minute) Therapeutics update at our next network meeting (Tuesday, December 8th).

If you could please confirm, it would be greatly appreciated.

Regards,
Angela

Angela Tracey
Administrative Assistant to Cindy MacQuarrie
Senior Director for Interprofessional Practice and Learning
Nova Scotia Health
716 King Street
New Waterford, NS B1H 3Z5
Office: 902-592-3421
Fax: 902-592-3344
Email: Angela.Tracey@nshealth.ca

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Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group

April 8, 2021

Agenda

- Minutes
- unrelated [redacted]
- Review recommendations:
  - unrelated [redacted]
  - **Bamlanivimab**
  - unrelated [redacted]
- Pandemic supply update

Minutes

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	March 11, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, Amanda Porter, Gabrielle Richard, Lisa Grandy Allen, Barbara Goodall, Kenneth Rockwood		

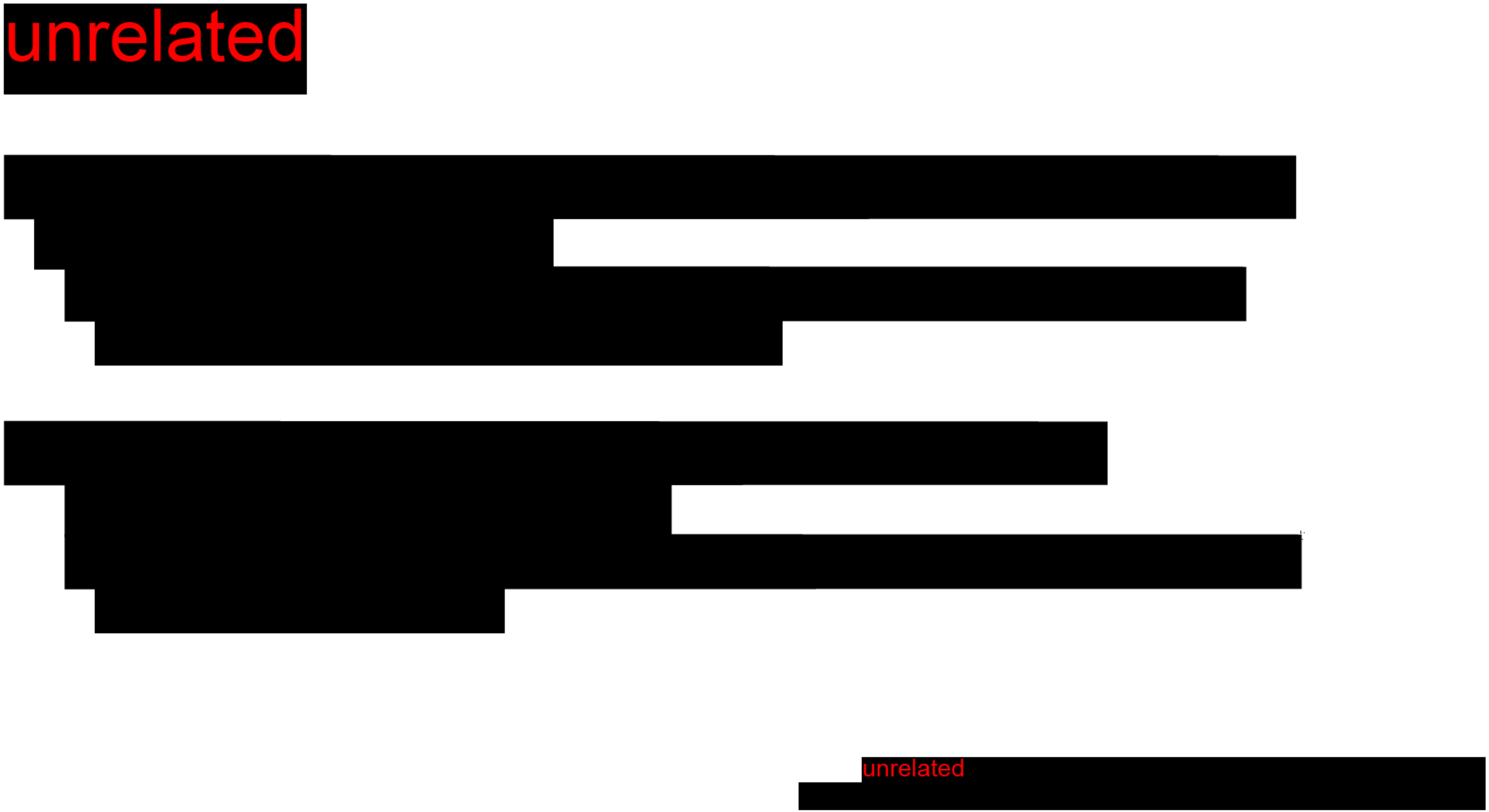
Items	Discussion
- **Minutes**	[redacted]
[redacted]	[redacted] Gabrielle provided a list of agents that are currently under discussion and being followed by PHAC: 1. Bamlanivimab + etesevimab [redacted]
[redacted] **Review recommendations:** - **Bamlanivimab** [redacted]	[redacted] Discussed current recommendations for bamlanivimab, [redacted] in light of most recent MSSU summaries. No evidence that we haven't previously reviewed and considered. There was agreement to continue with current recommendations. Briefly discussed bamlanivimab for prophylaxis – stakeholder meeting to discuss role in congregate living facilities such as long-term care happened earlier this week. s.14(1) [redacted] Group agreed that there was no need to update the current recommendation for bamlanivimab at this time.


unrelated

unrelated

unrelated

unrelated


unrelated
unrelated

unrelated

unrelated

Recommendation Review

COVID-19 Therapeutics and Prophylactics Advisory Group: Recommendations

Recommendation	Medication	Notes
unrelated	[redacted]	[redacted]
Research	**Bamlanivimab**	Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units.
	unrelated	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	
	[redacted]	
	[redacted]	
	[redacted]	

Bamlanivimab

Bamlanivimab monotherapy

- March 24, 2021: US government announces it will halt distribution of bamlanivimab monotherapy given sustained increased in SARS-CoV-2 viral variants
- EUA Fact Sheet updated:

Table 3: Pseudovirus Neutralization Data for SARS-CoV-2 Variant Substitutions with Bamlanivimab Alone

Lineage with Spike Protein Substitution	Key Substitutions Tested[a]	Fold Reduction in Susceptibility
B.1.1.7 (UK origin)	N501Y	no change[b]
B.1.351 (South Africa origin)	E484K	>2,360[c]
P.1 (Brazil origin)	E484K	>2,360[c]
B.1.427/B.1.429 (California origin)	L452R	>1,020[c]
B.1.526 (New York origin)[d]	E484K	>2,360[c]

Reduction of >1000 fold = likely no activity

https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab/Pages/default.aspx
https://www.fda.gov/media/143603/download

Bamlanivimab monotherapy

- Health Canada: remains authorized by Interim Order (April 6)

Applications received related to the COVID-19 pandemic

Applicant	Medicinal ingredient(s)	Therapeutic area	Date application was received	Outcome of application	Date of decision/outcome
Eli Lilly Canada Inc	Bamlanivimab (LY-CoV555)	Immune sera and immunoglobulins, for human use	2020-10-12	Authorized (with terms and conditions)	2020-11-20
Eli Lilly Canada Inc	Bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016)	Immune sera and immunoglobulins, for human use	2021-02-16	Under review	n/a

https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/authorization/applications.html

Table 2. Cumulative number of variants of concern (VOC) publically reported in Canada, by location, as of April 5, 2021

Location	B.1.1.7 variant	B.1.351 variant	P.1 variant
Canada	**14,010**	**337**	**857**
British Columbia	2,771	51	737
Alberta	6,273	22	15
Saskatchewan	943	8	0
Manitoba	235	20	0
Ontario	2,135	71	103
Quebec	1,424	154	2
Newfoundland and Labrador	178	1	0
New Brunswick	28	0	0
Nova Scotia	18	10	0
Prince Edward Island	4	0	0
Yukon	0	0	0
Northwest Territories	1	0	0
Nunavut	0	0	0

https://health-infobase.canada.ca/covid-19/epidemiological-summary-covid-19-cases.html#VOC

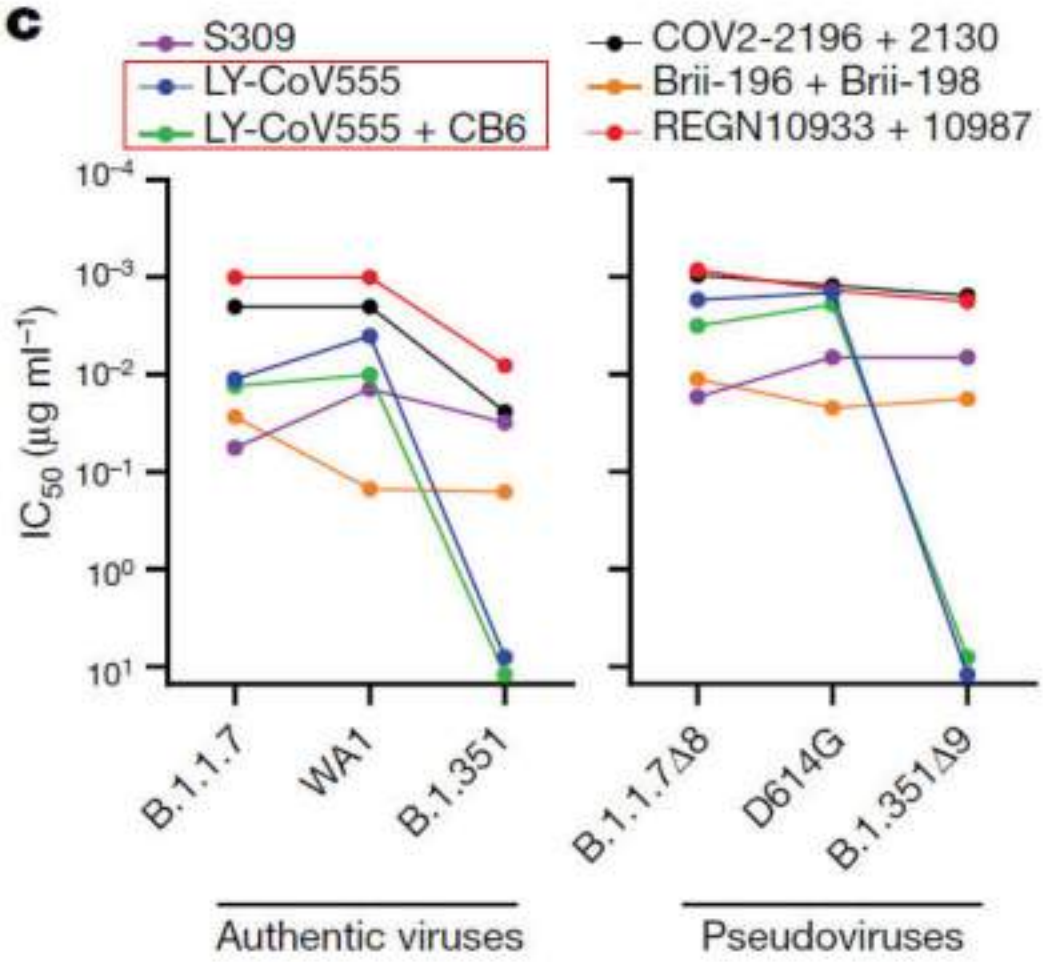
SA and UK variants

- Study testing the neutralizing activity of monoclonal antibodies against B.1.1.7, B.1.351, and pseudoviruses made to reflect individual mutations implicated in each
- Bamlanivimab (LY-CoV555) alone or in combination with etesevimab (CB6) no longer able to neutralize B.1.351
- Maintained activity against B.1.1.7

Article

Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7

Nature | www.nature.com



Nature. 2021 Mar 8. doi: 10.1038/s41586-021-03398-2.

COVID-19 Investigational Therapeutic Studies

	Study Summary	Study Drug	Ethics Approval	Site Activation
[redacted]				
	• Nosocomial Acquired COVID-19 Patients • Pragmatic, randomized, open-label, controlled clinical trial	Bamlanivimab		• Pending provincial Ontario ethics approval before circulating to other provinces (3-6 wks)
[redacted]				

COVID-19 Therapeutics and Prophylactics Advisory Group: Recommendations

Recommendation	Medication	Notes
unrelated	[redacted]	[redacted]
Research	**Bamlanivimab**	Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units.
	unrelated	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	
	[redacted]	
	[redacted]	
	[redacted]	

[redacted]

unrelated

COVID-19 Investigational Therapeutic Studies

	Study Summary	Study Drug	Ethics Approval	Site Activation
[redacted]				
CATCO NOS	• Nosocomial Acquired COVID-19 Patients • Pragmatic, randomized, open-label, controlled clinical trial	Bamlanivimab	...	• Pending provincial Ontario ethics approval before circulating to other provinces (3-6 wks)
[redacted]				

COVID-19 Therapeutics and Prophylactics Advisory Group: Recommendations

Recommendation	Medication	Notes
unrelated	[redacted]	[redacted]
Research	**Bamlanivimab**	Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units.
	unrelated	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	
	[redacted]	
	[redacted]	
	[redacted]	

[redacted]

Pandemic Supply Update

NS Health COVID-19 Medication Recommendations

Recommendation		Medication	Notes
unrelated		[redacted]	[redacted]
Research	50 + ?100	Bamlanivimab	Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units.
	unrelated	unrelated	[redacted]
unrelated		[redacted]	[redacted]
[redacted]			
		[redacted]	
		[redacted]	
		[redacted]	

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group

April 22, 2021

Agenda

- Minutes
- unrelated [redacted]
- Review recommendations:
  - **Bamlanivimab**
  - unrelated [redacted]
- Pandemic supply update

Minutes

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	April 8, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Kathleen Coleman, Emma Reid, Amanda Porter, Gabrielle Richard, Lisa Grandy Allen, Barbara Goodall, Kenneth Rockwood		

Items	Discussion
- **Minutes**	unrelated [redacted]
unrelated [redacted]	[redacted]
Review recommendations: - **Bamlanivimab** [redacted]	Bamlanivimab review: Emma reviewed brief update on bamlanivimab as monotherapy including recommendations from the USA (distribution for monotherapy has stopped given efficacy concerns for variants of concern) and current status in Canada. Tasha informed that variant strains are confirmed through National Micro Lab in Winnipeg which takes 7-10 days, but we do have an in-house preliminary screening test for S01y to identify variants. Barb provided update on a prospective study through which Nova Scotian bamlanivimab supply could be used, CATCO-NOS. It is a pragmatic trial that is the Canadian arm of Solidarity (Phase 4 study). Patients are still being enrolled in Calgary, and Ontario and BC have also recently received ethics approval. NS has received the CATCO-NOS protocol and we have been asked to move forward with ethics submission. Barb will take part in collaborator call next week and is hoping more information around bamlanivimab role as monotherapy will be shared. Noted that the Ontario clinical guidelines and BC recommendations do not include bamlanivimab outside of clinical trials. Discussion about updating our recommendation – until we have more information available and recognizing that no use of bamlanivimab will happen locally without the setting of a clinical trial, decision to leave recommendation as is. *Bamlanivimab recommendation: Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health-affiliated Regional Care Units.* unrelated [redacted]


unrelated

unrelated

unrelated

unrelated

unrelated

[redacted]

Recommendation Review

COVID-19 Therapeutics and Prophylactics Advisory Group: Recommendations

Recommendation	Medication	
unrelated	[redacted]	[redacted]
Research	**Bamlanivimab**	Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units.
	unrelated	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	
	[redacted]	
	[redacted]	
	[redacted]	

COVID-19 Investigational Therapeutic Studies

	Study Summary	Study Drug	Ethics Approval	Site Activation
[redacted]				
CATCO NOS	• Nosocomial Acquired COVID-19 Patients • Pragmatic, randomized, open-label, controlled clinical trial	Bamlanivimab	...	• Pending provincial Ontario ethics approval before circulating to other provinces (3-6 wks)
[redacted]				

Pandemic Supply Update

COVID-19 Therapeutics and Prophylactics Advisory Group: Recommendations

Recommendation		Medication	
unrelated		[redacted]	[redacted]
Research	50 vials	Bamlanivimab	Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units.
unrelated		unrelated	[redacted]
unrelated		unrelated	[redacted]
unrelated			
unrelated		[redacted]	
		[redacted]	
		[redacted]	

[redacted]

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group

February 4, 2021

Agenda

- Minutes
- unrelated [redacted]
- Recommendation review process
- unrelated [redacted] bamlanivimab: Review previous recommendations

Minutes

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	January 28, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, Barbara Goodall, Glenn Cox, Amanda Porter, Kenneth Rockwood, Lisa Grandy Allen		

Items	Discussion
- **Minutes**	unrelated [redacted]
-	unrelated [redacted]
-	
-	

unrelated

unrelated

unrelated

unrelated

[redacted]

Recommendation Review Process

unrelated

Bamlanivimab

Recommendation Review

- Bamlanivimab:
  - Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health-affiliated Regional Care Units.

MSSU Review
CADTH Advice

unrelated

CADTH

CADTH DRUG IMPLEMENTATION ADVICE

Bamlanivimab for Mild-to-Moderate Symptoms of COVID-19

(Eli Lilly Inc.)

Health Canada Approved Indication: Treatment of COVID-19 in adults and adolescents (12 years and older with a body weight of at least 40 kg) with mild-to-moderate symptoms of COVID-19 and who are at high risk of progressing to severe COVID-19 illness and/or hospitalization

unrelated

Background Summary

Bamlanivimab for COVID-19

MSSU
USSM

What is bamlanivimab?

Bamlanivimab is an rgG1 monoclonal antibody developed specifically as a treatment for COVID-19. It goes by the codename LY-CoV555. It is unapproved by the FDA, but authorized for emergency treatment of mild to moderate COVID-19. It is not authorized for use in severe COVID-19 or in hospitalized patients.[1]

In Canada

Bamlanivimab and **remdesivir** are currently the only COVID-19 treatments approved by Health Canada.

In a regulatory decision on November 20, 2020, Health Canada authorized bamlanivimab in an interim order for use in relation to the COVID-19 pandemic. "Bamlanivimab is indicated for the treatment of adults and pediatric patients 12 years of age or older with **mild to moderate** coronavirus disease 2019(COVID-19), who weigh at least 40 kg and who are at **high risk of progressing to severe** COVID-19 illness and/or hospitalization."[2]

However...

On January 11, 2021, the BC Ministry of Health rejected Health Canada's approval of bamlanivimab, citing a lack of published evidence, particularly regarding patient safety data.[3]

BLAZE-2: Press Release

January 21, 2021

Lilly's neutralizing antibody bamlanivimab (LY-CoV555) prevented COVID-19 at nursing homes in the BLAZE-2 trial, reducing risk by up to 80 percent for residents

Phase 3 multi-centre, double-blinded RCT (Part 1 exploratory analysis**)**	
Clinical Question	Does administration of bamlanivimab reduce the rate of symptomatic COVID-19 infections amongst all staff and residents in nursing homes with a high risk of COVID-19 exposure?
Participants	Residents or staff aged 18+ in a nursing home with at least 1 confirmed SARS-CoV-2 detection in previous 7 days • n = 965 participants with negative baseline COVID-19 test (299 residents, 666 staff) • n = 132 participants with positive baseline COVID-19 tests (41 residents, 91 staff)
Intervention	• Bamlanivimab 4200 mg IV x 1
Comparator	• Placebo IV x 1
Outcomes	[1°] Percentage of participants with COVID-19 within 21 days of detection (at 8 weeks) • **OR 0.43; p = 0.00021** • Pre-specified subgroup of nursing home residents **OR 0.20; p = 0.00026** • Serious adverse events: similar frequency to placebo

COVID-attributed deaths: 4, all in placebo

COVID-attributed deaths: 4, all in placebo

https://clinicaltrials.gov/ct2/show/NCT04497987

https://www.prnewswire.com/news-releases/lillys-neutralizing-antibody-bamlanivimab-ly-cov555-prevented-covid-19-at-nursing-homes-in-the-blaze-2-trial-reducing-risk-by-up-to-80-percent-for-residents-301212159.html

BLAZE-2: Press Release

Limitations:

- Preliminary reporting of exploratory analysis – no pre-print
  - Estimated study completion June 2021

Practical considerations:

- Administration to all staff/residents of a facility not aligned with NS procedures for LTC resident with COVID-19
  - RCU admission, vaccination of staff
  - Limited availability of pandemic supply of bamlanivimab

Suggest: no change to current bamlanivimab recommendation:

Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health-affiliated Regional Care Units.

BLAZE-1: Phase 3 Press Release

January 26, 2021

New data show treatment with Lilly's neutralizing antibodies bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016) together reduced risk of COVID-19 hospitalizations and death by 70 percent

Phase 3 multi-centre, double-blinded RCT	
Clinical Question	Does administration of bamlanivimab in combination with etesevimab in high-risk, recently diagnosed mild-mod COVID-19 prevent COVDI-19-related hospitalizations and death?
Participants	n = 1035 outpatients age ≥ 18, COVID-19 positive in past ≤ 3 days, 1 or more mild-moderate COVID-19 symptom AND have at least one high-risk factor
Intervention	• Bamlanivimab 2800 mg IV and etesevimab 2800 mg IV x 1
Comparator	• Placebo IV x 1
Outcomes	[1°] Percentage of participants with COVID-19-related hospitalization or all-cause death (by day 29) • **Intervention: 2.1% vs Placebo: 7.0%, p = 0.0004** • "Statistically significant key secondary endpoints" – symptom resolution, viral clearance, composite of hospitalization + ER visit + death

BLAZE-4: initial PK/PD results suggest lower bamlanivimab 700 mg /etesevimab 1400 mg doses together similar to 2800 mg doses

https://clinicaltrials.gov/ct2/show/NCT04427501

https://investor.lilly.com/news-releases/news-release-details/new-data-show-treatment-lillys-neutralizing-antibodies

BLAZE-1: Phase 3 Press Release

Limitations:

- Preliminary reporting – no pre-print
  - Results available for combination arm only

Practical considerations:

- Results suggest patient-important benefit similar to Phase 2 results

Suggest: no change to current bamlanivimab recommendation:

Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health-affiliated Regional Care Units.

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group

February 25, 2021

Agenda

- Minutes
- [redacted]
- Review recommendations:
  - [redacted]
    - Bamlanivimab
- Pandemic supply update

Minutes

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	February 4, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, Barbara Goodall, Glenn Cox, Amanda Porter, Kenneth Rockwood, Lisa Grandy Allen, Gabrielle Richard		

Items	Discussion
- Minutes	unrelated [redacted]
- unrelated [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
- unrelated [redacted]	[redacted]

unrelated

COVID-19 Therapeutics and Prophylactics Advisory Group: Recommendations

Recommendation	Medication	Notes
unrelated	[redacted]	[redacted]
Research	Bamlanivimab	Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units.
	unrelated	[redacted]
	[redacted]	[redacted]
[redacted]		
	[redacted]	
	[redacted]	
	[redacted]	

unrelated

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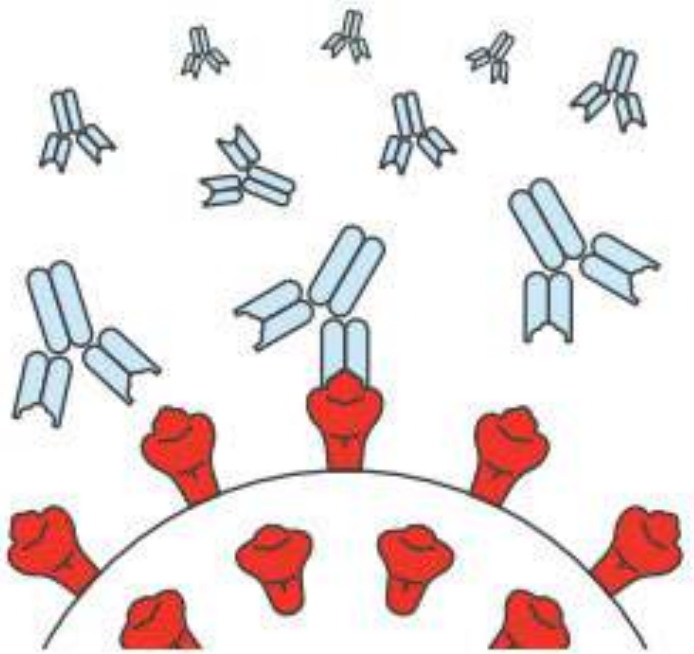
Bamlanivimab Update



Nova Scotia COVID-19 Therapeutics & Prophylaxis Advisory Group
Emma Reid
Feb 25, 2021

Bamlanivimab Update

- Discussed last meeting:

  BLAZE-1 Phase 3 preliminary results available via press release

  - In outpatients ≥ 12 with early mild-mod COVID-19 and ≥ 1 high risk factor for severe disease, the administration of bamlanivimab + etesevimab IV x 1 resulted in **reduced COVID-19-related hospitalization and all-cause death versus placebo (2.1% vs 7.0%, p = 0.0004)**

- Feb 9, 2021 – Emergency Use Authorization for bamlanivimab + etesevimab issued by FDA
  - Indicated in same population studied in BLAZE-1

FDA NEWS RELEASE

Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibodies for Treatment of COVID-19

https://investor.lilly.com/news-releases/news-release-details/new-data-show-treatment-lillys-neutralizing-antibodies

Health Canada

- Application for bamlanivimab + etesevimab approval under review Feb 16

Applications received related to the COVID-19 pandemic

Applicant	Medicinal ingredient(s)	Therapeutic area	Date application was received	Outcome of application	Date of decision/outcome
Eli Lilly Canada Inc	Bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016)	Immune sera and immunoglobulins, for human use	2021-02-16	Under review	n/a

unrelated

https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/authorization/applications.html

Bamlanivimab for Prophylaxis

- To date, BLAZE-2 findings shared in press release Jan 21 are only publicly available results
  - In nursing homes with at least one COVID-19 case in past 7 days, administering bamlanivimab 4200 mg IV x 1 to staff and residents resulted in reduced incidence of COVID-19 overall at 21 days
    - All participants OR 0.43, p = 0.00021
    - Subgroup of nursing home residents OR 0.20, p = 0.00026

https://clinicaltrials.gov/ct2/show/NCT04497987

https://www.prnewswire.com/news-releases/lillys-neutralizing-antibody-bamlanivimab-ly-cov555-prevented-covid-19-at-nursing-homes-in-the-blaze-2-trial-reducing-risk-by-up-to-80-percent-for-residents-301212159.html

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group

January 28, 2021

Agenda

- Minutes
- [redacted], Bamlanivimab: Review previous recommendation

unrelated

unrelated

[redacted]

unrelated

[redacted]

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Bamlanivimab

Recommendation Review

- Bamlanivimab:
  - Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health-affiliated Regional Care Units.

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group

May 6, 2021

Agenda

- Minutes

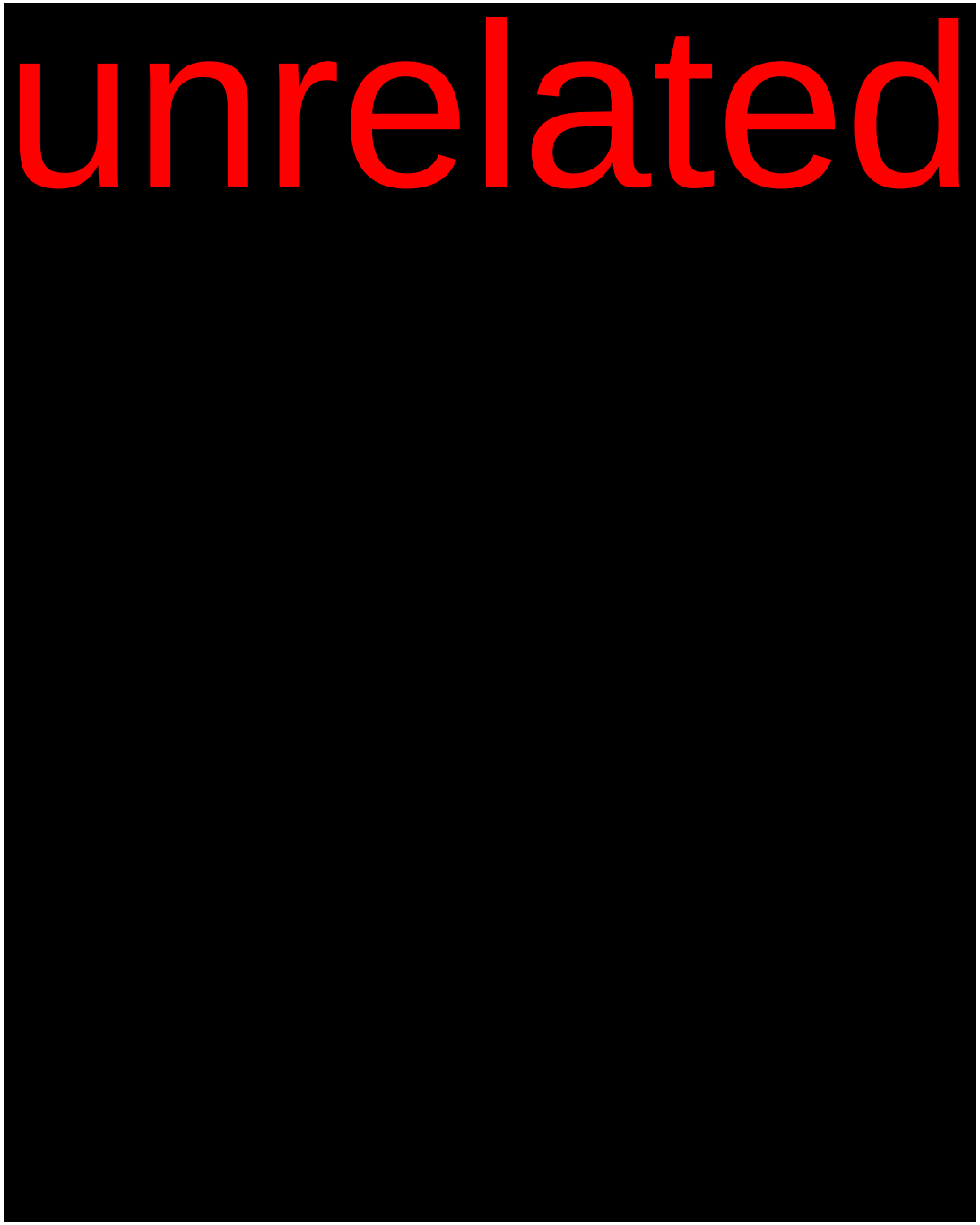
- Pandemic supply update

Minutes

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	April 22, 2021	**Meeting Time**	0800-0900
Present	**Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, , Gabrielle Richard, Lisa Grandy Allen, Kenneth Rockwood**		

Items	Discussion
[redacted]	[redacted]
Review recommendations: - **Bamlanivimab** [redacted]	**Bamlanivimab** – s. 14(1) [redacted]. Note that CATCO-NOS was the study intended to operationalize bamlanivimab use here locally – population in protocol is people who acquire COVID-19 in hospital. - Lisa led discussion: CATCO is changing rapidly all the time. Challenges with CATCO-NOS which looks like nosocomial in-hospital population, but intended population was instead people needing hospitalization. s.14(1) [redacted] Meeting attendees agreed that our current recommendation should be updated to reflect offering bamlanivimab as an option for those who are at high risk for clinical deterioration due to previous risk factors. Current recommendation: *Bamlanivimab to be used in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units.* **Updated recommendation: *Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19*:** • ***65 years of age and older in NS Health affiliated Regional Care Units OR*** • ***18 years of age and older hospitalized for other reasons at high risk for progression (e.g.: early transplant)*** unrelated [redacted]

unrelated



Recommendation Review

NS Health COVID-19 Medication Recommendations

Recommendation	Medication	Notes
unrelated	[redacted]	[redacted]
Research	Bamlanivimab	Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19: • 65 years of age and older in NS Health affiliated Regional Care Units OR • 18 years of age and older hospitalized for other reasons at high risk for progression (e.g.: early transplant)
	unrelated	[redacted]
	[redacted]	[redacted]
[redacted]		
	[redacted]	
	[redacted]	
	[redacted]	

unrelated

unrelated

[redacted]

unrelated

[redacted]

unrelated

[redacted]

unrelated [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

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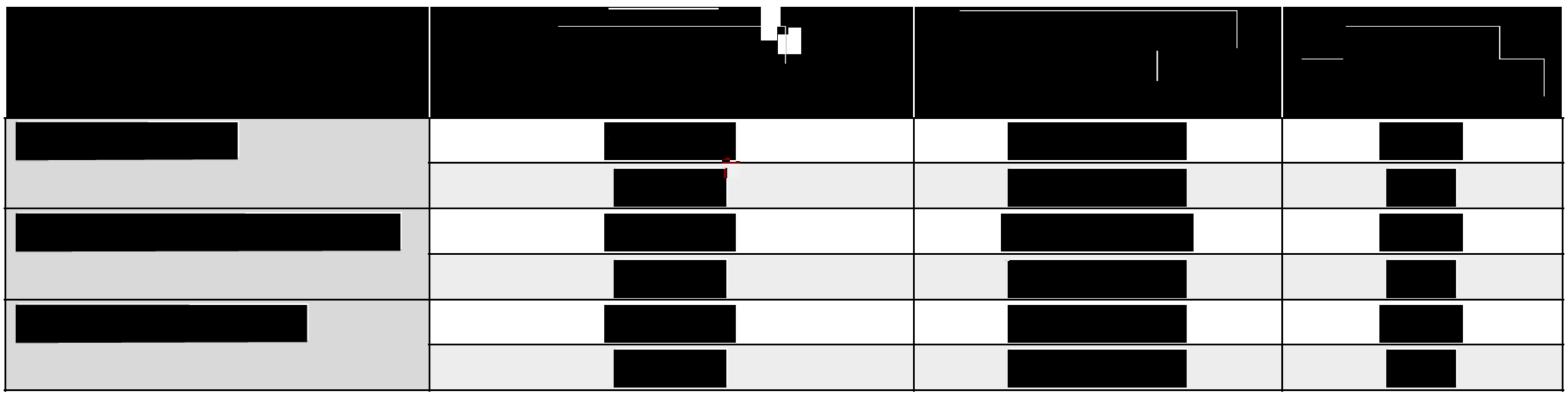
unrelated

[redacted]



[redacted]

unrelated

[redacted]

[redacted]

unrelated

[redacted]

unrelated

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]


unrelated


unrelated


unrelated

NS Health COVID-19 Medication Recommendations

Recommendation	Medication	Notes
unrelated	[redacted]	[redacted]
Research	Bamlanivimab	Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19: • 65 years of age and older in NS Health affiliated Regional Care Units OR • 18 years of age and older hospitalized for other reasons at high risk for progression (e.g.: early transplant)
	unrelated	[redacted]
	[redacted]	[redacted]
[redacted]		
	[redacted]	
	[redacted]	
	[redacted]	

Pandemic Supply Update

NS Health COVID-19 Medication Recommendations

Recommendation	Medication	Notes
Routine Care	unrelated	[redacted]
Research 50 vials	Bamlanivimab	Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19: • 65 years of age and older in NS Health affiliated Regional Care Units OR • 18 years of age and older hospitalized for other reasons at high risk for progression (e.g.: early transplant)
unrelated	unrelated	[redacted]
unrelated	[redacted]	[redacted]
[redacted]		
	[redacted]	
	[redacted]	
	[redacted]	

Bamlanivimab

What is it?

- A monoclonal antibody that attaches to the spike protein on the SARS-CoV-2 virus, preventing entry into cells. Also known as a "neutralizing antibody". By reducing viral load, may prevent worsening of COVID-19 symptoms and reduce severity of illness.
- Given as a one-time intravenous (IV) infusion soon after COVID-19 diagnosis.

On November 20, 2020 bamlanivimab was **authorized for use by Health Canada with terms and conditions**: e.g., it may be used within the context of a clinical trial to collect ongoing evidence of efficacy and safety

Health Canada Indication:	Patients ≥ 12 years of age (≥40 kg) with **mild to moderate COVID-19 at *high risk of progressing to severe COVID-19 illness and/or hospitalization**

***High risk**: meets one or more of

- ≥ 65 years old
- BMI ≥ 35 for adults
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or receiving immunosuppressive treatment
- ≥ 55 years old AND any of: cardiovascular disease, hypertension, or chronic respiratory disease
- 12-17 years of age AND have any of: BMI ≥ 85th percentile for age/gender, sickle cell disease, congenital or acquired heart disease, neurodevelopmental disorders (e.g., cerebral palsy), a medical-related technological dependence (e.g., tracheostomy), asthma or other chronic respiratory disease

Evidence: limited to **a single Phase II RCT** currently ongoing in 41 centres in the United States, BLAZE-1:[2]

- Included 452 non-hospitalized patients (≥ 18 years of age) with recently diagnosed mild to moderate COVID-19. Approx. 69% of patients had risk factors for severe COVID-19.
  - Randomized to: one dose bamlanivimab IV at one of three doses (700 mg, 2800 mg, 7000 mg) or placebo.
- A pre-planned **interim analysis** is published. Key findings:

Potential Benefits	Potential Harms
• **Fewer hospitalizations:** 1.6% (5/309) bamlanivimab^ vs 6.3% (9/143) placebo required hospitalization by day 29 **(no statistical comparison provided).** **Number needed to treat (NNT):** For every 22 patients with mild-mod COVID-19 who receive bamlanivimab, one hospitalization will be prevented by 29 days versus placebo. • **COVID-19 symptoms:** may be reduced *slightly* more quickly with bamlanivimab^ than placebo (clinically meaningful?) • **Viral clearance:** 2800 mg dose of bamlanivimab associated with higher viral clearance at day 11 vs placebo. No difference with 700 mg and 7000 mg doses, nor with all bamlanivimab doses pooled vs placebo.	• **More infusion-related reactions (pruritis, flushing, rash, facial swelling):** 2.3% (7/309) bamlanivimab^ vs 1.4% (2/143) placebo **(no statistical comparison provided).** All classified as mild; no reactions prevented dose completion. **Number needed to harm (NNH):** For every 111 patients with mild-mod COVID-19 who receive bamlanivimab, one additional infusion reaction will occur versus placebo. • **Other adverse events:** similar rates (bamlamivimab^ vs placebo): nausea (3.9% vs 3.5%), diarrhea (3.2% vs 4.9%), dizziness (3.2% vs 2.1%), headache (1.6% vs 2.1%). • **No difference in serious adverse events (SAE):** 0% bamlanivimab^ vs 0.7% (1/143) placebo

^ Pooled data from all Bamlanivimab arms (700 mg, 2800 mg, 7000 mg)

Infectious Diseases Society of America (IDSA): recommends against routine use of bamlanivimab in ambulatory patients given uncertainty of evidence. Reasonable option in high-risk patients after informed decision-making.[3]

Canadian Agency for Drugs and Technology in Health (CADTH): recognizes evidence limitations and suggests decision makers weigh uncertainties and potential risks against potential value of bamlanivimab in symptomatic patients at high risk of severe COVID-19.[4]

Practical Considerations

- No cost-effectiveness analysis is available at this time.
- Product must come to room temp before mixing (~20 min), requires approx. 5 min for product preparation, 1 hour for administration, and 1 hour afterwards to monitor for reaction.
- Staff administering bamlanivimab should be capable of managing anaphylaxis and infusion reactions.
- In theory, maximal benefit achieved if administered as early as possible in infection course (?bringing outpatients to a clinic when at highest risk of viral shedding).

References:

1. Bamlanivimab product monograph. Toronto (ON): Eli Lilly Canada Inc; Accessed 2020 December 2
2. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med 2020: Available at: https://doi.org/10.1056/nejmoa2029849 [Epub ahead of print]. Accessed 2020 December 1.
3. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious diseases Society of America guidelines on the treatment and management of patients with COVID-19. Updated November 2020: Available at: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-10 . Accessed 2020 December 2
4. Bamlanivimab in the treatment of outpatients with COVID-19: a critical appraisal of the BLAZE-1 trial. Ottawa: CADTH; December 2020. (CADTH Health Technology Review).

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3. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious diseases Society of America guidelines on the treatment and management of patients with COVID-19. Updated November 2020: Available at: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-10 . Accessed 2020 December 2
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Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	December 17, 2020	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Gabrielle Richard, Emma Reid, Barbara Goodall, Glenn Cox, Lisa Grandy Allen		

Items	Discussion
- **Review Minutes**	unrelated [redacted]
- **Bamlanivimab: role in therapy and implementation strategies**	Reviewed the COVID Network request for the Therapeutics and Prophylactics Advisory Group to provide information on unrelated [redacted], and bamlanivimab and suggestions about how bamlanivimab could potentially be implemented. Kathleen confirmed the province of Nova Scotia will receive 50 doses of bamlanivimab at the end of the month. Bamlanivimab discussion: - Lisa presented information on the progression of COVID-19 and the role of different treatments within the different stages. Targeting the pre-cellular entry stage may have effect beyond just the individual with infection, as it can impact infectivity and transmission risk. - Emma presented on the BLAZE-1 trial including a focus on methods and generalizability in the context of the Health Canada Interim Order authorization of bamlanivimab. Discussion followed around interpretation of BLAZE-1 results: [redacted] s.14(1) [redacted] Discussed public health considerations around administration, s.14(1) [redacted] Other thoughts: s.14(1) [redacted] To provide sufficient time for the bamlanivimab discussion, an additional one-hour meeting for December 18 was scheduled.
- **CO-VIC** [redacted]	Barb presented initial slides with background information on the pragmatic CO-VIC study. Presentation and discussion will continue Dec 18 meeting. **Action item: B. Goodall to provide slides to Tasha for distribution before Dec 18 meeting.**
[redacted]	[redacted]

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group

March 11, 2021

Agenda

- Minutes
- unrelated [redacted]
- Review recommendations:
  - Bamlanivimab
  - unrelated [redacted]
- Pandemic supply update

Minutes

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	February 25, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, Amanda Porter, Gabrielle Richard, Lisa Grandy Allen		

Items	Discussion
- **Minutes**	unrelated [redacted]
[redacted]	[redacted]
- **Review recommendations** - unrelated [redacted] **bamlanivimab**	unrelated [redacted] Addressed bamlanivimab: the prophylaxis in long term care discussion planned with stakeholders like Dr. Johnston, Dr. Rockwood, will occur March 9th s.14(1) [redacted] ill revisit this discussion after the meeting.

unrelated

unrelated

unrelated

Health Canada

Applications received related to the COVID-19 pandemic

Applicant	Medicinal ingredient(s)	Therapeutic area	Date application was received	Outcome of application	Date of decision/outcome
[redacted]					
Eli Lilly Canada Inc	Bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016)	Immune sera and immunoglobulins, for human use	2021-02-16	Under review	n/a

unrelated

unrelated

https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/authorization/applications.html


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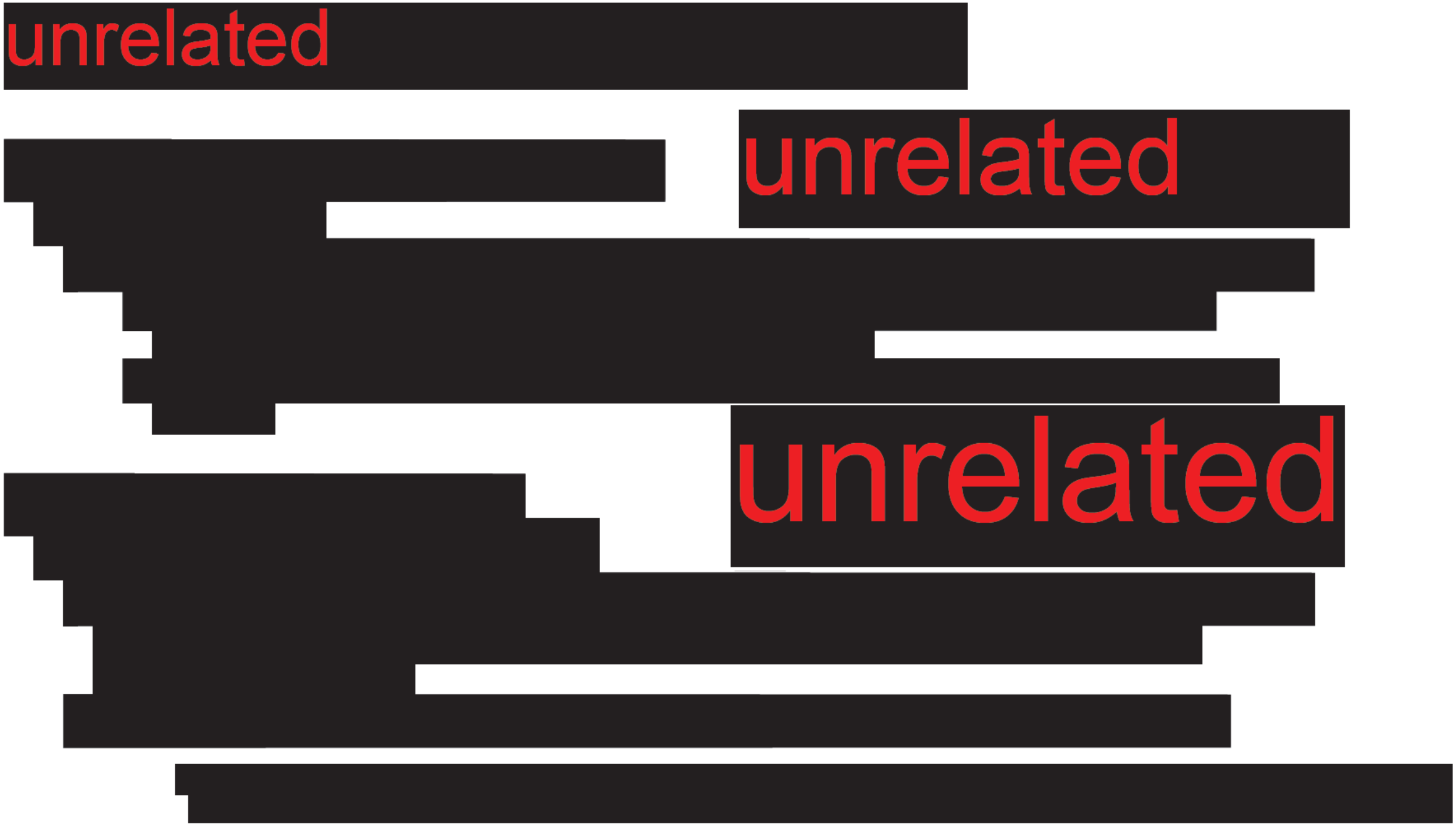
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COVID-19 Therapeutics and Prophylactics Advisory Group: Recommendations

Recommendation	Medication	Notes
unrelated	[redacted]	[redacted]
Research	Bamlanivimab	Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units.
	unrelated	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	
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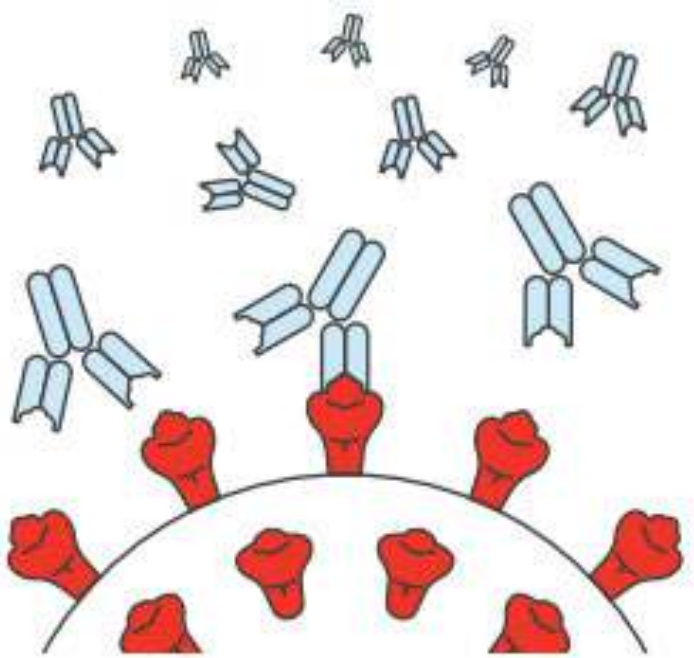
Bamlanivimab for COVID-19



Nova Scotia COVID-19 Therapeutics & Prophylaxis Advisory Group

Emma Reid

December 17, 2020

Monoclonal Antibodies

- Mechanisms:
  - Bind SARS-CoV-2 and flag for destruction
  - Bind SARS-CoV-2 spike protein on infected cell surface and flag for destruction
  - Block SARS-CoV-2 spike protein binding and prevent infection
    - Also known as: neutralizing antibodies

Monoclonal Antibodies

Monoclonal Antibody	Trial Stage	Study Population	Comment
Bamlanivimab (LY-CoV555)	Phase 3	Treatment (non-severe at high risk of progression) and prevention (LTC)	Health Canada approved interim order for treatment in non-severe at high risk of progression
unrelated			

Note: all bind to the S protein, thereby preventing the virus from binding to the host cell

Bamlanivimab: Mechanism

- Monoclonal antibody: targets SARS-CoV-2 spike protein preventing viral attachment and cell entry
  - ↓ viral replication → ↓ severity of illness

Adapted from Lilly Bamlanivimab Antibody Playbook, 2020

BLAZE-1: Overview

- Study started June 2020, recruitment ongoing
  - 25 amended versions of study report on clinicaltrials.gov

Protocol June 19, 2020

Treatment arms	LY3819253
1	placebo
2	700 mg
3	2800 mg
4	7000 mg

Planned sample size n = 400

Interim analysis

N ENGL J MED

Protocol July 31, 2020

Treatment arms	Dose	Intervention
1	---	placebo
2	700 mg	LY3819253
3	2800 mg	LY3819253
4	7000 mg	LY3819253
5	To Be Determined	LY3819253
6	2800 mg + 2800 mg	LY3819253+LY3832479
7	To Be Determined	LY3819253+LY3832479

Planned sample size n = 500

LY3819253 = Bamlanivimab
LY3832479 = Another investigational neutralizing mAb

Clinicaltrials.gov NCT04427501
BLAZE-1 Protocol

BLAZE-1: Interim Report

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Multi-centre, double-blind, Phase II RCT (41 sites USA)	
Patients	n = 452 outpatients age ≥ 18, COVID-19 positive in past ≤ 3 days, 1 or more mild-moderate COVID-19 symptom • Median age 45, 12% above 65, 55% female, 86% white, median 4 days since symptom onset • 44% BMI ≥30 (obese), 69% had risk factors for severe disease*, > 80% mild symptoms
Interventions	• Bamlanivimab 700 mg, 2800 mg, or 7000 mg IV x 1
Comparator	• Placebo infusion IV x 1
Outcomes (as specified at time of publication)	• [1°] Change from baseline in viral load via naso-pharyngeal (NP) swab (Day 11) • [2°] Safety: SAEs, AEs • [2°] Symptom severity • [2°] Hospitalization, ER visit, death • [2°] Viral load/clearance at various timepoints • [2°] PK: concentration of study drugs at various timepoints

Median: 4 days after symptom onset

*Risk factors for severe disease: Age 65+, BMI 35+, or at least one coexisting illness in certain pre-specified category (unclear what)

N Engl J Med 2020: https://doi.org/10.1056/nejmoa2029849

BLAZE-1: Interim Results - Efficacy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

	Bamlanivimab 700 mg (n = 101) Bamlanivimab 2800 mg (n = 107) Bamlanivimab 7000 mg (n = 101) Bamlanivimab pooled (n = 309)	Placebo (n = 143)	Difference from placebo (95% CI)
[1°] Mean change from baseline in log viral load at Day 11	• **700 mg:** -3.67 • **2800 mg:** -4.00 • **7000 mg:** -3.38 • **Pooled:** -3.70	-3.47	• -0.20 (-0.66 to 0.25) p = 0.38 • -0.53 (-0.98 to -0.08) p = 0.02** • 0.09 (0.09 to 0.55) p = 0.70 • -0.22 (-0.6 to 0.15) p = not provided
[2°] Hospitalization by Day 29 (%)	• **700 mg:** 1 (1.0%) • **2800 mg:** 2 (1.9%) • **7000 mg:** 2 (2.0%) • **Pooled:** 5 (1.6%)	9 (6.3%)	• *ARR 5.3%* • *ARR 4.4%* • *ARR 4.3%* • *ARR 4.7%* *NNT 19 to 24*
[Post hoc subgroup] Hospitalization by Day 29 (%)	**(n = 95)**	**Patients ≥65 or BMI ≥35 (n = 48)**	
	4 (4.2%)	7 (14.6%)	• *ARR 10.4%* *NNT 10*

** statistically significant

N Engl J Med 2020: https://doi.org/10.1056/nejmoa2029849

BLAZE-1: Interim Results - Efficacy

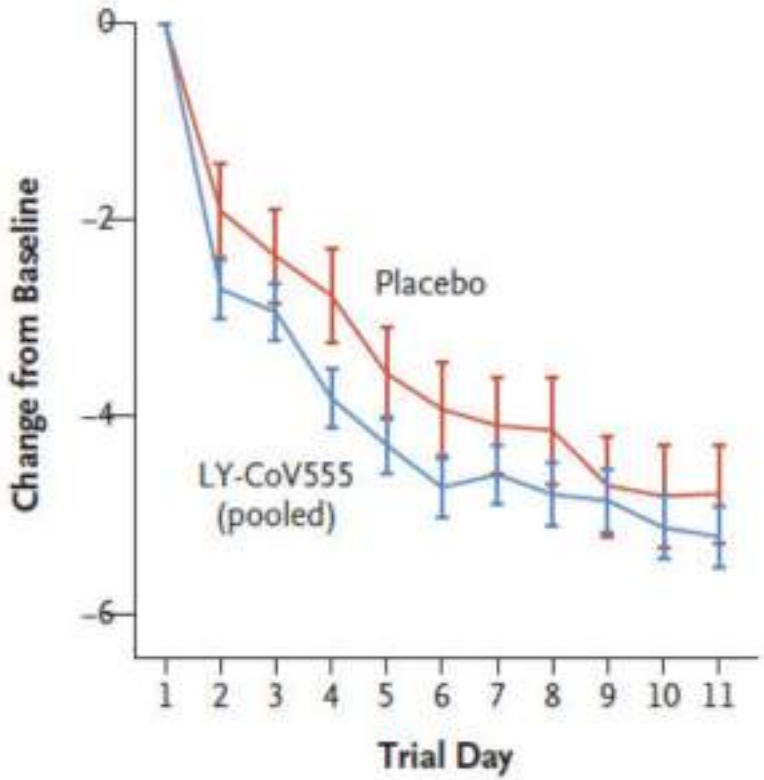
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

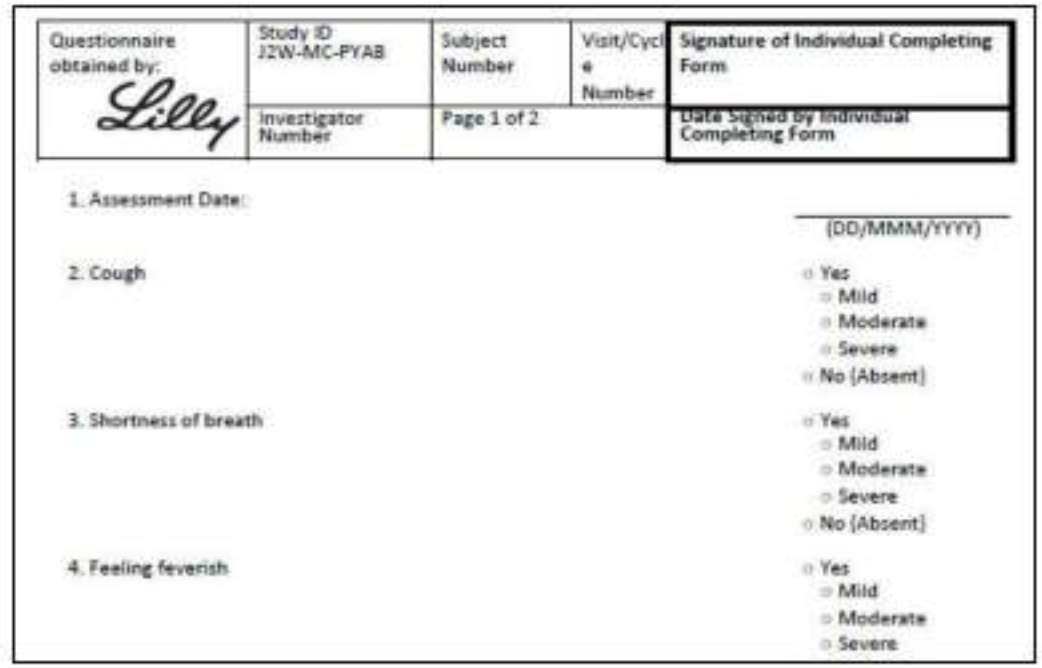
[2°] Mean daily change in symptom score (Days 2 to 11)

Bamlanivimab pooled only vs placebo



	Delta Value (95% CI)
Day 2	−0.79 (−1.35 to −0.24)**
Day 3	−0.57 (−1.12 to −0.01)**
Day 4	−1.04 (−1.60 to −0.49)**
Day 5	−0.73 (−1.28 to −0.17)**
Day 6	−0.79 (−1.35 to −0.23)**
Day 7	−0.50 (−1.06 to 0.07)
Day 8	−0.65 (−1.28 to −0.02)**
Day 9	−0.15 (−0.75 to 0.45)
Day 10	−0.32 (−0.94 to 0.29)
Day 11	−0.44 (−1.02 to 0.15)

** statistically significant



Questionnaire obtained by: Lilly	Study ID J2W-MC-PYAB	Subject Number	Visit/Cycle Number	Signature of Individual Completing Form
	Investigator Number	Page 1 of 2		Date Signed by Individual Completing Form

1. Assessment Date: _____ (DD/MMM/YYYY)

2. Cough
- Yes
  - Mild
  - Moderate
  - Severe
- No (Absent)

3. Shortness of breath
- Yes
  - Mild
  - Moderate
  - Severe
- No (Absent)

4. Feeling feverish
- Yes
  - Mild
  - Moderate
  - Severe

24-point questionnaire with 8 symptoms (No symptoms = 0, mild symptoms = 1, mod symptoms = 2, severe symptoms = 3)

N Engl J Med 2020: https://doi.org/10.1056/nejmoa2029849

BLAZE-1: Interim Results - Safety

The NEW ENGLAND JOURNAL of MEDICINE

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[2°] Serious Adverse Events (SAEs) (%)	• **700 mg:** 0 (0%) • **2800 mg:** 0 (0%) • **7000 mg:** 0 (0%) • **Pooled:** 0 (0%)	1 (0.7%)	• No statistical comparison provided
[2°] Adverse Events (AEs) – Any (%)	• **700 mg:** 24 (23.8%) • **2800 mg:** 23 (21.5%) • **7000 mg:** 22 (21.8%) • **Pooled:** 69 (22.3%)	35 (24.5%)	• No statistical comparison provided
Infusion-Related reaction	• **Pooled:** 7 (2.3%)	2 (1.4%)	• *ARI 0.9%* *NNH 111*

Nausea, vomiting, diarrhea, dizziness, headache

N Engl J Med 2020: https://doi.org/10.1056/nejmoa2029849

Bamlanivimab: Health Canada Interim Order Indication

- Patients ≥ 12 years of age (≥40 kg) with mild to moderate COVID-19 at *<u>high risk</u> of progressing to severe COVID-19 illness and/or hospitalization

BLAZE-1 Interim Analysis inclusion: outpatients age ≥ 18, COVID-19 positive in past ≤ 3 days, 1 or more mild-moderate COVID-19 symptom

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*<u>High risk</u>: meets one or more of

- ≥ 65 years old
- BMI ≥ 35 for adults
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or receiving immunosuppressive treatment
- ≥ 55 years old AND any of: cardiovascular disease, hypertension, or chronic respiratory disease
- 12-17 years of age AND have any of: BMI ≥ 85th percentile for age/gender, sickle cell disease, congenital or acquired heart disease, neurodevelopmental disorders (e.g., cerebral palsy), a medical-related technological dependence (e.g., tracheostomy), asthma or other chronic respiratory disease

Health Canada Interim Order https://covid-vaccine.canada.ca/bamlanivimab/product-details

BLAZE-1: Overview

ClinicalTrials.gov

- **Registry amendment Nov 9, 2020**

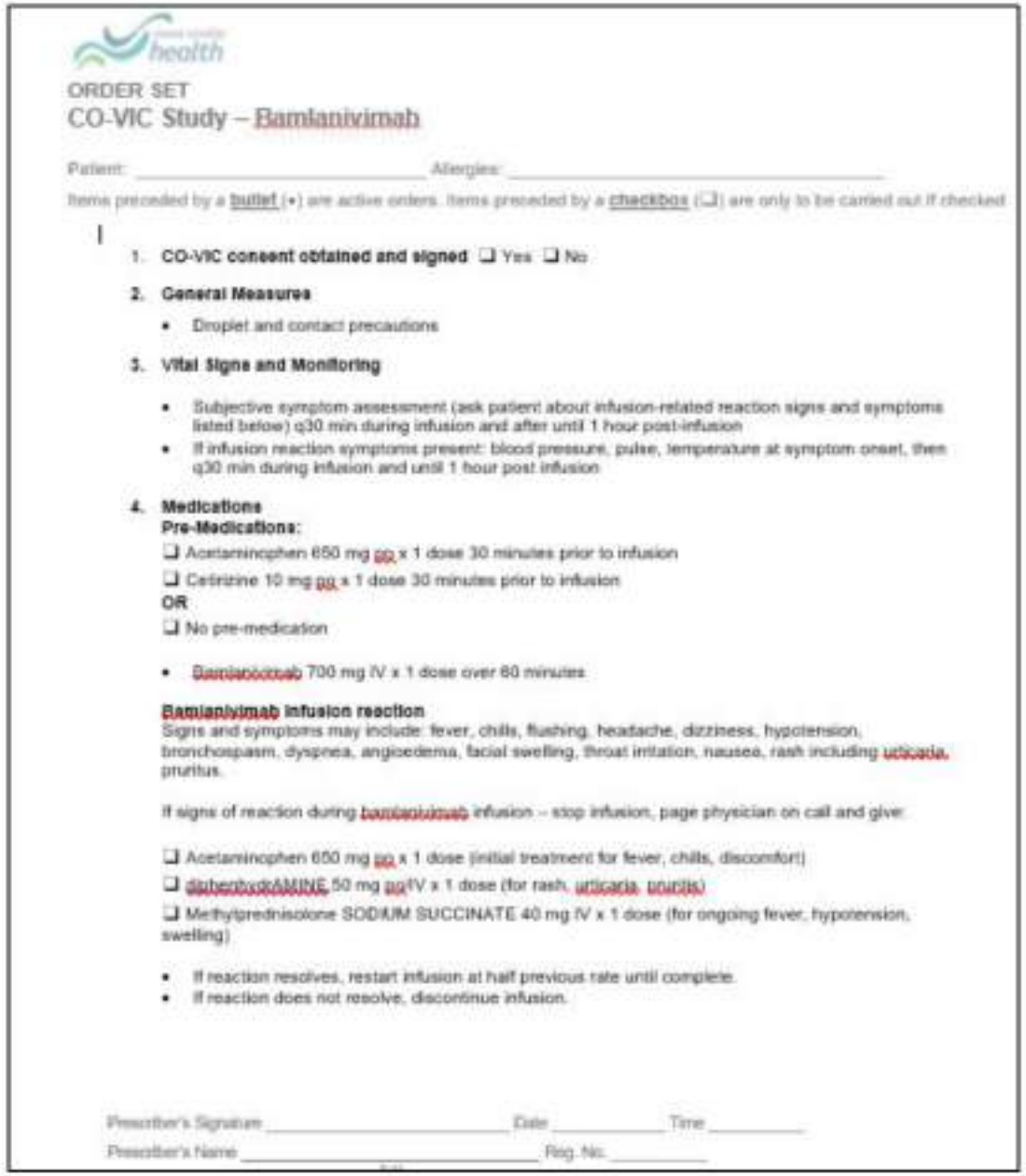
Participants in treatment arms 7 and 8 ONLY

- *Are greater than or equal to (≥)18 years of age and must satisfy at least one of the following at the time of screening*
  - *≥65 years old*
  - *BMI ≥35*
  - *Chronic kidney disease (CKD)*
  - *Type 1 or type 2 diabetes*
  - *Have immunosuppressive disease* or *receiving immunosuppressive treatment*
  - *Are ≥55 years of age AND have: cardiovascular disease, OR hypertension, OR chronic respiratory disease*
- *Are 12-17 years of age (inclusive) AND satisfy at least one of the following at the time of screening*
  - *BMI ≥85th percentile for their age and gender*
  - *Sickle cell disease*
  - *Congenital or acquired heart disease*
  - *Neurodevelopmental disorders, for example, cerebral palsy*
  - *Medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)*
  - *Asthma or reactive airway or other chronic respiratory disease*
  - *Type 1 or type 2 diabetes*
  - *Have immunosuppressive disease, or receiving immunosuppressive treatment*

Clinicaltrials.gov NCT04427501

Practical Considerations

- One-time IV dose: ~2.5 hours from start of prep to end of recommended monitoring
- Preparing for and managing infusion reactions, potential for anaphylaxis
- Logistics of infusion clinic: location, infection control, staffing
- Clinic options:
  - NS Health
    - New or existing outpatient clinic
  - Contract out to private infusion clinic



health

ORDER SET

CO-VIC Study – Bamlanivimab

Patient: _____ Allergies: _____

Items preceded by a bullet (•) are active orders. Items preceded by a checkbox (❑) are only to be carried out if checked

1. **CO-VIC consent obtained and signed** ❑ Yes ❑ No
2. **General Measures**
   - Droplet and contact precautions
3. **Vital Signs and Monitoring**
   - Subjective symptom assessment (ask patient about infusion-related reaction signs and symptoms listed below) q30 min during infusion and after until 1 hour post-infusion
   - If infusion reaction symptoms present: blood pressure, pulse, temperature at symptom onset, then q30 min during infusion and until 1 hour post infusion
4. **Medications**

Pre-Medications:

❑ Acetaminophen 650 mg po x 1 dose 30 minutes prior to infusion

❑ Cetirizine 10 mg po x 1 dose 30 minutes prior to infusion

OR

❑ No pre-medication

- Bamlanivimab 700 mg IV x 1 dose over 60 minutes

Bamlanivimab infusion reaction

Signs and symptoms may include: fever, chills, flushing, headache, dizziness, hypotension, bronchospasm, dyspnea, angioedema, facial swelling, throat irritation, nausea, rash including urticaria, pruritus.

If signs of reaction during bamlanivimab infusion – stop infusion, page physician on call and give:

❑ Acetaminophen 650 mg po x 1 dose (initial treatment for fever, chills, discomfort)

❑ diphenhydrAMINE 50 mg po/IV x 1 dose (for rash, urticaria, pruritis)

❑ Methylprednisolone SODIUM SUCCINATE 40 mg IV x 1 dose (for ongoing fever, hypotension, swelling)

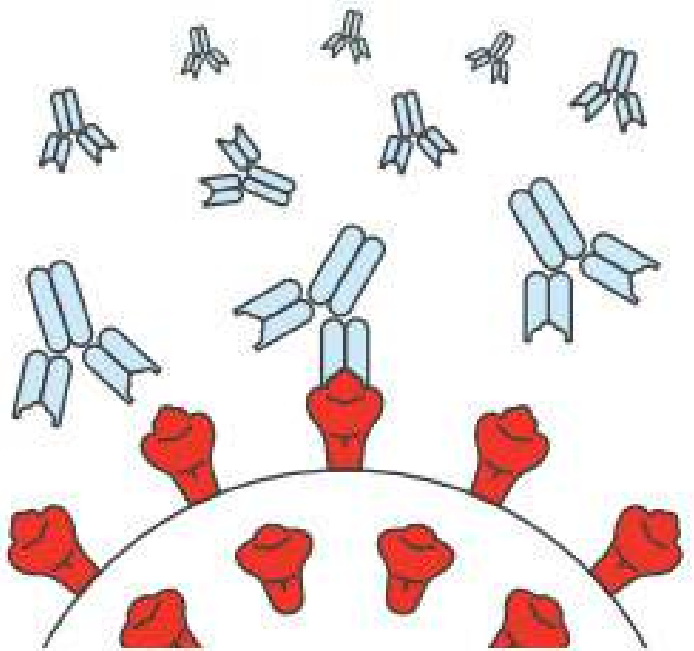
- If reaction resolves, restart infusion at half previous rate until complete.
- If reaction does not resolve, discontinue infusion.

Prescriber's Signature _____ Date _____ Time _____

Prescriber's Name _____ Reg. No. _____

Discussion

Bamlanivimab for COVID-19



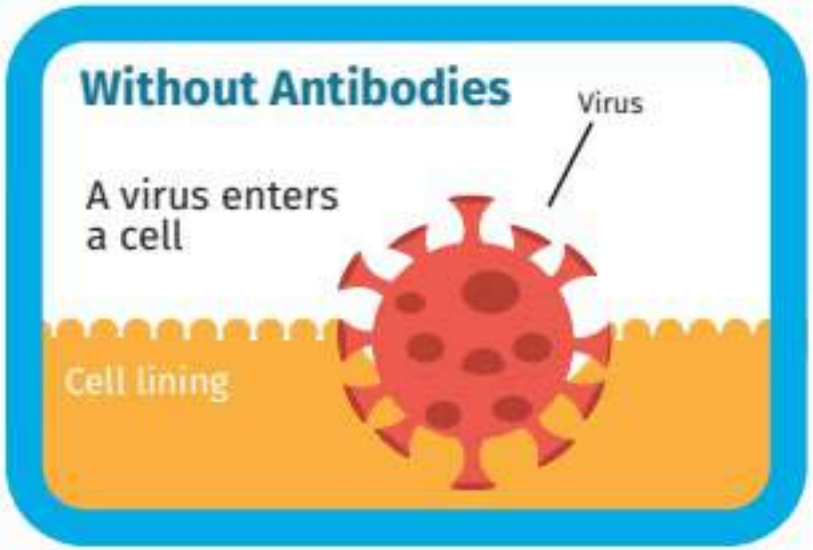
Nova Scotia COVID-19 Therapeutics & Prophylaxis Advisory Group

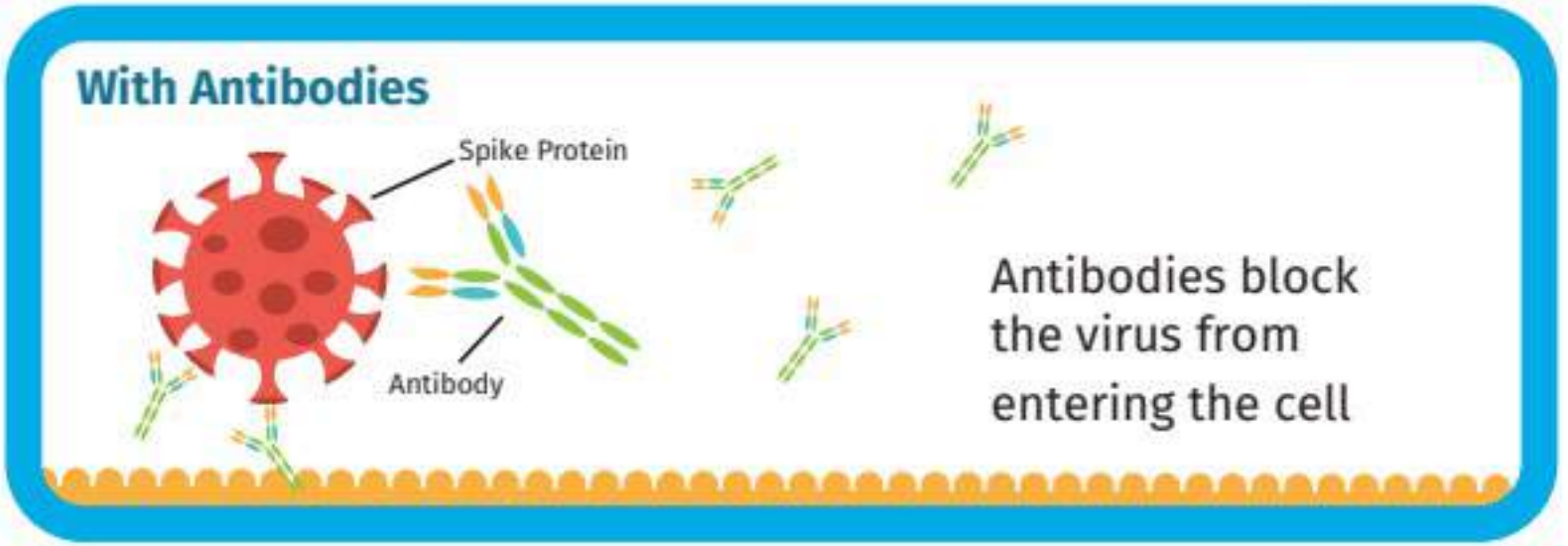
Emma Reid

December 17, 2020

Bamlanivimab: Mechanism

- Monoclonal antibody: targets SARS-CoV-2 spike protein preventing viral attachment and cell entry
  - ↓ viral replication → ↓ severity of illness





Adapted from Lilly Bamlanivimab Antibody Playbook, 2020

Other Monoclonal Antibodies

BLAZE-1: Overview

- Study started June 2020, recruitment ongoing
  - 25 amended versions of study report on clinicaltrials.gov

Protocol June 19, 2020

Treatment arms	LY3819253
1	placebo
2	700 mg
3	2800 mg
4	7000 mg

Planned sample size n = 400

Interim analysis

N ENGL J MED

Protocol July 31, 2020

Treatment arms	Dose	Intervention
1	---	placebo
2	700 mg	LY3819253
3	2800 mg	LY3819253
4	7000 mg	LY3819253
5	To Be Determined	LY3819253
6	2800 mg + 2800 mg	LY3819253+LY3832479
7	To Be Determined	LY3819253+LY3832479

Planned sample size n = 500

LY3819253 = Bamlanivimab
LY3832479 = Another investigational neutralizing mAb

Clinicaltrials.gov NCT04427501
BLAZE-1 Protocol

BLAZE-1: Interim Report

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Multi-centre, double-blind, Phase II RCT (41 sites USA)	
Patients	n = 452 outpatients age ≥ 18, COVID-19 positive in past ≤ 3 days, 1 or more mild-moderate COVID-19 symptom • Median age 45, 12% above 65, 55% female, 86% white, median 4 days since symptom onset • 44% BMI ≥30 (obese), 69% had risk factors for severe disease*, > 80% mild symptoms
Interventions	• Bamlanivimab 700 mg, 2800 mg, or 7000 mg IV x 1
Comparator	• Placebo infusion IV x 1
Outcomes (as specified at time of publication)	• [1°] Change from baseline in viral load via naso-pharyngeal (NP) swab (Day 11) • [2°] Safety: SAEs, AEs • [2°] Symptom severity • [2°] Hospitalization, ER visit, death • [2°] Viral load/clearance at various timepoints • [2°] PK: concentration of study drugs at various timepoints

Median: 4 days after symptom onset

*Risk factors for severe disease: Age 65+, BMI 35+, or at least one coexisting illness in certain pre-specified category (unclear what)

N Engl J Med 2020: https://doi.org/10.1056/nejmoa2029849

BLAZE-1: Interim Results - Efficacy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

	Bamlanivimab 700 mg (n = 101) Bamlanivimab 2800 mg (n = 107) Bamlanivimab 7000 mg (n = 101) Bamlanivimab pooled (n = 309)	Placebo (n = 143)	Difference from placebo (95% CI)
[1°] Mean change from baseline in log viral load at Day 11	• **700 mg:** -3.67 • **2800 mg:** -4.00 • **7000 mg:** -3.38 • **Pooled:** -3.70	-3.47	• -0.20 (-0.66 to 0.25) p = 0.38 • -0.53 (-0.98 to -0.08) p = 0.02** • 0.09 (0.09 to 0.55) p = 0.70 • -0.22 (-0.6 to 0.15) p = not provided
[2°] Hospitalization by Day 29 (%)	• **700 mg:** 1 (1.0%) • **2800 mg:** 2 (1.9%) • **7000 mg:** 2 (2.0%) • **Pooled:** 5 (1.6%)	9 (6.3%)	• *ARR 5.3%* • *ARR 4.4%* • *ARR 4.3%* • *ARR 4.7%* *NNT 19 to 24*
[Post hoc subgroup] Hospitalization by Day 29 (%)	**(n = 95)**	**Patients ≥65 or BMI ≥35 (n = 48)**	
	4 (4.2%)	7 (14.6%)	• *ARR 10.4%* *NNT 10*

** statistically significant

N Engl J Med 2020: https://doi.org/10.1056/nejmoa2029849

BLAZE-1: Interim Results - Efficacy

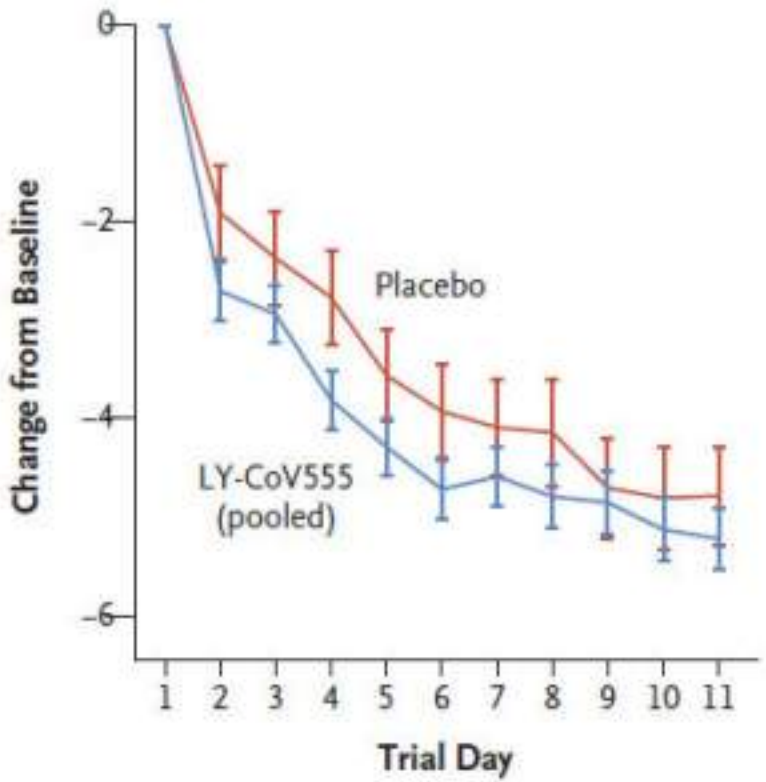
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

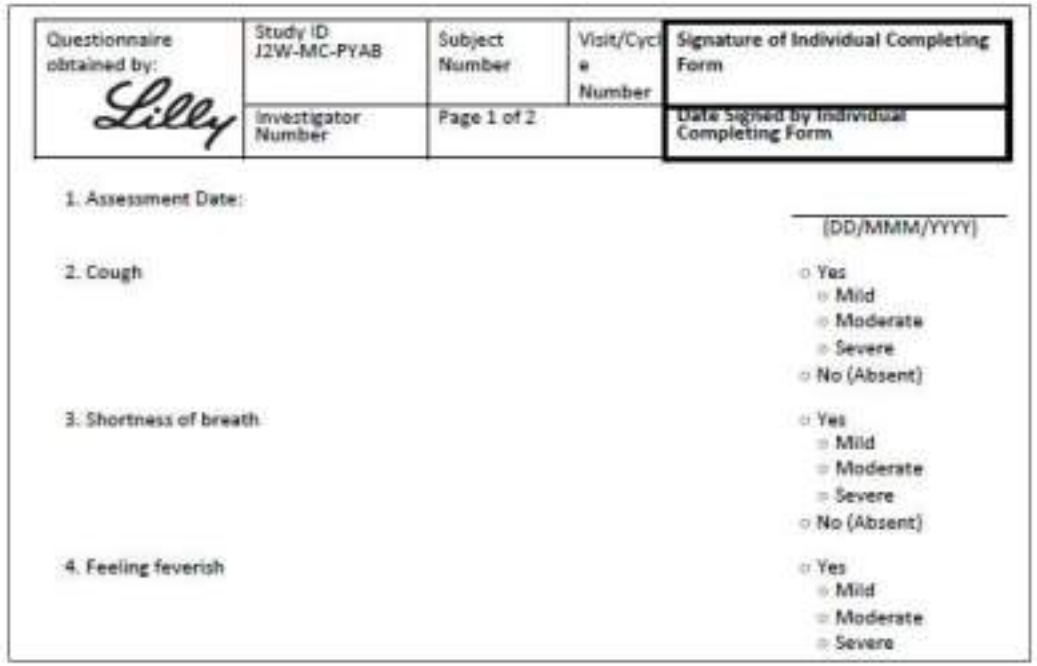
[2°] Mean daily change in symptom score (Days 2 to 11)

Bamlanivimab pooled only vs placebo



	Delta Value (95% CI)
Day 2	−0.79 (−1.35 to −0.24)**
Day 3	−0.57 (−1.12 to −0.01)**
Day 4	−1.04 (−1.60 to −0.49)**
Day 5	−0.73 (−1.28 to −0.17)**
Day 6	−0.79 (−1.35 to −0.23)**
Day 7	−0.50 (−1.06 to 0.07)
Day 8	−0.65 (−1.28 to −0.02)**
Day 9	−0.15 (−0.75 to 0.45)
Day 10	−0.32 (−0.94 to 0.29)
Day 11	−0.44 (−1.02 to 0.15)

** statistically significant



Questionnaire obtained by: Lilly	Study ID J2W-MC-PYAB	Subject Number	Visit/Cycle Number	Signature of Individual Completing Form
	Investigator Number	Page 1 of 2		Date Signed by Individual Completing Form

1. Assessment Date: _____ (DD/MMM/YYYY)

2. Cough
- Yes
  - Mild
  - Moderate
  - Severe
- No (Absent)

3. Shortness of breath
- Yes
  - Mild
  - Moderate
  - Severe
- No (Absent)

4. Feeling feverish
- Yes
  - Mild
  - Moderate
  - Severe

24-point questionnaire with 8 symptoms (No symptoms = 0, mild symptoms = 1, mod symptoms = 2, severe symptoms = 3)

N Engl J Med 2020: https://doi.org/10.1056/nejmoa2029849

BLAZE-1: Interim Results - Safety

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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	Bamlanivimab 700 mg (n = 101) Bamlanivimab 2800 mg (n = 107) Bamlanivimab 7000 mg (n = 101) Bamlanivimab pooled (n = 309)	Placebo (n = 143)	Difference from placebo (95% CI)
[2°] Serious Adverse Events (SAEs) (%)	• **700 mg:** 0 (0%) • **2800 mg:** 0 (0%) • **7000 mg:** 0 (0%) • **Pooled:** 0 (0%)	1 (0.7%)	• No statistical comparison provided
[2°] Adverse Events (AEs) – Any (%)	• **700 mg:** 24 (23.8%) • **2800 mg:** 23 (21.5%) • **7000 mg:** 22 (21.8%) • **Pooled:** 69 (22.3%)	35 (24.5%)	• No statistical comparison provided
Infusion-Related reaction	• **Pooled:** 7 (2.3%)	2 (1.4%)	• *ARI 0.9%* *NNH 111*

Nausea, vomiting, diarrhea, dizziness, headache

N Engl J Med 2020: https://doi.org/10.1056/nejmoa2029849

Bamlanivimab: Health Canada Interim Order Indication

- Patients ≥ 12 years of age (≥40 kg) with mild to moderate COVID-19 at *<u>high risk</u> of progressing to severe COVID-19 illness and/or hospitalization

BLAZE-1 Interim Analysis inclusion: outpatients age ≥ 18, COVID-19 positive in past ≤ 3 days, 1 or more mild-moderate COVID-19 symptom

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*<u>High risk</u>: meets one or more of

- ≥ 65 years old
- BMI ≥ 35 for adults
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or receiving immunosuppressive treatment
- ≥ 55 years old AND any of: cardiovascular disease, hypertension, or chronic respiratory disease
- 12-17 years of age AND have any of: BMI ≥ 85th percentile for age/gender, sickle cell disease, congenital or acquired heart disease, neurodevelopmental disorders (e.g., cerebral palsy), a medical-related technological dependence (e.g., tracheostomy), asthma or other chronic respiratory disease

Health Canada Interim Order https://covid-vaccine.canada.ca/bamlanivimab/product-details

BLAZE-1: Overview

ClinicalTrials.gov

- **Registry amendment Nov 9, 2020**

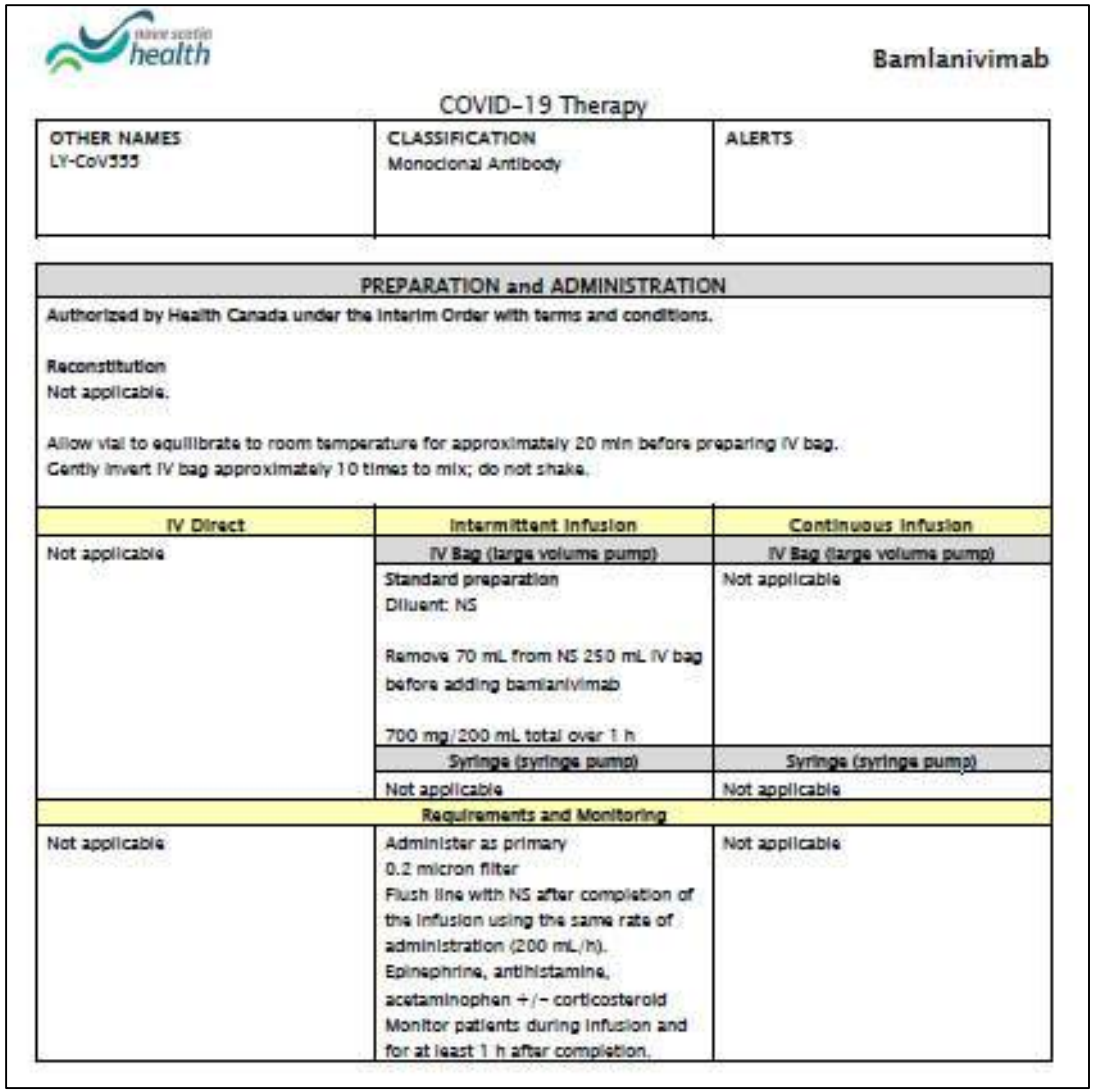
Participants in treatment arms 7 and 8 ONLY

- *Are greater than or equal to (≥)18 years of age and must satisfy at least one of the following at the time of screening*
  - *≥65 years old*
  - *BMI ≥35*
  - *Chronic kidney disease (CKD)*
  - *Type 1 or type 2 diabetes*
  - *Have immunosuppressive disease* or *receiving immunosuppressive treatment*
  - *Are ≥55 years of age AND have: cardiovascular disease, OR hypertension, OR chronic respiratory disease*
- *Are 12-17 years of age (inclusive) AND satisfy at least one of the following at the time of screening*
  - *BMI ≥85th percentile for their age and gender*
  - *Sickle cell disease*
  - *Congenital or acquired heart disease*
  - *Neurodevelopmental disorders, for example, cerebral palsy*
  - *Medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)*
  - *Asthma or reactive airway or other chronic respiratory disease*
  - *Type 1 or type 2 diabetes*
  - *Have immunosuppressive disease, or receiving immunosuppressive treatment*

Clinicaltrials.gov NCT04427501

Practical Considerations

- One-time IV dose: ~2.5 hours from start of prep to end of recommended monitoring
- Preparing for and managing infusion reactions, potential for anaphylaxis



nova scotia health

Bamlanivimab

COVID-19 Therapy

OTHER NAMES	CLASSIFICATION	ALERTS
LY-CoV555	Monoclonal Antibody	

PREPARATION and ADMINISTRATION

Authorized by Health Canada under the Interim Order with terms and conditions.

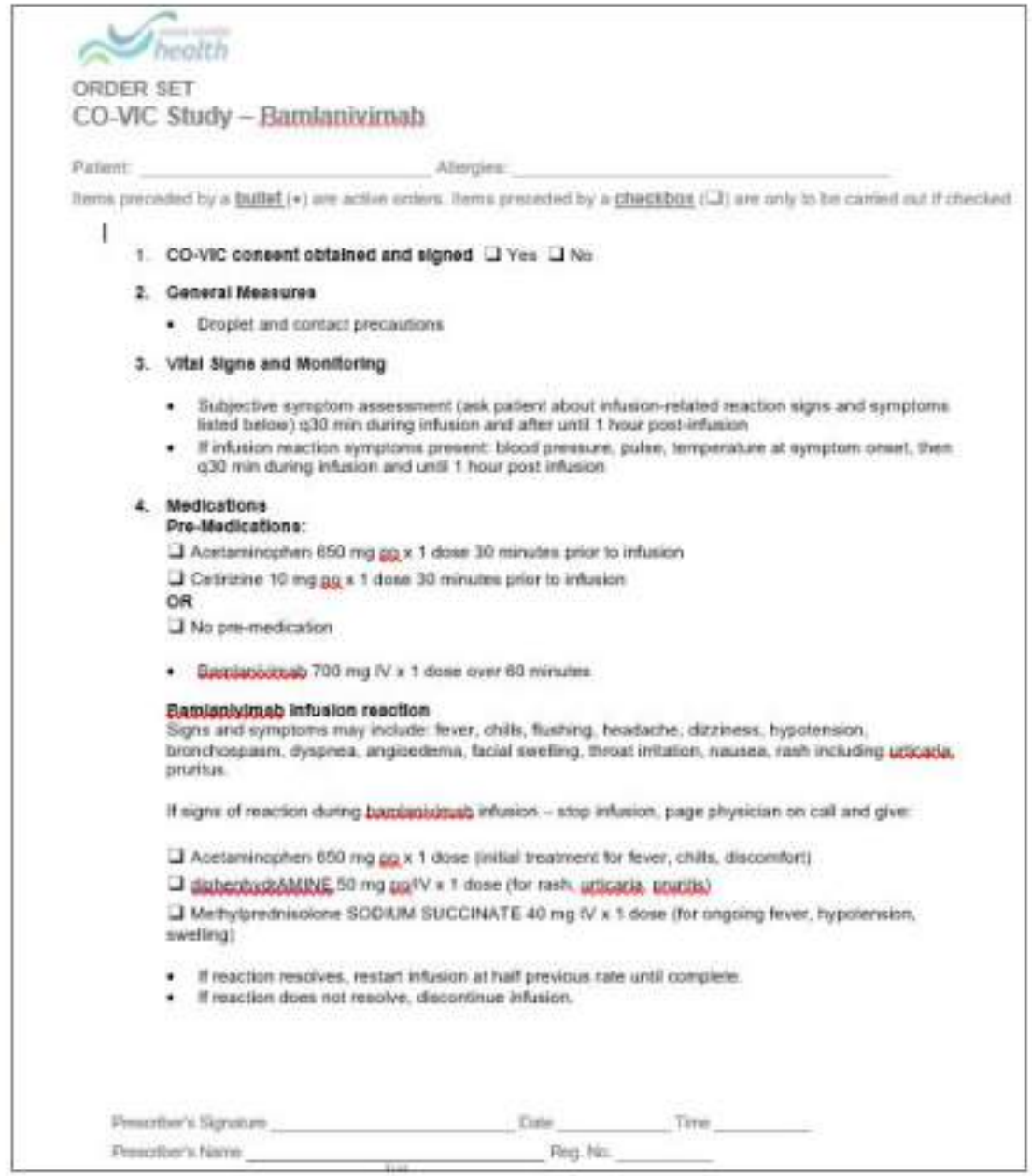
Reconstitution
Not applicable.

Allow vial to equilibrate to room temperature for approximately 20 min before preparing IV bag.
Gently invert IV bag approximately 10 times to mix; do not shake.

IV Direct	Intermittent Infusion	Continuous Infusion
Not applicable	IV Bag (large volume pump)	IV Bag (large volume pump)
	Standard preparation Diluent: NS Remove 70 mL from NS 250 mL IV bag before adding bamlanivimab 700 mg/200 mL total over 1 h	Not applicable
	Syringe (syringe pump)	Syringe (syringe pump)
	Not applicable	Not applicable
Requirements and Monitoring		
Not applicable	Administer as primary 0.2 micron filter Flush line with NS after completion of the infusion using the same rate of administration (200 mL/h). Epinephrine, antihistamine, acetaminophen +/- corticosteroid Monitor patients during infusion and for at least 1 h after completion.	Not applicable

Practical Considerations

- One-time IV dose: ~2.5 hours from start of prep to end of recommended monitoring
- Preparing for and managing infusion reactions, potential for anaphylaxis
- Logistics of outpatient infusion clinic: location, infection control, staffing



ORDER SET

CO-VIC Study – Bamlanivimab

Patient: _____ Allergies: _____

Items preceded by a bullet (•) are active orders. Items preceded by a checkbox (❑) are only to be carried out if checked

1. **CO-VIC consent obtained and signed** ❑ Yes ❑ No
2. **General Measures**
   - Droplet and contact precautions
3. **Vital Signs and Monitoring**
   - Subjective symptom assessment (ask patient about infusion-related reaction signs and symptoms listed below) q30 min during infusion and after until 1 hour post-infusion
   - If infusion reaction symptoms present: blood pressure, pulse, temperature at symptom onset, then q30 min during infusion and until 1 hour post infusion
4. **Medications**

Pre-Medications:

❑ Acetaminophen 650 mg po x 1 dose 30 minutes prior to infusion

❑ Cetirizine 10 mg po x 1 dose 30 minutes prior to infusion

OR

❑ No pre-medication

- Bamlanivimab 700 mg IV x 1 dose over 60 minutes

Bamlanivimab infusion reaction

Signs and symptoms may include: fever, chills, flushing, headache, dizziness, hypotension, bronchospasm, dyspnea, angioedema, facial swelling, throat irritation, nausea, rash including urticaria, pruritus.

If signs of reaction during bamlanivimab infusion – stop infusion, page physician on call and give:

❑ Acetaminophen 650 mg po x 1 dose (initial treatment for fever, chills, discomfort)

❑ diphenhydrAMINE 50 mg po/IV x 1 dose (for rash, urticaria, pruritis)

❑ Methylprednisolone SODIUM SUCCINATE 40 mg IV x 1 dose (for ongoing fever, hypotension, swelling)

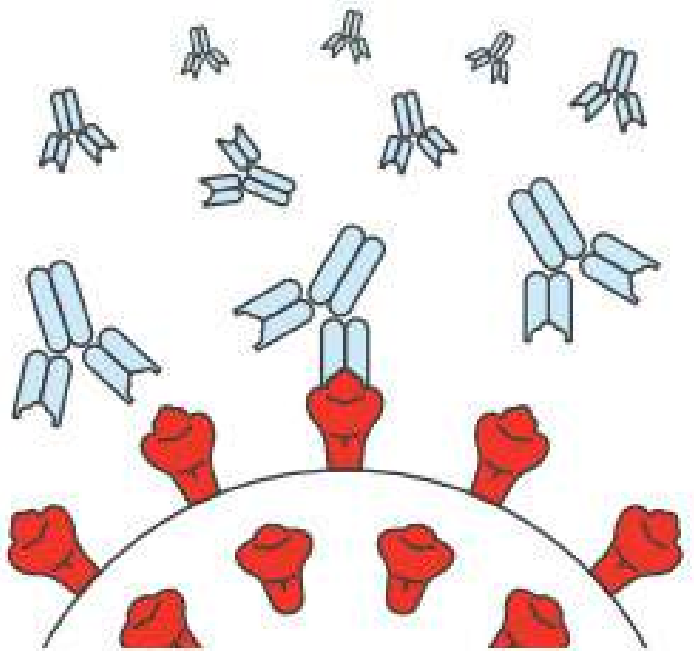
- If reaction resolves, restart infusion at half previous rate until complete.
- If reaction does not resolve, discontinue infusion.

Prescriber's Signature _____ Date _____ Time _____

Prescriber's Name _____ Reg. No. _____

Discussion

Bamlanivimab for COVID-19



Nova Scotia COVID-19 Therapeutics & Prophylaxis Advisory Group

Emma Reid

December 17, 2020

Monoclonal Antibodies

- Mechanisms:
  - Bind SARS-CoV-2 and flag for destruction
  - Bind SARS-CoV-2 spike protein on infected cell surface and flag for destruction
  - Block SARS-CoV-2 spike protein binding and prevent infection
    - Also known as: neutralizing antibodies

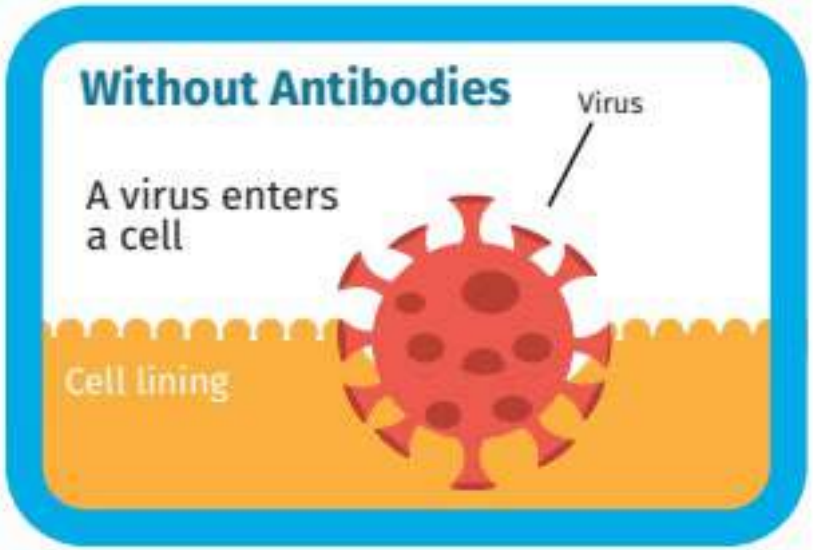
Monoclonal Antibodies

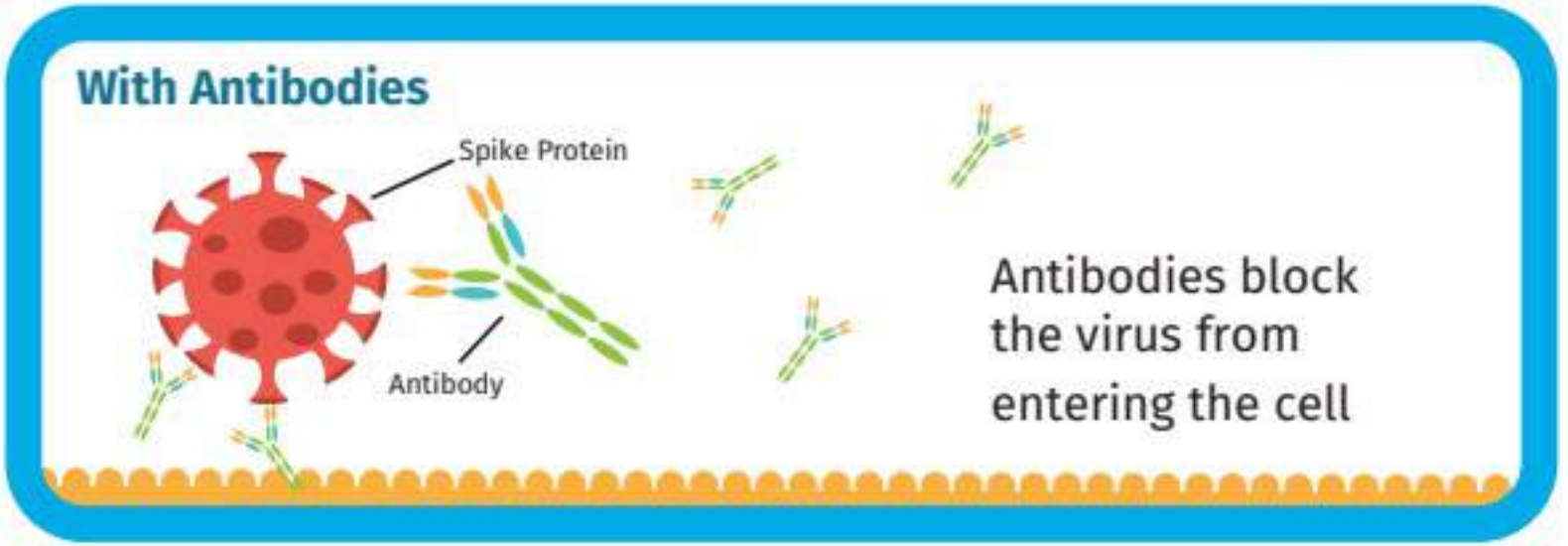
Monoclonal Antibody	Trial Stage	Study Population	Comment
Bamlanivimab (LY-CoV555)	Phase 3	Treatment (non-severe at high risk of progression) and prevention (LTC)	Health Canada approved interim order for treatment in non-severe at high risk of progression
unrelated [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	

Note: all bind to the S protein, thereby preventing the virus from binding to the host cell

Bamlanivimab: Mechanism

- Monoclonal antibody: targets SARS-CoV-2 spike protein preventing viral attachment and cell entry
  - ↓ viral replication → ↓ severity of illness





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  - 25 amended versions of study report on clinicaltrials.gov

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Planned sample size n = 400

Interim analysis

N ENGL J MED

Protocol July 31, 2020

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Planned sample size n = 500

LY3819253 = Bamlanivimab
LY3832479 = Another investigational neutralizing mAb

Clinicaltrials.gov NCT04427501
BLAZE-1 Protocol

BLAZE-1: Interim Report

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Multi-centre, double-blind, Phase II RCT (41 sites USA)	
Patients	n = 452 outpatients age ≥ 18, COVID-19 positive in past ≤ 3 days, 1 or more mild-moderate COVID-19 symptom • Median age 45, 12% above 65, 55% female, 86% white, median 4 days since symptom onset • 44% BMI ≥30 (obese), 69% had risk factors for severe disease*, > 80% mild symptoms
Interventions	• Bamlanivimab 700 mg, 2800 mg, or 7000 mg IV x 1
Comparator	• Placebo infusion IV x 1
Outcomes (as specified at time of publication)	• [1°] Change from baseline in viral load via naso-pharyngeal (NP) swab (Day 11) • [2°] Safety: SAEs, AEs • [2°] Symptom severity • [2°] Hospitalization, ER visit, death • [2°] Viral load/clearance at various timepoints • [2°] PK: concentration of study drugs at various timepoints

Median: 4 days after symptom onset

*Risk factors for severe disease: Age 65+, BMI 35+, or at least one coexisting illness in certain pre-specified category (unclear what)

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[2°] Hospitalization by Day 29 (%)	• **700 mg:** 1 (1.0%) • **2800 mg:** 2 (1.9%) • **7000 mg:** 2 (2.0%) • **Pooled:** 5 (1.6%)	9 (6.3%)	• *ARR 5.3%* • *ARR 4.4%* • *ARR 4.3%* • *ARR 4.7%* *NNT 19 to 24*
[Post hoc subgroup] Hospitalization by Day 29 (%)	**(n = 95)**	**Patients ≥65 or BMI ≥35 (n = 48)**	
	4 (4.2%)	7 (14.6%)	• *ARR 10.4%* *NNT 10*

** statistically significant

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BLAZE-1: Interim Results - Efficacy

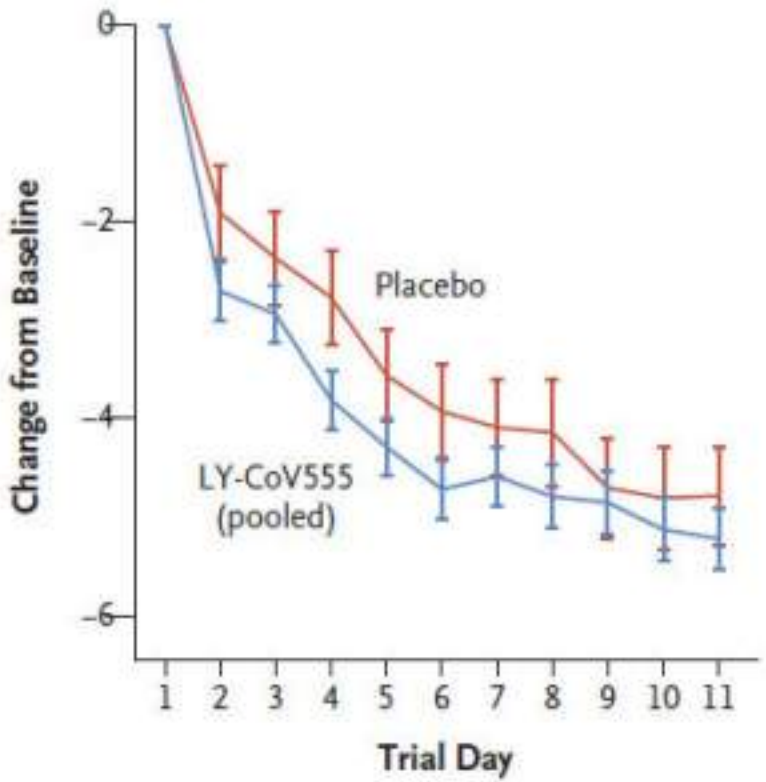
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

[2°] Mean daily change in symptom score (Days 2 to 11)

Bamlanivimab pooled only vs placebo



	Delta Value (95% CI)
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Day 3	−0.57 (−1.12 to −0.01)**
Day 4	−1.04 (−1.60 to −0.49)**
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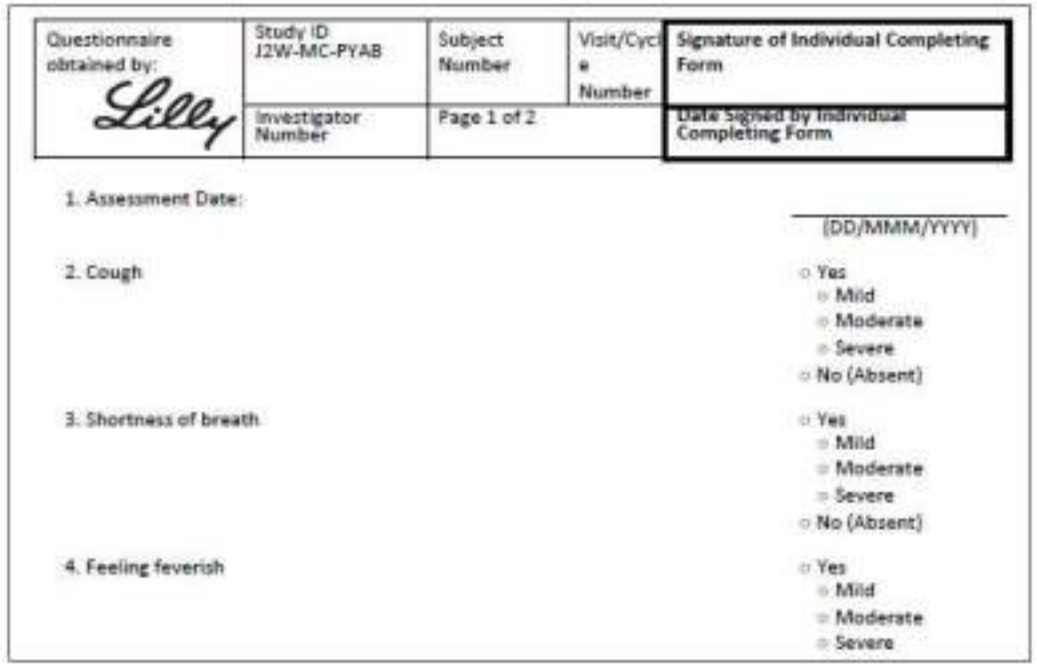
Day 6	−0.79 (−1.35 to −0.23)**
Day 7	−0.50 (−1.06 to 0.07)
Day 8	−0.65 (−1.28 to −0.02)**
Day 9	−0.15 (−0.75 to 0.45)
Day 10	−0.32 (−0.94 to 0.29)
Day 11	−0.44 (−1.02 to 0.15)

** statistically significant



Questionnaire obtained by: Lilly	Study ID J2W-MC-PYAB	Subject Number	Visit/Cycle Number	Signature of Individual Completing Form
	Investigator Number	Page 1 of 2		Date Signed by Individual Completing Form

1. Assessment Date: _____ (DD/MMM/YYYY)

2. Cough
- Yes
  - Mild
  - Moderate
  - Severe
- No (Absent)

3. Shortness of breath
- Yes
  - Mild
  - Moderate
  - Severe
- No (Absent)

4. Feeling feverish
- Yes
  - Mild
  - Moderate
  - Severe

24-point questionnaire with 8 symptoms (No symptoms = 0, mild symptoms = 1, mod symptoms = 2, severe symptoms = 3)

N Engl J Med 2020: https://doi.org/10.1056/nejmoa2029849

BLAZE-1: Interim Results - Safety

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

	Bamlanivimab 700 mg (n = 101) Bamlanivimab 2800 mg (n = 107) Bamlanivimab 7000 mg (n = 101) Bamlanivimab pooled (n = 309)	Placebo (n = 143)	Difference from placebo (95% CI)
[2°] Serious Adverse Events (SAEs) (%)	• **700 mg:** 0 (0%) • **2800 mg:** 0 (0%) • **7000 mg:** 0 (0%) • **Pooled:** 0 (0%)	1 (0.7%)	• No statistical comparison provided
[2°] Adverse Events (AEs) – Any (%)	• **700 mg:** 24 (23.8%) • **2800 mg:** 23 (21.5%) • **7000 mg:** 22 (21.8%) • **Pooled:** 69 (22.3%)	35 (24.5%)	• No statistical comparison provided
Infusion-Related reaction	• **Pooled:** 7 (2.3%)	2 (1.4%)	• *ARI 0.9%* *NNH 111*

Nausea, vomiting, diarrhea, dizziness, headache

N Engl J Med 2020: https://doi.org/10.1056/nejmoa2029849

Bamlanivimab: Health Canada Interim Order Indication

- Patients ≥ 12 years of age (≥40 kg) with mild to moderate COVID-19 at *<u>high risk</u> of progressing to severe COVID-19 illness and/or hospitalization

BLAZE-1 Interim Analysis inclusion: outpatients age ≥ 18, COVID-19 positive in past ≤ 3 days, 1 or more mild-moderate COVID-19 symptom

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*<u>High risk</u>: meets one or more of

- ≥ 65 years old
- BMI ≥ 35 for adults
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or receiving immunosuppressive treatment
- ≥ 55 years old AND any of: cardiovascular disease, hypertension, or chronic respiratory disease
- 12-17 years of age AND have any of: BMI ≥ 85th percentile for age/gender, sickle cell disease, congenital or acquired heart disease, neurodevelopmental disorders (e.g., cerebral palsy), a medical-related technological dependence (e.g., tracheostomy), asthma or other chronic respiratory disease

Health Canada Interim Order https://covid-vaccine.canada.ca/bamlanivimab/product-details

BLAZE-1: Overview

ClinicalTrials.gov

- **Registry amendment Nov 9, 2020**

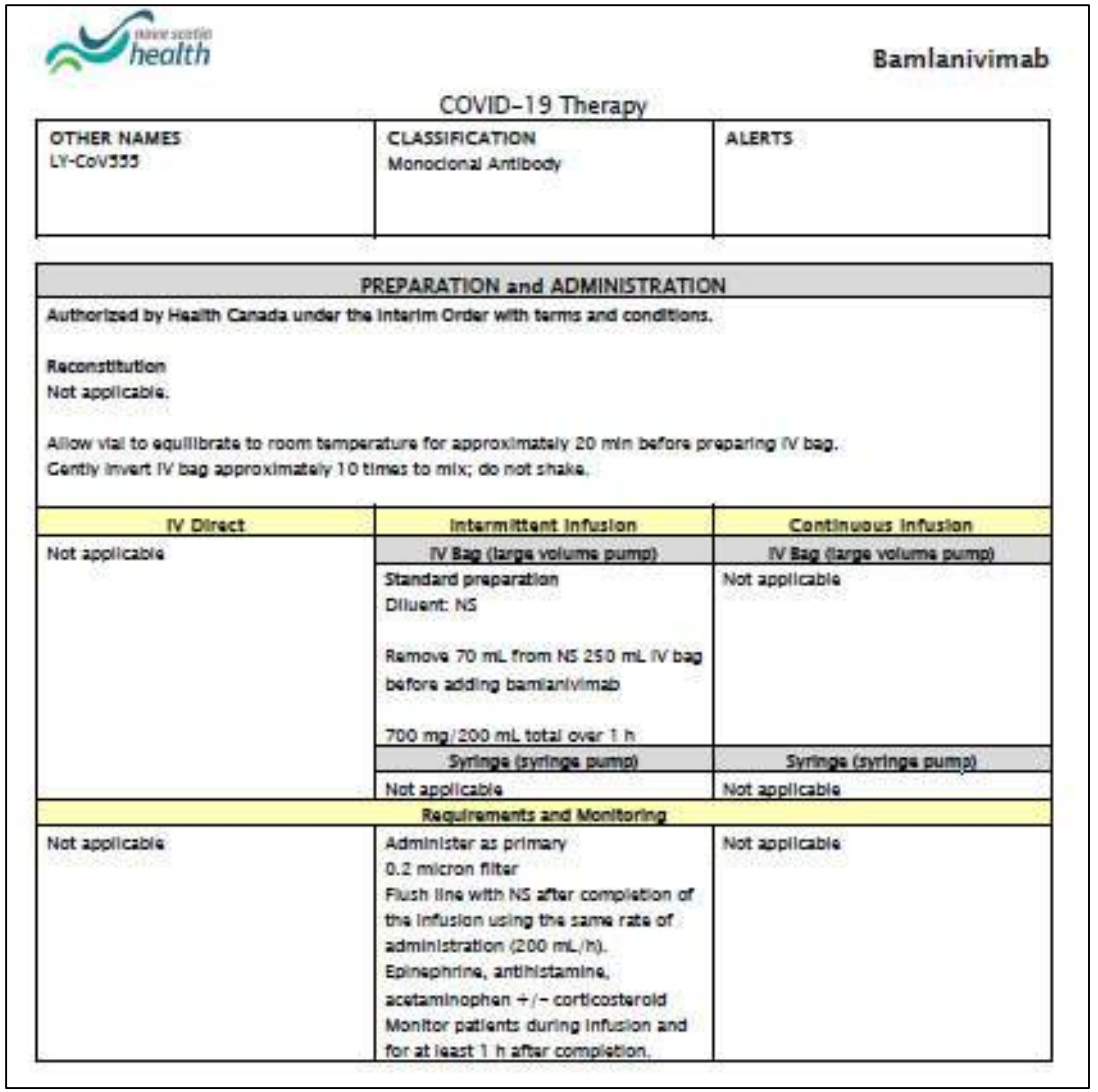
Participants in treatment arms 7 and 8 ONLY

- *Are greater than or equal to (≥)18 years of age and must satisfy at least one of the following at the time of screening*
  - *≥65 years old*
  - *BMI ≥35*
  - *Chronic kidney disease (CKD)*
  - *Type 1 or type 2 diabetes*
  - *Have immunosuppressive disease* or *receiving immunosuppressive treatment*
  - *Are ≥55 years of age AND have: cardiovascular disease, OR hypertension, OR chronic respiratory disease*
- *Are 12-17 years of age (inclusive) AND satisfy at least one of the following at the time of screening*
  - *BMI ≥85th percentile for their age and gender*
  - *Sickle cell disease*
  - *Congenital or acquired heart disease*
  - *Neurodevelopmental disorders, for example, cerebral palsy*
  - *Medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)*
  - *Asthma or reactive airway or other chronic respiratory disease*
  - *Type 1 or type 2 diabetes*
  - *Have immunosuppressive disease, or receiving immunosuppressive treatment*

Clinicaltrials.gov NCT04427501

Practical Considerations

- One-time IV dose: ~2.5 hours from start of prep to end of recommended monitoring
- Preparing for and managing infusion reactions, potential for anaphylaxis



nova scotia health

Bamlanivimab

COVID-19 Therapy

OTHER NAMES	CLASSIFICATION	ALERTS
LY-CoV555	Monoclonal Antibody	

PREPARATION and ADMINISTRATION

Authorized by Health Canada under the Interim Order with terms and conditions.

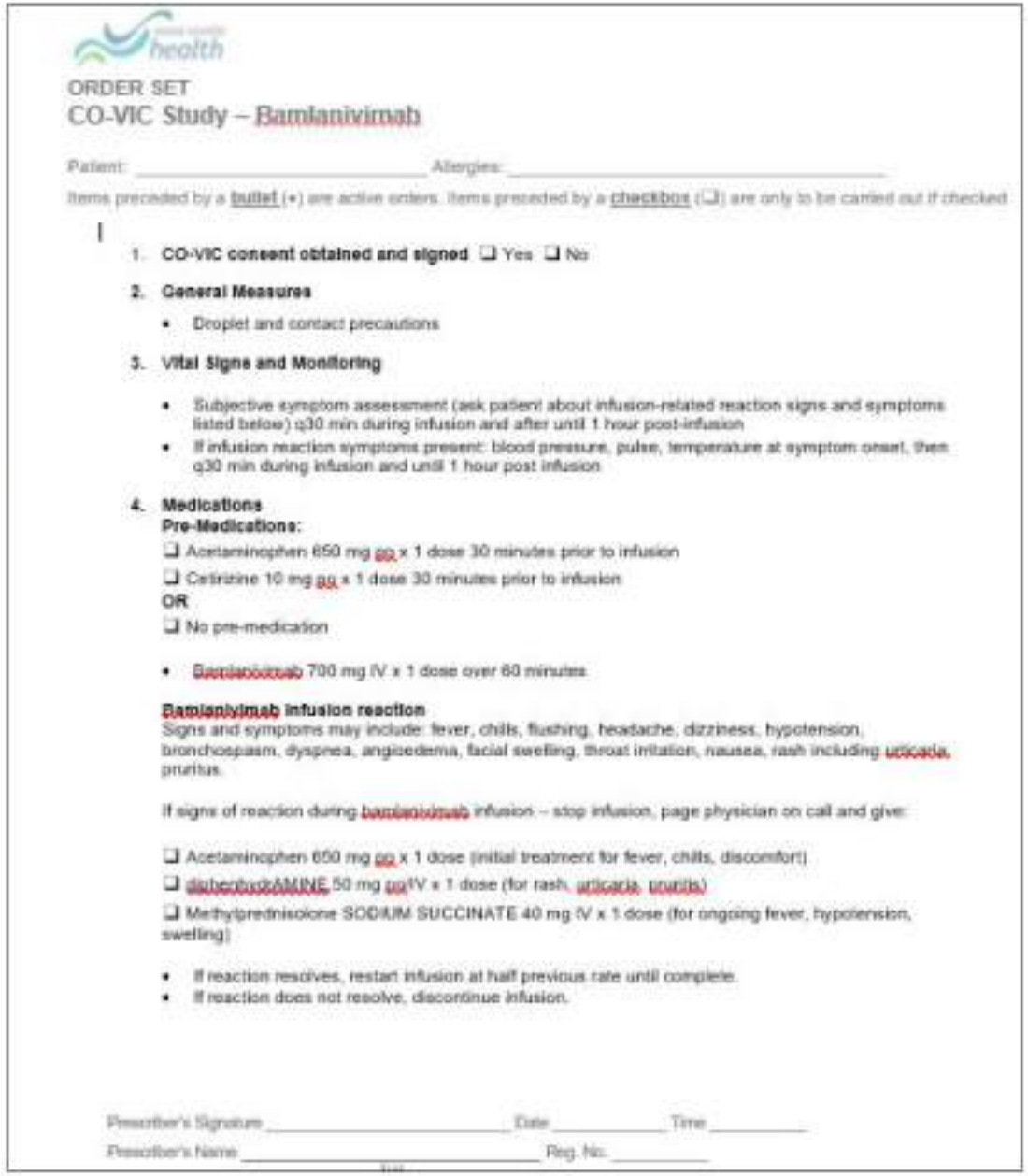
Reconstitution
Not applicable.

Allow vial to equilibrate to room temperature for approximately 20 min before preparing IV bag.
Gently invert IV bag approximately 10 times to mix; do not shake.

IV Direct	Intermittent Infusion	Continuous Infusion
Not applicable	IV Bag (large volume pump)	IV Bag (large volume pump)
	Standard preparation Diluent: NS Remove 70 mL from NS 250 mL IV bag before adding bamlanivimab 700 mg/200 mL total over 1 h	Not applicable
	Syringe (syringe pump)	Syringe (syringe pump)
	Not applicable	Not applicable
Requirements and Monitoring		
Not applicable	Administer as primary 0.2 micron filter Flush line with NS after completion of the infusion using the same rate of administration (200 mL/h). Epinephrine, antihistamine, acetaminophen +/- corticosteroid Monitor patients during infusion and for at least 1 h after completion.	Not applicable

Practical Considerations

- One-time IV dose: ~2.5 hours from start of prep to end of recommended monitoring
- Preparing for and managing infusion reactions, potential for anaphylaxis
- Logistics of infusion clinic: location, infection control, staffing
- Clinic options:
  - NS Health
    - New or existing outpatient clinic
  - Contract out to private infusion clinic



health

ORDER SET

CO-VIC Study – Bamlanivimab

Patient: _____ Allergies: _____

Items preceded by a bullet (•) are active orders. Items preceded by a checkbox (❑) are only to be carried out if checked

1. **CO-VIC consent obtained and signed** ❑ Yes ❑ No
2. **General Measures**
   - Droplet and contact precautions
3. **Vital Signs and Monitoring**
   - Subjective symptom assessment (ask patient about infusion-related reaction signs and symptoms listed below) q30 min during infusion and after until 1 hour post-infusion
   - If infusion reaction symptoms present: blood pressure, pulse, temperature at symptom onset, then q30 min during infusion and until 1 hour post infusion
4. **Medications**

Pre-Medications:

❑ Acetaminophen 650 mg po x 1 dose 30 minutes prior to infusion

❑ Cetirizine 10 mg po x 1 dose 30 minutes prior to infusion

OR

❑ No pre-medication

- Bamlanivimab 700 mg IV x 1 dose over 60 minutes

Bamlanivimab infusion reaction

Signs and symptoms may include: fever, chills, flushing, headache, dizziness, hypotension, bronchospasm, dyspnea, angioedema, facial swelling, throat irritation, nausea, rash including urticaria, pruritus.

If signs of reaction during bamlanivimab infusion – stop infusion, page physician on call and give:

❑ Acetaminophen 650 mg po x 1 dose (initial treatment for fever, chills, discomfort)

❑ diphenhydrAMINE 50 mg po/IV x 1 dose (for rash, urticaria, pruritis)

❑ Methylprednisolone SODIUM SUCCINATE 40 mg IV x 1 dose (for ongoing fever, hypotension, swelling)

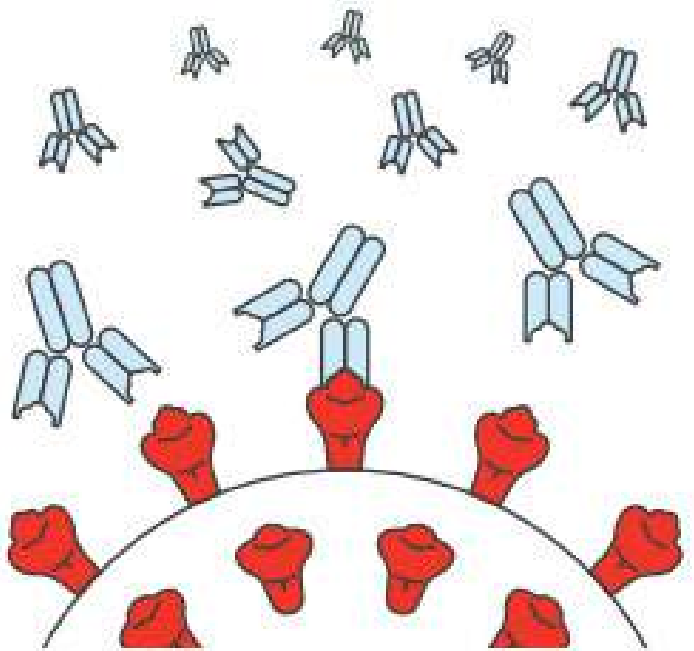
- If reaction resolves, restart infusion at half previous rate until complete.
- If reaction does not resolve, discontinue infusion.

Prescriber's Signature _____ Date _____ Time _____

Prescriber's Name _____ Reg. No. _____

Discussion

Bamlanivimab for COVID-19



Nova Scotia COVID-19 Therapeutics & Prophylaxis Advisory Group

Emma Reid

December 17, 2020

Monoclonal Antibodies

- Mechanisms:
  - Bind SARS-CoV-2 and flag for destruction
  - Bind SARS-CoV-2 spike protein on infected cell surface and flag for destruction
  - Block SARS-CoV-2 spike protein binding and prevent infection
    - Also known as: neutralizing antibodies

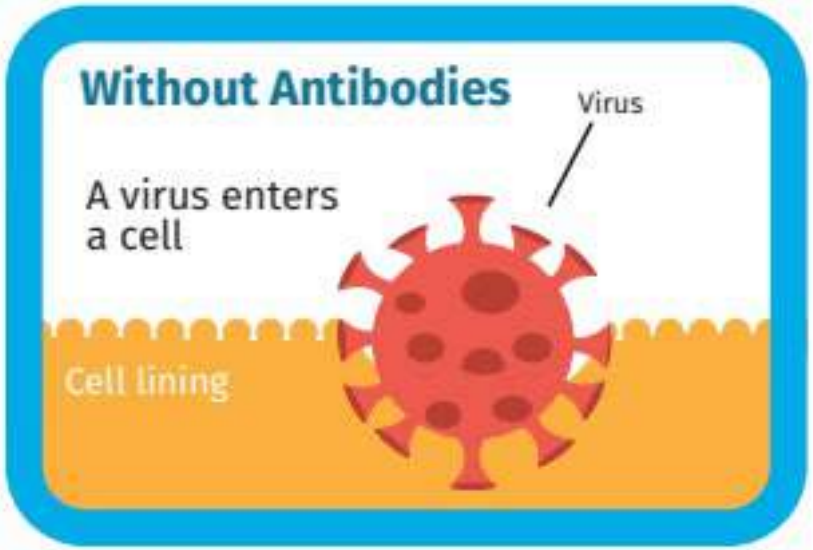
Monoclonal Antibodies

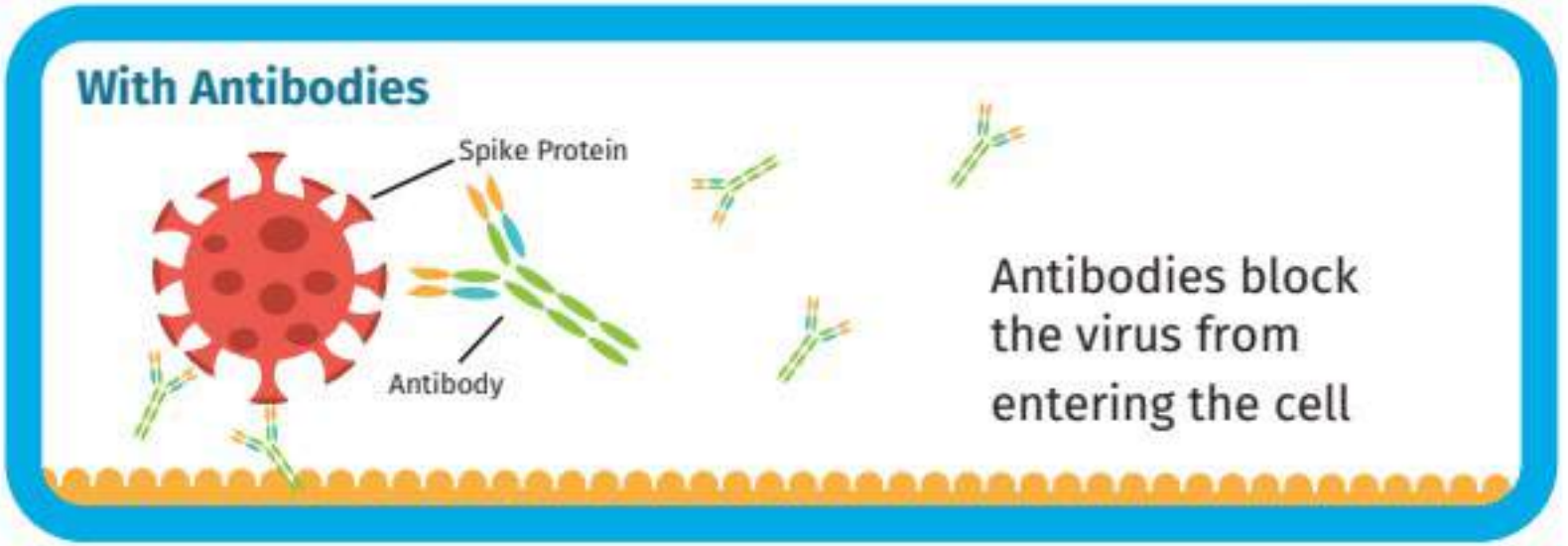
Monoclonal Antibody	Trial Stage	Study Population	Comment
Bamlanivimab (LY-CoV555)	Phase 3	Treatment (non-severe at high risk of progression) and prevention (LTC)	Health Canada approved interim order for treatment in non-severe at high risk of progression
unrelated [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	

Note: all bind to the S protein, thereby preventing the virus from binding to the host cell

Bamlanivimab: Mechanism

- Monoclonal antibody: targets SARS-CoV-2 spike protein preventing viral attachment and cell entry
  - ↓ viral replication → ↓ severity of illness





Adapted from Lilly Bamlanivimab Antibody Playbook, 2020

BLAZE-1: Overview

- Study started June 2020, recruitment ongoing
  - 26 amended versions of study report on clinicaltrials.gov

Protocol June 19, 2020

Treatment arms	LY3819253
1	placebo
2	700 mg
3	2800 mg
4	7000 mg

Planned sample size n = 400

Interim analysis

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Protocol July 31, 2020

Treatment arms	Dose	Intervention
1	---	placebo
2	700 mg	LY3819253
3	2800 mg	LY3819253
4	7000 mg	LY3819253
5	To Be Determined	LY3819253
6	2800 mg + 2800 mg	LY3819253+LY3832479
7	To Be Determined	LY3819253+LY3832479

Planned sample size n = 500

LY3819253 = Bamlanivimab
LY3832479 =Etesevimab

Clinicaltrials.gov NCT04427501
BLAZE-1 Protocol

BLAZE-1: Interim Report

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Multi-centre, double-blind, Phase II RCT (41 sites USA)	
Patients	n = 452 outpatients age ≥ 18, COVID-19 positive in past ≤ 3 days, 1 or more mild-moderate COVID-19 symptom • Median age 45, 12% above 65, 55% female, 86% white, 44% BMI ≥30 (obese) • > 80% mild symptoms only • 69% had risk factors for severe disease*
Interventions	• Bamlanivimab 700 mg, 2800 mg, or 7000 mg IV x 1
Comparator	• Placebo infusion IV x 1
Outcomes (as specified at time of publication)	• [1°] Change from baseline in viral load via naso-pharyngeal (NP) swab (Day 11) • [2°] Safety: SAEs, AEs • [2°] Symptom severity • [2°] Hospitalization, ER visit, death • [2°] Viral load/clearance at various timepoints • [2°] PK: concentration of study drugs at various timepoints

Median: 4 days after symptom onset

*Risk factors for severe disease: Age 65+, BMI 35+, or at least one coexisting illness in certain pre-specified category (unclear what)

N Engl J Med 2020: https://doi.org/10.1056/nejmoa2029849

BLAZE-1: Interim Results - Efficacy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

	Bamlanivimab 700 mg (n = 101) Bamlanivimab 2800 mg (n = 107) Bamlanivimab 7000 mg (n = 101) Bamlanivimab pooled (n = 309)	**Placebo (n = 143)**	**Difference from placebo (95% CI)**
[1°] Mean change from baseline in log viral load at Day 11	• **700 mg:** -3.67 • **2800 mg:** -4.00 • **7000 mg:** -3.38 • **Pooled:** -3.70	-3.47	• -0.20 (-0.66 to 0.25) p = 0.38 • -0.53 (-0.98 to -0.08) p = 0.02** • 0.09 (0.09 to 0.55) p = 0.70 • -0.22 (-0.6 to 0.15) p = not provided
[2°] Hospitalization by Day 29 (%)	• **700 mg:** 1 (1.0%) • **2800 mg:** 2 (1.9%) • **7000 mg:** 2 (2.0%) • **Pooled:** 5 (1.6%)	9 (6.3%)	• No statistical comparison provided
[Post hoc subgroup] Hospitalization by Day 29 (%)	**Patients ≥65 or BMI ≥35 (n = 95)**	**(n = 48)**	
	4 (4.2%)	7 (14.6%)	• No statistical comparison provided

** statistically significant

N Engl J Med 2020: https://doi.org/10.1056/nejmoa2029849

BLAZE-1: Interim Results - Efficacy

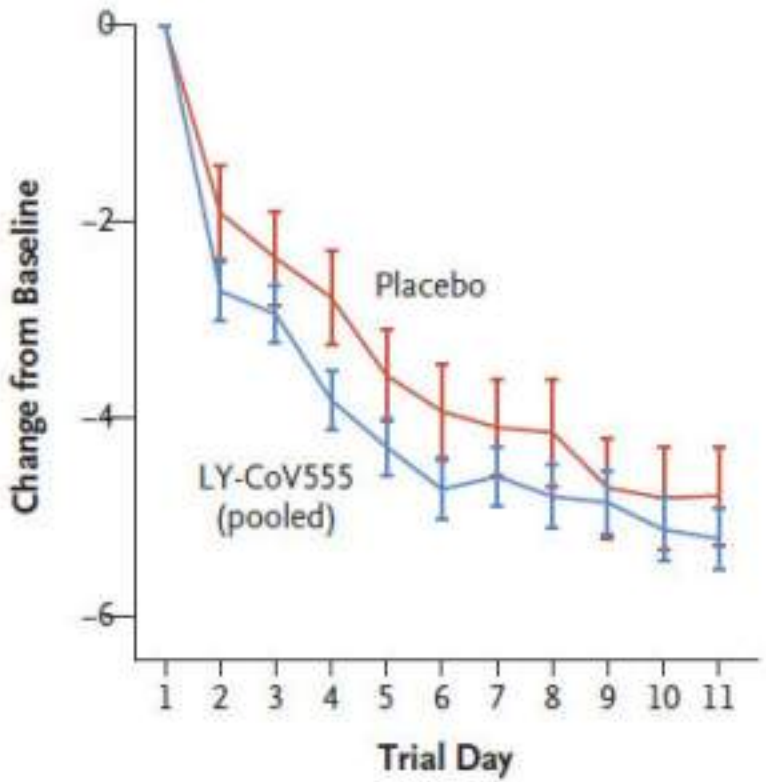
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

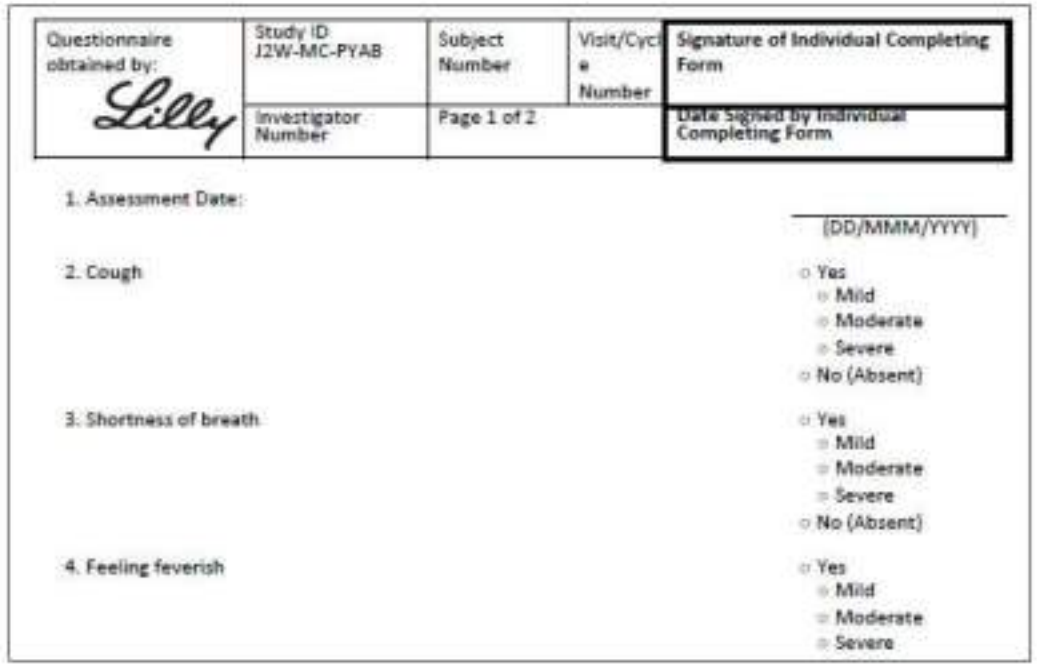
[2°] Mean daily change in symptom score (Days 2 to 11)

Bamlanivimab pooled only vs placebo



	Delta Value (95% CI)
Day 2	−0.79 (−1.35 to −0.24)**
Day 3	−0.57 (−1.12 to −0.01)**
Day 4	−1.04 (−1.60 to −0.49)**
Day 5	−0.73 (−1.28 to −0.17)**
Day 6	−0.79 (−1.35 to −0.23)**
Day 7	−0.50 (−1.06 to 0.07)
Day 8	−0.65 (−1.28 to −0.02)**
Day 9	−0.15 (−0.75 to 0.45)
Day 10	−0.32 (−0.94 to 0.29)
Day 11	−0.44 (−1.02 to 0.15)

** statistically significant



Questionnaire obtained by: Lilly	Study ID J2W-MC-PYAB	Subject Number	Visit/Cycle Number	Signature of Individual Completing Form
	Investigator Number	Page 1 of 2		Date Signed by Individual Completing Form

1. Assessment Date: _____ (DD/MMM/YYYY)

2. Cough
- Yes
  - Mild
  - Moderate
  - Severe
- No (Absent)

3. Shortness of breath
- Yes
  - Mild
  - Moderate
  - Severe
- No (Absent)

4. Feeling feverish
- Yes
  - Mild
  - Moderate
  - Severe

24-point questionnaire with 8 symptoms (No symptoms = 0, mild symptoms = 1, mod symptoms = 2, severe symptoms = 3)

N Engl J Med 2020: https://doi.org/10.1056/nejmoa2029849

BLAZE-1: Interim Results - Safety

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ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

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[2°] Serious Adverse Events (SAEs) (%)	• **700 mg:** 0 (0%) • **2800 mg:** 0 (0%) • **7000 mg:** 0 (0%) • **Pooled:** 0 (0%)	1 (0.7%)	• No statistical comparison provided
[2°] Adverse Events (AEs) – Any (%)	• **700 mg:** 24 (23.8%) • **2800 mg:** 23 (21.5%) • **7000 mg:** 22 (21.8%) • **Pooled:** 69 (22.3%)	35 (24.5%)	• No statistical comparison provided
Infusion-Related reaction	• **Pooled:** 7 (2.3%)	2 (1.4%)	• No statistical comparison provided

Nausea, vomiting, diarrhea, dizziness, headache

N Engl J Med 2020: https://doi.org/10.1056/nejmoa2029849

Bamlanivimab: Health Canada Interim Order Indication

- Patients ≥ 12 years of age (≥40 kg) with mild to moderate COVID-19 at *<u>high risk</u> of progressing to severe COVID-19 illness and/or hospitalization

BLAZE-1 Interim Analysis inclusion: outpatients age ≥ 18, COVID-19 positive in past ≤ 3 days, 1 or more mild-moderate COVID-19 symptom

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*<u>High risk</u>: meets one or more of

- ≥ 65 years old
- BMI ≥ 35 for adults
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or receiving immunosuppressive treatment
- ≥ 55 years old AND any of: cardiovascular disease, hypertension, or chronic respiratory disease
- 12-17 years of age AND have any of: BMI ≥ 85th percentile for age/gender, sickle cell disease, congenital or acquired heart disease, neurodevelopmental disorders (e.g., cerebral palsy), a medical-related technological dependence (e.g., tracheostomy), asthma or other chronic respiratory disease

Health Canada Interim Order https://covid-vaccine.canada.ca/bamlanivimab/product-details

BLAZE-1: Overview

ClinicalTrials.gov

- **Registry amendment Nov 9, 2020**

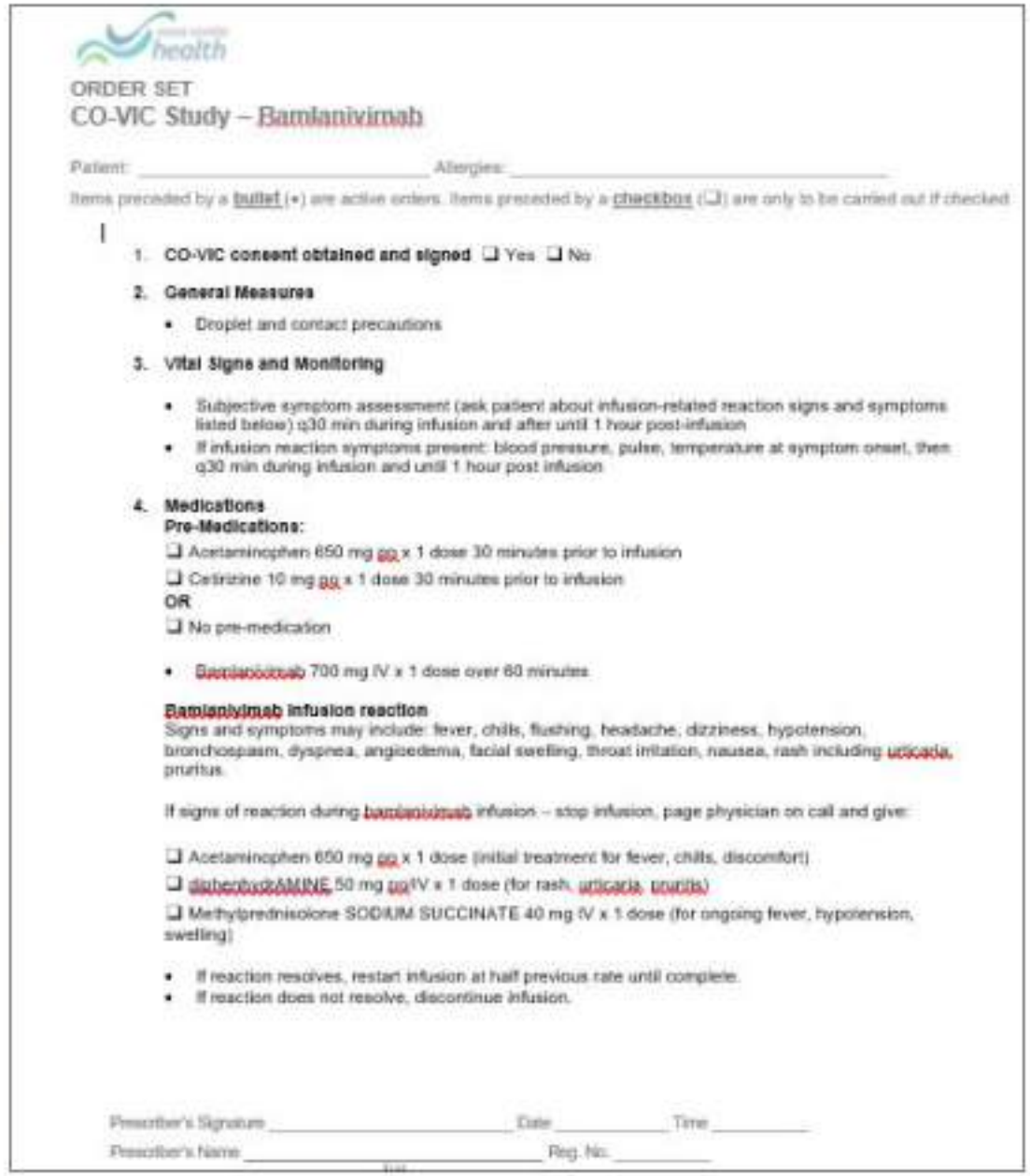
Participants in treatment arms 7 and 8 ONLY

- *Are greater than or equal to (≥)18 years of age and must satisfy at least one of the following at the time of screening*
  - *≥65 years old*
  - *BMI ≥35*
  - *Chronic kidney disease (CKD)*
  - *Type 1 or type 2 diabetes*
  - *Have immunosuppressive disease* or *receiving immunosuppressive treatment*
  - *Are ≥55 years of age AND have: cardiovascular disease, OR hypertension, OR chronic respiratory disease*
- *Are 12-17 years of age (inclusive) AND satisfy at least one of the following at the time of screening*
  - *BMI ≥85th percentile for their age and gender*
  - *Sickle cell disease*
  - *Congenital or acquired heart disease*
  - *Neurodevelopmental disorders, for example, cerebral palsy*
  - *Medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)*
  - *Asthma or reactive airway or other chronic respiratory disease*
  - *Type 1 or type 2 diabetes*
  - *Have immunosuppressive disease, or receiving immunosuppressive treatment*

Clinicaltrials.gov NCT04427501

Practical Considerations

- One-time IV dose: ~2.5 hours from start of prep to end of recommended monitoring
- Preparing for and managing infusion reactions, potential for anaphylaxis
- Logistics for infusion setting (clinic, existing site, etc)



ORDER SET

CO-VIC Study – Bamlanivimab

Patient: _____ Allergies: _____

Items preceded by a bullet (•) are active orders. Items preceded by a checkbox (❑) are only to be carried out if checked

1. **CO-VIC consent obtained and signed** ❑ Yes ❑ No
2. **General Measures**
   - Droplet and contact precautions
3. **Vital Signs and Monitoring**
   - Subjective symptom assessment (ask patient about infusion-related reaction signs and symptoms listed below) q30 min during infusion and after until 1 hour post-infusion
   - If infusion reaction symptoms present: blood pressure, pulse, temperature at symptom onset, then q30 min during infusion and until 1 hour post infusion
4. **Medications**

Pre-Medications:

❑ Acetaminophen 650 mg po x 1 dose 30 minutes prior to infusion

❑ Cetirizine 10 mg po x 1 dose 30 minutes prior to infusion

OR

❑ No pre-medication

- Bamlanivimab 700 mg IV x 1 dose over 60 minutes

Bamlanivimab infusion reaction

Signs and symptoms may include: fever, chills, flushing, headache, dizziness, hypotension, bronchospasm, dyspnea, angioedema, facial swelling, throat irritation, nausea, rash including urticaria, pruritus.

If signs of reaction during bamlanivimab infusion – stop infusion, page physician on call and give:

❑ Acetaminophen 650 mg po x 1 dose (initial treatment for fever, chills, discomfort)

❑ diphenhydrAMINE 50 mg po/IV x 1 dose (for rash, urticaria, pruritis)

❑ Methylprednisolone SODIUM SUCCINATE 40 mg IV x 1 dose (for ongoing fever, hypotension, swelling)

- If reaction resolves, restart infusion at half previous rate until complete.
- If reaction does not resolve, discontinue infusion.

Prescriber's Signature _____ Date _____ Time _____

Prescriber's Name _____ Reg. No. _____

Next Steps

- Stay tuned for potential incorporation into local pragmatic clinical research

Bamlanivimab

Therapeutic class/target: Neutralizing monoclonal antibody to the spike protein on SARS-CoV-2

Approved indications: Authorized by Health Canada under the Interim Order (i.e., expedited approval on condition that ongoing use is supported but further evidence of efficacy/safety) for:
Treatment of patients ≥ 12 years of age (≥40 kg) with mild to moderate COVID-19 at high risk of progressing to severe COVID-19 illness and/or hospitalization (1).
High risk: meets one or more of

> ≥ 65 years of age; body mass index (BMI) ≥ 35 for adults; chronic kidney disease; diabetes; immunosuppressive disease or currently receiving immunosuppressive treatment; ≥ 55 years of age AND have any of: cardiovascular disease, hypertension, or chronic obstructive pulmonary disease/other chronic respiratory disease; 12-17 years of age AND have any of: BMI ≥ 85th percentile for their age and gender, sickle cell disease, congenital or acquired heart disease, neurodevelopmental disorders (e.g., cerebral palsy), a medical-related technological dependence (e.g., tracheostomy), asthma, reactive airway or other chronic respiratory disease that requires daily medication.

Evidence of efficacy: Published evidence is limited to a pre-specified interim analysis of a single RCT, BLAZE-1 (2). 452 outpatients with recently diagnosed COVID-19 and mild-moderate symptoms were randomized to receive a single IV infusion of bamlanivimab (at 700 mg, 2800 mg or 7000 mg) or placebo. The primary endpoint was the change in viral load from baseline as determined from nasopharyngeal collection on day 11. At this time point reductions in viral RNA were similarly large across all groups (the mean reduction representing ~99.97% clearance), and the bamlanivimab 2800 mg dose alone was associated with a statistically greater viral load reduction than placebo. Secondary clinical outcomes are perhaps more compelling. Hospitalization by day 29 occurred in 1.6% (5/309) of bamlanivimab patients [1.0% (1/101), 1.9% (2/107) and 2.0% (2/101) in the 700 mg, 2800 mg and 7000 mg groups respectively] and 6.3% (9/143) of placebo patients (no statistical comparison). Patient symptoms were also tracked daily via a questionnaire and from days 2 to 6, bamlanivimab-treated patients had statistically greater symptom reductions than the placebo arm. For context, out of 24 possible symptom points, mean symptom score reductions versus placebo ranged from -0.57 to -1.04 during this time period.

At this time, the IDSA recommends against routine administration of bamlanivimab for ambulatory COVID-19 patients due to uncertainty around efficacy and safety(3).

Evidence of safety: In the BLAZE-1 interim analysis, only a single serious adverse event (SAE) was documented, occurring in the placebo arm. Adverse events occurred at similar rates across treatment arms, with 21.5% to 23.5% in the bamlanivimab arms (69/309 pooled) and 24.5% (35/142) in the placebo arm. Nausea, diarrhea, dizziness and headache were most common. Infusion-related reactions, including pruritis, flushing, rash, and facial swelling occurred in 2.3% (7/309) of bamlanivimab-treated and 1.4% (2/143) of placebo-treated patients. In all instances the symptoms were classified as mild and the infusions completed.

Product and preparation: Bamlanivimab is supplied as a preservative-free, single use 700mg/20 mL vial (35 mg/mL). It must be refrigerated and stored in its original box to protect from light.

The bamlanivimab vial must equilibrate to room temperature for about 20 minutes before preparation. 70 mL is withdrawn from a 0.9% sodium chloride 250 mL bag, then the 700mg/20 mL contents of bamlanivimab vial added. The IV bag should be inverted gently about ten times to mix. Do not shake.

Immediate administration after preparation is recommended. If administration must be delayed, the bag may be stored in the refrigerator for up to 48 hours or at room temperature for up to 14 hours (1).

Dosage and administration: Recommended dose is 700 mg IV as a single infusion over a minimum of 60 minutes. A PVC infusion set with in-line 0.2 micron filter is required. After the infusion is complete, the infusion line should be flushed with volume sufficient to clear residual volume in the tubing to ensure the entire dose has been administered.

No renal dosage adjustment is required, nor dosage adjustment in mild hepatic impairment. Bamlanivimab has not been studied in moderate or severe hepatic impairment.

Monitoring: The manufacturer recommends that bamlanivimab be administered in a healthcare setting capable of anaphylaxis management. Clinical monitoring (for allergy or infusion-related reaction) is recommended during the infusion and for one hour after completion.

In the event of an infusion-related reaction, the rate of infusion may be reduced. Antihistamines were documented to be administered in the BLAZE-1 trial.

Place in therapy: Bamlanivimab will be accessible only within the context of enrolment in a clinical trial, i.e. CO-VIC. A patient should be informed as to the investigational nature of the drug.

A patient should be considered if a positive COVID-19 test was confirmed within the previous 3 days, and if symptoms (including fever, cough, sore throat, malaise, headache, muscle pain, GI symptoms or shortness of breath on exertion) are mild enough to be managed as an outpatient. Notably there is possible harm associated with administering bamlanivimab in the hospitalized population (1).

No specific contraindication to administration has been determined aside from known sensitivity to the drug itself.

References:

1. Bamlanivimab product monograph. Toronto (ON): Eli Lilly Canada Inc; Accessed 2020 December 2
2. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med 2020: Available at: https://doi.org/10.1056/nejmoa2029849 [Epub ahead of print]. Accessed 2020 December 1.
3. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious diseases Society of America guidelines on the treatment and management of patients with COVID-19. Updated November 2020: Available at: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-10 . Accessed 2020 December 2.

To:	NS Health COVID Network
Date:	22 December 2020
From:	Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group
Subject:	Bamlanivimab, unrelated [redacted] recommendation

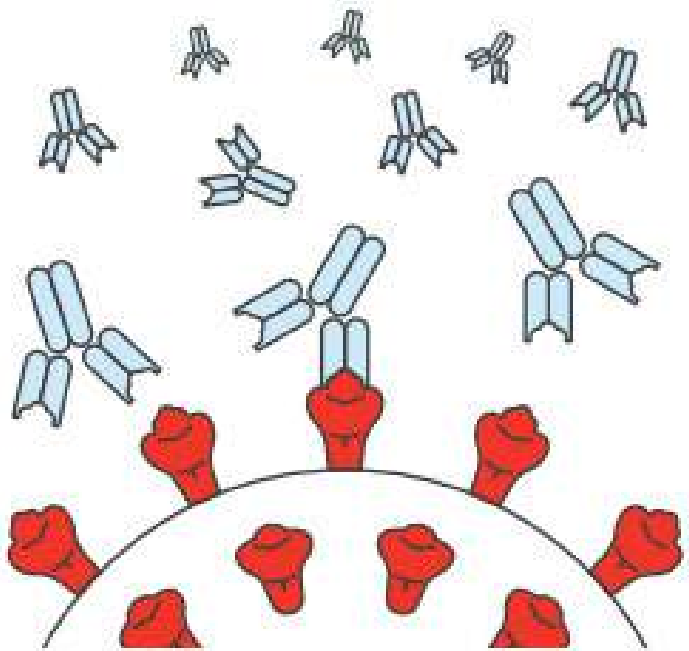
Bamlanivimab Recommendation: use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health-affiliated Regional Care Units.

Rationale:

- **Health Canada indication**:
  - Bamlanivimab is authorized for use under an interim order for patients ≥ 12 years of age (≥40 kg) with mild to moderate COVID-19 at high risk of progressing to severe COVID-19 illness and/or hospitalization
- **Evidence**: BLAZE-1 (interim analysis of a Phase II trial)
  - Non-hospitalized patients (≥ 18 years of age) with recently diagnosed mild to moderate COVID-19. Approximately 69% of patients had risk factors for severe COVID-19.
  - **Efficacy:** Numerically reduced hospital admissions (signal of increased benefit in those >/= 65 and BMI >/= 35), however statistical analysis of this clinical outcome not provided
  - **Safety**: No signal of serious harm
- **Role in therapy**: **Pragmatic research**
  - Bamlanivimab cannot be endorsed for use in routine care based on the published evidence to date
  - Until further efficacy and safety data are published to support bamlanivimab in routine care, the advisory group recommends use in the context of pragmatic research to evaluate real-world clinical safety and effectiveness in NS Health
- **Population:**
  - **Non-severe COVID-19 aged 65 and older**
  - Bamlanivimab is a neutralizing monoclonal antibody and is ideal for early disease in non-severe patients as it targets pre-cellular viral entry
  - Blaze-1 supports use in non-severe COVID-19 population, however evidence from BLAZE-1 is not clear in terms of which patients with risk factors benefit most. There was increased benefit for those aged 65 and greater and BMI greater than 35.
  - Individuals 65 years of age and up are at highest risk for progression to severe disease and death and mount less of an immune response
- **Setting:**
  - **Regional care units (RCU)**
  - Health Canada approved a relatively broad indication that is not feasible to implement in the context of pragmatic research using our existing NS Health infrastructure
  - One NS Health affiliated setting that may be able to incorporate bamlanivimab administration in non-severe outpatients are the RCUs
  - Use of RCUs would allow patients who are very vulnerable to COVID-19 to receive bamlanivimab and allow data collection in individuals at high risk of disease progression
- **Public health/IPAC considerations**:
  - Advisory group discussed inherent infection-control issues if community-based COVID-19 positive patients were directed to existing healthcare facilities or infusion centers. RCUs were suggested as a practical setting to administer bamlanivimab without having to introduce COVID-19 positive patients into a new healthcare environment, and aligns with the pragmatic research method of using existing systems. Would not require an infusion center and would administer to patients in their RCU bed. An order set, IV monograph, pre medications, anaphylaxis kit, and nurse to infuse bamlanivimab and monitor for infusion reactions will be needed.

unrelated

Bamlanivimab Update



Nova Scotia COVID-19 Therapeutics & Prophylaxis Advisory Group
Emma Reid
Feb 25, 2021

Bamlanivimab Update

- Discussed last meeting:

  BLAZE-1 Phase 3 preliminary results available via press release

  - In outpatients ≥ 12 with early mild-mod COVID-19 and ≥ 1 high risk factor for severe disease, the administration of bamlanivimab + etesevimab IV x 1 resulted in **reduced COVID-19-related hospitalization and all-cause death versus placebo (2.1% vs 7.0%, p = 0.0004)**

- Feb 9, 2021 – Emergency Use Authorization for bamlanivimab + etesevimab issued by FDA
  - Indicated in same population studied in BLAZE-1

https://investor.lilly.com/news-releases/news-release-details/new-data-show-treatment-lillys-neutralizing-antibodies

Health Canada

- Application for bamlanivimab + etesevimab approval under review Feb 16

Applications received related to the COVID-19 pandemic

Applicant	Medicinal ingredient(s)	Therapeutic area	Date application was received	Outcome of application	Date of decision/outcome
Eli Lilly Canada Inc	Bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016)	Immune sera and immunoglobulins, for human use	2021-02-16	Under review	n/a

unrelated

https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/authorization/applications.html

Bamlanivimab for Prophylaxis

- To date, BLAZE-2 findings shared in press release Jan 21 are only publicly available results
  - In nursing homes with at least one COVID-19 case in past 7 days, administering bamlanivimab 4200 mg IV x 1 to staff and residents resulted in reduced incidence of COVID-19 overall at 21 days
    - All participants OR 0.43, p = 0.00021
    - Subgroup of nursing home residents OR 0.20, p = 0.00026

https://clinicaltrials.gov/ct2/show/NCT04497987

https://www.prnewswire.com/news-releases/lillys-neutralizing-antibody-bamlanivimab-ly-cov555-prevented-covid-19-at-nursing-homes-in-the-blaze-2-trial-reducing-risk-by-up-to-80-percent-for-residents-301212159.html

Background Summary

Bamlanivimab for COVID-19

MSSU USSM

What is bamlanivimab?

Bamlanivimab is an IgG1 monoclonal antibody developed specifically as a treatment for COVID-19. It goes by the codename LY-CoV555. It is unapproved by the FDA, but authorized for emergency treatment of mild to moderate COVID-19. It is not authorized for use in severe COVID-19 or in hospitalized patients. [1]

In Canada

Bamlanivimab [redacted] are currently the only COVID-19 treatments approved by Health Canada.

In a regulatory decision on November 20, 2020, Health Canada **authorized bamlanivimab** in an interim order for use in relation to the COVID-19 pandemic. "Bamlanivimab is indicated for the treatment of adults and pediatric patients 12 years of age or older with **mild to moderate** coronavirus disease 2019 (COVID-19), who weigh at least 40 kg and who are at **high risk of progressing to severe** COVID-19 illness and/or hospitalization." [2]

However...

On January 11, 2021, the BC Ministry of Health rejected Health Canada's approval of bamlanivimab, citing a lack of published evidence, particularly regarding patient safety data. [3]

BLAZE trials

BLAZE-1 (NCT04427501) is the most high-profile RCT of bamlanivimab, sponsored by the drug's creator Eli Lilly [4]. They released a publication reporting on Phase 2 findings in JAMA on January 21, 2021 [5].

STUDY SPOTLIGHT

BLAZE-1 trial: Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19 [5]

Summary

- Phase 2 results from the BLAZE-1 RCT, sponsored by Eli Lilly: trial is ongoing
- 47 US study sites
- Treatment: single, 1-hour, IV infusion of placebo, bamlanivimab, or bamlanivimab and etesevimab; final analysis includes results for the 5 treatment groups: placebo, 700 mg of bamlanivimab, 2800 mg of bamlanivimab, 7000 mg of bamlanivimab, and a combination treatment with 2800 mg of bamlanivimab and 2800 mg of etesevimab
- Primary outcome: effect of bamlanivimab monotherapy and combination therapy with bamlanivimab and etesevimab compared with placebo on SARS-CoV-2 log viral load from baseline to day 11 (±4 days)
- 577 patients enrolled: 156 given placebo vs. 401 distributed among other 4 treatment groups
- Results: "The change in log viral load from baseline at day 11 was −3.72 for 700 mg, −4.08 for 2800 mg, −3.49 for 7000 mg, −4.37 for combination treatment, and −3.80 for placebo. Compared with placebo, the differences in the change in log viral load at day 11 were 0.09 (95% CI, −0.35 to 0.52; P = .69) for 700 mg, −0.27 (95% CI, −0.71 to 0.16; P = .21) for 2800 mg, 0.31 (95% CI, −0.13 to 0.76; P = .16) for 7000 mg, and −0.57 (95% CI, −1.00 to −0.14; P = .01) for combination treatment."

Conclusions

- **"Among nonhospitalized patients with mild to moderate COVID-19 illness, treatment with bamlanivimab and etesevimab, compared with placebo, was associated with a statistically significant reduction in SARS-CoV-2 viral load at day 11; no significant difference in viral load reduction was observed for bamlanivimab monotherapy."**

Prepared by Leah Boulos, Evidence Synthesis Coordinator, Maritime SPOR SUPPORT Unit

February 2, 2021

CADTH response to BLAZE-1

In October 2020, the BLAZE-1 team previous published an interim update on the trial in the New England Journal of Medicine (SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19) [6]. The Canadian Agency for Drugs and Technology in Health (**CADTH**) produced a **critical appraisal** of this report in January 2021, concluding that "more robust, published, peer-reviewed evidence is needed", particularly pertaining to phase 3 of the trial. [7]

Also in January 2021, CADTH released **drug implementation advice** for bamlanivimab. While continuing to acknowledge the need for more robust evidence, and highlighting some logistical challenges with administrating bamlanivimab, CADTH conceded that "unprecedented times require unprecedented system responses", and that "in some specific circumstances and for reasons that may be unique and situational, clinicians and patients may decide that although the evidence of clinical benefit is not overwhelmingly strong, a product's use presents value in an area of unmet clinical need." [8]

BLAZE-1 phase 3 results in the news

Although no phase 3 results have yet been published, Eli Lilly issued a press release on January 26, 2021 sharing some phase 3 results. They stated that the combination treatment of bamlanivimab and etesevimab (2800mg each) resulted in a 70% risk reduction in COVID-19 related hospitalizations and deaths across 1035 patients. [9]

BLAZE-2 in the news

BLAZE-2 focuses on the efficacy of bamlanivimab and etesevimab in **nursing home residents and staff** (NCT04497987) [10]. Eli Lilly issued a press release on January 26, 2021, stating that in exploratory analyses for assessing treatment, 4200mg of bamlanivimab alone resulted in "a significantly lower frequency of symptomatic COVID-19 (the primary endpoint) in the bamlanivimab treatment arm versus placebo (odds ratio 0.43, p=0.00021)" in all participants. [11]

Please note: This summary reflects evidence up to and including February 2, 2021 only.

Search Methods

Date searched: 2021-02-01

- Google for news items and clinical trials in progress
- Epistemonikos L-OVE on COVID-19 (manual search)
- Ovid MEDLINE search with built-in COVID-19 filter: (bamlanivimab or LY-CoV555 or LY3819253).ti,ab.

References

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5. Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, Huhn G, Cardona J, Mocherla B, Stosor V, Shawa I, Kumar P, Adams AC, Van Naarden J, Custer KL, Durante M, Oakley G, Schade AE, Holzer TR, Ebert PJ, Higgs RE, Kallewaard NL, Sabo J, Patel DR, Klekotka P, Shen L, Skovronsky DM. Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. JAMA. 2021 Jan 21:e210202. doi: 10.1001/jama.2021.0202. Epub ahead of print. PMID: 33475701; PMCID: PMC7821080.
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7. Bresee L. Bamlanivimab in the treatment of outpatients with COVID-19: a critical appraisal of the BLAZE-1 trial [Internet]. Ottawa: CADTH; 2021 Jan 12 [cited 2021 Feb 2]. Available from: https://cadth.ca/sites/default/files/covid-19/ha0010-fcs-blaze1-bamlanivimab-final-update-2-jan12.pdf

8. CADTH. CADTH drug implementation advice: bamlanivimab for mild-to-moderate symptoms of COVID-19 [Internet]. Ottawa: CADTH; 2021 Jan [cited 2021 Feb 2]. Available from: https://cadth.ca/sites/default/files/covid-19/HD0004-bamlanivimab-post-panel-final-jan14.pdf
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What is bamlanivimab?

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New in this update (March 9, 2021)

Since the last background summary on bamlanivimab was completed (Feb 2), the following information is new. New information is also highlighted in blue below.

- The European Medicines Agency (EMA) completed their review of bamlanivimab on March 5, 2021, concluding that bamlanivimab and etesevimab can be used together to treat confirmed COVID-19 in patients who do not require supplemental oxygen and who are at high risk of their COVID-19 disease becoming severe; these recommendations can now be used to support national advice on the possible use of the antibodies before a marketing authorization is issued [2]
- The BLAZE-1 trial report in JAMA has been converted from in press to published

In Canada

Bamlanivimab and unrelated are currently the only COVID-19 treatments approved by Health Canada.

In a regulatory decision on November 20, 2020, Health Canada **authorized bamlanivimab** in an interim order for use in relation to the COVID-19 pandemic. "Bamlanivimab is indicated for the treatment of adults and pediatric patients 12 years of age or older with **mild to moderate** coronavirus disease 2019 (COVID-19), who weigh at least 40 kg and who are at **high risk of progressing to severe** COVID-19 illness and/or hospitalization." [3]

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STUDY SPOTLIGHT

BLAZE-1 trial: Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19 [6]

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- Phase 2 results from the BLAZE-1 RCT, sponsored by Eli Lilly; trial is ongoing
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- Treatment: single, 1-hour, IV infusion of placebo, bamlanivimab, or bamlanivimab and etesevimab; final analysis includes results for the 5 treatment groups: placebo, 700 mg of bamlanivimab, 2800 mg of bamlanivimab, 7000 mg of bamlanivimab, and a combination treatment with 2800 mg of bamlanivimab and 2800 mg of etesevimab
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CADTH response to BLAZE-1

In October 2020, the BLAZE-1 team previous published an interim update on the trial in the New England Journal of Medicine (SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19) [7]. The Canadian Agency for Drugs and Technology in Health (**CADTH**) produced a **critical appraisal** of this report in January 2021, concluding that "more robust, published, peer-reviewed evidence is needed", particularly pertaining to phase 3 of the trial. [8]

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Please note: This summary reflects evidence up to and including March 9, 2021 only.

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References

1. DailyMed. LABEL: BAMLANIVIMAB injection, solution [Internet]. Bethesda, MD: National Institutes of Health; 2020 Dec 11 [cited 2021 Feb 2]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c7e9d8a6-e8c2-4681-9362-51d5bdbae00d
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New in this update (April 6, 2021)

Since the last background summary on bamlanivimab was completed (March 9), there has been no new significant data released.

In Canada

Bamlanivimab and [redacted] are currently the only COVID-19 treatments approved by Health Canada.

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However...

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Major trials

BLAZE trials

Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19[6] - January 21, 2021 [6]

BLAZE-1 (NCT04427501) is the most high-profile RCT of bamlanivimab, sponsored by the drug's creator Eli Lilly [5]. They released a publication reporting on Phase 2 findings in JAMA on January 21, 2021.

Summary

- Phase 2 results from the BLAZE-1 RCT, sponsored by Eli Lilly; trial is ongoing
- 47 US study sites
- Treatment: single, 1-hour, IV infusion of placebo, bamlanivimab, or bamlanivimab and etesevimab; final analysis includes results for the 5 treatment groups: placebo, 700 mg of bamlanivimab, 2800 mg of bamlanivimab, 7000 mg of bamlanivimab, and a combination treatment with 2800 mg of bamlanivimab and 2800 mg of etesevimab
- Primary outcome: effect of bamlanivimab monotherapy and combination therapy with bamlanivimab and etesevimab compared with placebo on SARS-CoV-2 log viral load from baseline to day 11 (±4 days)
- 577 patients enrolled; 156 given placebo vs. 401 distributed among other 4 treatment groups
- Results: "The change in log viral load from baseline at day 11 was –3.72 for 700 mg, –4.08 for 2800 mg, –3.49 for 7000 mg, –4.37 for combination treatment, and –3.80 for placebo. Compared with placebo, the differences in the change in log viral load at day 11 were 0.09 (95% CI, –0.35 to 0.52; P = .69) for 700 mg, –0.27 (95% CI, –0.71 to 0.16; P = .21) for 2800 mg, 0.31 (95% CI, –0.13 to 0.76; P = .16) for 7000 mg, and –0.57 (95% CI, –1.00 to –0.14; P = .01) for combination treatment."

Conclusions

- **"Among nonhospitalized patients with mild to moderate COVID-19 illness, treatment with bamlanivimab and etesevimab, compared with placebo, was associated with a statistically significant reduction in SARS-CoV-2 viral load at day 11; no significant difference in viral load reduction was**

observed for bamlanivimab monotherapy."

CADTH response to BLAZE-1

In October 2020, the BLAZE-1 team previous published an interim update on the trial in the New England Journal of Medicine (SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19) [7]. The Canadian Agency for Drugs and Technology in Health (**CADTH**) produced a **critical appraisal** of this report in January 2021, concluding that "more robust, published, peer-reviewed evidence is needed", particularly pertaining to phase 3 of the trial. [8]

Also in January 2021, CADTH released **drug implementation advice** for bamlanivimab. While continuing to acknowledge the need for more robust evidence, and highlighting some logistical challenges with administrating bamlanivimab, CADTH conceded that "unprecedented times require unprecedented system responses", and that "in some specific circumstances and for reasons that may be unique and situational, clinicians and patients may decide that although the evidence of clinical benefit is not overwhelmingly strong, a product's use presents value in an area of unmet clinical need." [9]

BLAZE-1 phase 3 results in the news

Although no phase 3 results have yet been published, Eli Lilly issued a press release on January 26, 2021 sharing some phase 3 results. They stated that the combination treatment of bamlanivimab and etesevimab (2800mg each) resulted in a 70% risk reduction in COVID-19 related hospitalizations and deaths across 1035 patients. [10]

BLAZE-2 in the news

BLAZE-2 focuses on the efficacy of bamlanivimab and etesevimab in **nursing home residents and staff** (NCT04497987) [11]. Eli Lilly issued a press release on January 26, 2021, stating that in exploratory analyses for assessing treatment, 4200mg of bamlanivimab alone resulted in "a significantly lower frequency of symptomatic COVID-19 (the primary endpoint) in the bamlanivimab treatment arm versus placebo (odds ratio 0.43, p=0.00021)" in all participants. [12].

Evidence syntheses

There are currently no published high-quality evidence syntheses on bamlanivimab for COVID-19.

Please note: This summary reflects evidence up to and including April 6, 2021 only.

Search Methods

Date searched: 2021-04-06

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Background Summary

Bamlanivimab for COVID-19

What is bamlanivimab?

Bamlanivimab is an IgG1 monoclonal antibody developed specifically as a treatment for COVID-19. It goes by the codename LY-CoV555. It is unapproved by the FDA, but authorized for emergency treatment of mild to moderate COVID-19. It is not authorized for use in severe COVID-19 or in hospitalized patients. [1]

New in this update (April 6, 2021)

Since the last background summary on bamlanivimab was completed (March 9), the following information is new. New information is also highlighted in blue below.

- RCT publication in Nature recommending that bamlanivimab not be used as monotherapy for COVID-19 variants due to resistance
- Eli Lilly updated their press release of the BLAZE-1 phase 3 trial on March 10, 2021. New information includes updated result percentages and combinations of therapies used.

Federal Approval

Bamlanivimab and [redacted] are the only COVID-19 treatments approved by Health Canada.

In a regulatory decision on November 20, 2020, Health Canada authorized bamlanivimab in an interim order for use in relation to the COVID-19 pandemic. "Bamlanivimab is indicated for the treatment of adults and pediatric patients 12 years of age or older with **mild to moderate** coronavirus disease 2019 (COVID-19), who weigh at least 40 kg and who are at **high risk of progressing to severe** COVID-19 illness and/or hospitalization." [3]

However...

On January 11, 2021, the BC Ministry of Health rejected Health Canada's approval of bamlanivimab, citing a lack of published evidence, particularly regarding patient safety data. [4]

An American study was also published in *Nature* in March of 2021 recommending that bamlanivimab not be used as monotherapy for COVID-19 variants due to resistance [5]. As of April 6, 2021, Health Canada and has not updated their records to reflect the findings from this study

Major trials

BLAZE trials

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CADTH response to BLAZE-1

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New in this update (April 12, 2021)

Since the last background summary on bamlanivimab was completed (March 9), the following information is new. New information is also highlighted in blue below.

- New evidence has emerged relating to the SARS-CoV-2 variants of concern (VOCs) and monoclonal antibody therapy, including bamlanivimab – see **Variants of Concern** below
- Eli Lilly updated their press release of the BLAZE-1 phase 3 trial on March 10, 2021. New information includes updated result percentages and combinations of therapies used. No formal publication has yet been released

Federal Approval

Bamlanivimab and unrelated are the only COVID-19 treatments approved by Health Canada.

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However...

On January 11, 2021, the BC Ministry of Health rejected Health Canada's approval of bamlanivimab, citing a lack of published evidence, particularly regarding patient safety data. [4]

Variants of Concern

The US Food & Drug Administration (FDA) issued an emergency use authorization (EUA) for bamlanivimab in November 2020; the drug still does not have formal FDA approval. On March 24, 2021, the FDA **updated their EUA** [5] in light of new evidence suggesting **bamlanivimab is less effective as a monotherapy against the SARS-CoV-2 variants of concern** (VOCs) B.1.351 (South Africa), P.1 (Brazil), and other emerging VOCs in California and New York; no change was reported in effectiveness against B.1.1.7 (UK). Eli Lilly's **Fact Sheet for Health Care Providers** [6] has been updated to recommend bamlanivimab be offered in combination with etesevimab if infection with a VOC is suspected. This decision mirrors findings from a **study published in *Nature*** on March 8, 2021 [7]. As of April 12, 2021, Health Canada and has not updated their records to reflect the findings from this study.

Major trials

BLAZE trials

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Evidence syntheses

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Please note: This summary reflects evidence up to and including April 12, 2021 only.

Prepared by Leah Boulos & Ashley Crawford, Maritime SPOR SUPPORT Unit

April 12, 2021

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Background Summary

Bamlanivimab for COVID-19

What is bamlanivimab?

Bamlanivimab is an IgG1 monoclonal antibody developed specifically as a treatment for COVID-19. It goes by the codename LY-CoV555. It is currently approved for use by Health Canada [1], but unapproved by the FDA [2]

New in this update (May 3, 2021)

Since the last background summary on bamlanivimab was completed (April 6), the following information is new. New information is also highlighted in blue below.

- The FDA revoked their original statement authorizing emergency use of bamlanivimab
- The Government of Canada released a statement noting potential risk of treatment failure due to COVID-19 variant resistance to bamlanivimab

Approval in Canada

Bamlanivimab and unrelated are the only COVID-19 treatments approved by Health Canada.

In a regulatory decision on November 20, 2020, Health Canada **authorized bamlanivimab** in an interim order for use in relation to the COVID-19 pandemic. "Bamlanivimab is indicated for the treatment of adults and pediatric patients 12 years of age or older with **mild to moderate** coronavirus disease 2019 (COVID-19), who weigh at least 40 kg and who are at **high risk of progressing to severe** COVID-19 illness and/or hospitalization." [1]

Approval in Europe

The European Medicine Agency has recommended that bamlanivimab and etesevimab be used together to treat confirmed COVID-19 in patients who do not require supplemental oxygen and who are at high risk of their COVID-19 disease becoming severe. This may pave the way for the use of bamlanivimab, in combination with other treatments, for COVID-19 [3].

Approval in the US

On April 16, 2021, the US FDA revoked their original statement authorizing emergency use of bamlanivimab for the treatment of mild to moderate COVID-19 in adults and certain pediatric patients [4]. Based on its ongoing analysis of emerging scientific data, specifically the sustained increase of SARS-CoV-2 viral variants that are resistant to bamlanivimab alone resulting in the increased risk for treatment failure, the FDA has determined that the known and potential benefits of bamlanivimab, when administered alone, no longer outweigh the known and potential risks for its authorized use.

As of May 3, 2021, Health Canada and has not updated their records to reflect the FDA's guidance. However, the Government of Canada released a statement on April 28, 2021 noting potential risk of treatment failure due to COVID-19 variant resistance to bamlanivimab [5]. Provincial authority bodies have also expressed concern over the use of bamlanivimab. On January 11, 2021, the BC Ministry of Health rejected Health Canada's approval of bamlanivimab, citing a lack of published evidence, particularly regarding patient safety data. [6]

Major trials

BLAZE trials

BLAZE-1 (NCT04427501) is the most high-profile RCT of bamlanivimab, sponsored by the drug's creator Eli Lilly [7]. They released a publication reporting on Phase 2 findings in JAMA on January 21, 2021: **Effect of Bamlanivimab as**

Monotherapy or in Combination with Etesevimab on Viral Load in Patients with Mild to Moderate COVID-19 - January 21, 2021 [8]

Summary

- Phase 2 results from the BLAZE-1 RCT, sponsored by Eli Lilly; trial is ongoing
- 47 US study sites
- Treatment: single, 1-hour, IV infusion of placebo, bamlanivimab, or bamlanivimab and etesevimab; final analysis includes results for the 5 treatment groups: placebo, 700 mg of bamlanivimab, 2800 mg of bamlanivimab, 7000 mg of bamlanivimab, and a combination treatment with 2800 mg of bamlanivimab and 2800 mg of etesevimab
- Primary outcome: effect of bamlanivimab monotherapy and combination therapy with bamlanivimab and etesevimab compared with placebo on SARS-CoV-2 log viral load from baseline to day 11 (±4 days)
- 577 patients enrolled; 156 given placebo vs. 401 distributed among other 4 treatment groups
- Results: "The change in log viral load from baseline at day 11 was −3.72 for 700 mg, −4.08 for 2800 mg, −3.49 for 7000 mg, −4.37 for combination treatment, and −3.80 for placebo. Compared with placebo, the differences in the change in log viral load at day 11 were 0.09 (95% CI, −0.35 to 0.52; P = .69) for 700 mg, −0.27 (95% CI, −0.71 to 0.16; P = .21) for 2800 mg, 0.31 (95% CI, −0.13 to 0.76; P = .16) for 7000 mg, and −0.57 (95% CI, −1.00 to −0.14; P = .01) for combination treatment."

Conclusions

- **"Among nonhospitalized patients with mild to moderate COVID-19 illness, treatment with bamlanivimab and etesevimab, compared with placebo, was associated with a statistically significant reduction in SARS-CoV-2 viral load at day 11; no significant difference in viral load reduction was observed for bamlanivimab monotherapy."**

CADTH response to BLAZE-1

In October 2020, the BLAZE-1 team previous published an interim update on the trial in the New England Journal of Medicine (SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19) [9]. The Canadian Agency for Drugs and Technology in Health (**CADTH**) produced a **critical appraisal** of this report in January 2021, concluding that "more robust, published, peer-reviewed evidence is needed", particularly pertaining to phase 3 of the trial. [10]

Also in January 2021, CADTH released **drug implementation advice** for bamlanivimab. While continuing to acknowledge the need for more robust evidence, and highlighting some logistical challenges with administrating bamlanivimab, CADTH conceded that "unprecedented times require unprecedented system responses", and that "in some specific circumstances and for reasons that may be unique and situational, clinicians and patients may decide that although the evidence of clinical benefit is not overwhelmingly strong, a product's use presents value in an area of unmet clinical need." [11]

BLAZE-1 phase 3 results in the news

Although no phase 3 results have yet been published, Eli Lilly issues a press release on March 10, 2021 sharing some phase 3 results. They stated that the combination treatment of bamlanivimab (700mg) and etesevimab (1400mg) resulted in a 87% risk reduction in COVID-19 related hospitalizations and deaths across 1035 patients. [12]

BLAZE-2 in the news

BLAZE-2 focuses on the efficacy of bamlanivimab and etesevimab in **nursing home residents and staff** (NCT04497987) [13]. Eli Lilly issued a press release on January 26, 2021, stating that in exploratory analyses for assessing treatment, 4200mg of bamlanivimab alone resulted in "a significantly lower frequency of symptomatic COVID-19 (the primary endpoint) in the bamlanivimab treatment arm versus placebo (odds ratio 0.43, p=0.00021)" in all participants [14].

Single studies

Clinical trials: Epistemonikos lists 18 reports of RCTs, of which only 9 have reported data.

Overviews: Wang et. al. [15] published in *Nature* in March of 2021 recommending that bamlanivimab not be used as monotherapy for COVID-19 variants due to resistance.

Evidence syntheses

There are currently no published high-quality evidence syntheses on bamlanivimab for COVID-19.

Please note: This summary reflects evidence up to and including May 3, 2021 only.

Search Methods

Date searched: 2021-05-03

- Google for news items and clinical trials in progress
- Epistemonikos L-OVE on COVID-19 (manual search)
- Ovid MEDLINE search with built-in COVID-19 filter: (bamlanivimab or LY-CoV555 or LY3819253).ti,ab.

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ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Peter Chen, M.D., Ajay Nirula, M.D., Ph.D., Barry Heller, M.D., Robert L. Gottlieb, M.D., Ph.D., Joseph Boscia, M.D., Jason Morris, M.D., Gregory Huhn, M.D., M.P.H.T.M., Jose Cardona, M.D., Bharat Mocherla, M.D., Valentina Stosor, M.D., Imad Shawa, M.D., Andrew C. Adams, Ph.D., Jacob Van Naarden, B.S., Kenneth L. Custer, Ph.D., Lei Shen, Ph.D., Michael Durante, M.S., Gerard Oakley, M.D., Andrew E. Schade, M.D., Ph.D., Janelle Sabo, Pharm.D., Dipak R. Patel, M.D., Ph.D., Paul Klekotka, M.D., Ph.D., and Daniel M. Skovronsky, M.D., Ph.D., for the BLAZE-1 Investigators*

ABSTRACT

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (Covid-19), which is most frequently mild yet can be severe and life-threatening. Virus-neutralizing monoclonal antibodies are predicted to reduce viral load, ameliorate symptoms, and prevent hospitalization.

METHODS

In this ongoing phase 2 trial involving outpatients with recently diagnosed mild or moderate Covid-19, we randomly assigned 452 patients to receive a single intravenous infusion of neutralizing antibody LY-CoV555 in one of three doses (700 mg, 2800 mg, or 7000 mg) or placebo and evaluated the quantitative virologic end points and clinical outcomes. The primary outcome was the change from baseline in the viral load at day 11. The results of a preplanned interim analysis as of September 5, 2020, are reported here.

RESULTS

At the time of the interim analysis, the observed mean decrease from baseline in the log viral load for the entire population was −3.81, for an elimination of more than 99.97% of viral RNA. For patients who received the 2800-mg dose of LY-CoV555, the difference from placebo in the decrease from baseline was −0.53 (95% confidence interval [CI], −0.98 to −0.08; P=0.02), for a viral load that was lower by a factor of 3.4. Smaller differences from placebo in the change from baseline were observed among the patients who received the 700-mg dose (−0.20; 95% CI, −0.66 to 0.25; P=0.38) or the 7000-mg dose (0.09; 95% CI, −0.37 to 0.55; P=0.70). On days 2 to 6, the patients who received LY-CoV555 had a slightly lower severity of symptoms than those who received placebo. The percentage of patients who had a Covid-19–related hospitalization or visit to an emergency department was 1.6% in the LY-CoV555 group and 6.3% in the placebo group.

CONCLUSIONS

In this interim analysis of a phase 2 trial, one of three doses of neutralizing antibody LY-CoV555 appeared to accelerate the natural decline in viral load over time, whereas the other doses had not by day 11. (Funded by Eli Lilly; BLAZE-1 ClinicalTrials.gov number, NCT04427501.)

From the Department of Medicine, Women's Guild Lung Institute, Cedars–Sinai Medical Center, Los Angeles (P.C.), and Long Beach Clinical Trials, Long Beach (B.H.) — both in California; Eli Lilly, Indianapolis (A.N., A.C.A., J.V.N., K.L.C., L.S., M.D., G.O., A.E.S., J.S., D.R.P., P.K., D.M.S.), and Franciscan Health, Greenwood (I.S.) — both in Indiana; Baylor University Medical Center and Baylor Scott and White Research Institute, Dallas (R.L.G.); Vitalink Research, Union, SC (J.B.); Imperial Health, Lake Charles, LA (J.M.); Cook County Health (G.H.) and Northwestern University Feinberg School of Medicine (V.S.), Chicago; Indago Research and Health Center, Hialeah, FL (J.C.); and Las Vegas Medical Research Center, Las Vegas (B.M.). Address reprint requests to Dr. Skovronsky at Eli Lilly, 893 Delaware St., Indianapolis, IN 46225, or at skovronsky_daniel@lilly.com.

*A list of the BLAZE-1 investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Chen and Nirula contributed equally to this article.

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Coronavirus disease 2019 (COVID-19) emerged in late 2019 and spread rapidly, resulting in a global pandemic. Infected persons can have a wide range of disease severity, with many patients showing mild or even asymptomatic disease. However, for unknown reasons, up to 10% of asymptomatic and mild infections lead to more severe outcomes, including respiratory distress requiring hospitalization.[1] Although risk factors for more severe outcomes have been described (including an older age, obesity, hypertension, and underlying chronic medical conditions),[2,3] the connection between viral load and outcomes has not previously been tested in a longitudinal study. Several treatment options have been explored for hospitalized patients with Covid-19 (e.g., antimalarial drugs,[4] antiviral agents,[5-7] immunomodulators,[8-12] glucocorticoids,[13,14] and convalescent plasma[15,16]) with varying results. However, there have been no large randomized, controlled trials of targeted treatments that are specific for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and that are intended to attenuate disease progression in patients with early disease.

Preclinical studies of neutralizing-antibody treatments for SARS-CoV-2 infection in several animal models have shown promising results, with marked reductions in viral loads in the upper and lower respiratory tracts.[17] SARS-CoV-2 gains entry into cells through binding of its spike protein to receptors for angiotensin-converting enzyme 2 on target cells.[18] LY-CoV555 (also known as LY3819253), a potent antispike neutralizing monoclonal antibody that binds with high affinity to the receptor-binding domain of SARS-CoV-2, was derived from convalescent plasma obtained from a patient with Covid-19. The antibody was developed by Eli Lilly after its discovery by researchers at AbCellera and at the Vaccine Research Center of the National Institute of Allergy and Infectious Diseases. The discovery of LY-CoV555 and its passive protection against SARS-CoV-2 in nonhuman primates has been reported previously.[19]

Here, we report interim results from the Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE-1) trial, an ongoing phase 2 trial to evaluate the efficacy and safety of LY-CoV555 in patients with recently diagnosed mild or moderate Covid-19 in the outpatient setting. We examined the effect of the neutralizing antibody on viral load, symptom scores, and clinical outcomes and also report an observed connection between a persistently high viral load and disease severity.

Methods

Trial Design, Treatment, and Oversight

In this randomized, double-blind, placebo-controlled, single-dose trial conducted at 41 centers in the United States, all the patients had positive results on testing for SARS-CoV-2 and presented with one or more mild or moderate symptoms. The investigators reviewed the symptoms, risk factors, and other inclusion and exclusion criteria before enrollment. (A full list of the inclusion and exclusion criteria is provided in the protocol, available with the full text of this article at NEJM.org.) Each patient received a single intravenous infusion of LY-CoV555 or placebo monotherapy over approximately 1 hour. Although the trial contains additional treatment groups, here we focus on the interim analysis of results from only four of these groups: LY-CoV555 at doses of 700 mg, 2800 mg, and 7000 mg and placebo. (Clinical details are also provided in the protocol.)

The preplanned interim analysis was triggered on September 5, 2020, when the last patient who was randomly assigned to receive LY-CoV555 reached day 11. The analysis includes all the data regarding virologic features and symptoms that were available at the time of the database lock. The doses of LY-CoV555 that were evaluated in this trial were based on pharmacologic modeling that predicted that the 700-mg dose would be efficacious. (Details about dose selection are provided in the Supplementary Appendix, available at NEJM.org.) Given the gravity of the pandemic, the doses that were administered in this trial were increased by up to a factor of 10 over the predicted efficacious dose to ensure adequate target coverage. The use of these doses was supported by safety data from a phase 1 trial of LY-CoV555 involving hospitalized patients. Dose levels were fixed, and either LY-CoV555 or placebo was administered within 3 days after positive results on SARS-CoV-2 testing.

The trial, which was sponsored by Eli Lilly, was conducted in accordance with principles of

the Declaration of Helsinki and the ethical guidelines of the Council for International Organizations of Medical Sciences. All the patients provided written informed consent.

OUTCOMES

The primary outcome was the change from baseline in the SARS-CoV-2 viral load at day 11 (±4 days) after positive results on testing. Data regarding virologic features and symptoms were collected up to day 29 in this trial. The viral load was measured by means of a nasopharyngeal swab, which was followed by quantitative reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay at a central laboratory. (Details regarding testing are provided in the Methods section in the Supplementary Appendix.) Key secondary outcomes were safety assessments, symptom burden as reported by the patient on a questionnaire, and clinical outcomes. The major clinical outcome was defined as Covid-19–related in-patient hospitalization, a visit to the emergency department, or death. No deaths were reported, and since most emergency department visits resulted in hospital admissions, we refer to a composite of emergency department visits and in-patient hospitalizations simply as hospitalizations. This report includes an analysis of the primary outcome as well as safety and adverse-event data, information regarding symptoms, and clinical outcomes.

STATISTICAL ANALYSIS

To determine the sample size, we used a dynamic model to simulate viral load over time in patients treated with LY-CoV555 or placebo. This simulated population was used to estimate the statistical power and comparisons in the change from baseline in viral load. (Details are provided in Section 5.2 in the statistical analysis plan, which is included in the protocol document.) All the patients who had undergone randomization and who had received either LY-CoV555 or placebo were included in the primary analysis if their viral-load measures were available both at baseline and at least once after baseline.

Treatment effects were compared with the use of two-sided tests with an alpha level of 0.05. Adjustments for multiple testing were not performed. Significance testing for the primary outcome was performed with the use of a repeated-measures analysis as a mixed model. (Details regarding these methods are provided in Section 6.10 in the statistical analysis plan.)

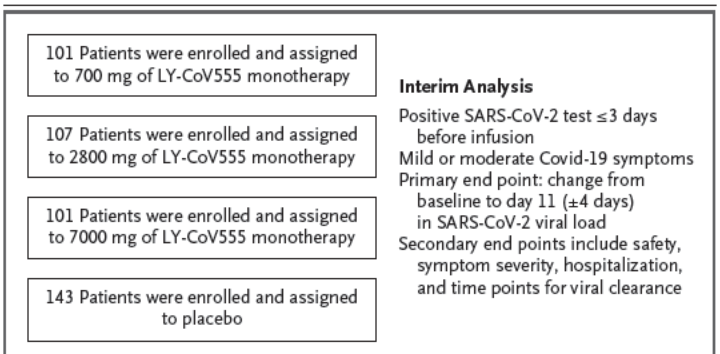

Figure 1. Enrollment and Trial Design.

RESULTS

PATIENTS

From June 17 through August 21, 2020, a total of 467 patients underwent randomization to receive either LY-CoV555 (317 patients) or placebo (150 patients), and the patients in the LY-CoV555 group were assigned to one of three dose subgroups. Of the patients who had undergone randomization, 452 met the criteria for inclusion in the primary analysis (309 in the LY-CoV555 group and 143 in the placebo group). LY-CoV555 was administered to these patients in doses of 700 mg (101 patients), 2800 mg (107 patients), or 7000 mg (101 patients) (Fig. 1). The two trial groups were well balanced regarding risk factors at the time of enrollment (Table 1). Nearly 70% of the patients had at least one risk factor — an age of 65 years or older, a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 35 or more, or at least one relevant coexisting illness — for severe Covid-19. After undergoing randomization, patients received an infusion of LY-CoV555 or placebo within a median of 4 days after the onset of symptoms; at the time of randomization, more than 80% of the patients had only mild symptoms. The observed mean PCR cycle threshold (Ct) value of 23.9 on the day of infusion (equating to approximately 2.5 million RNA equivalents) matched expectations that a recently diagnosed population would have a high viral burden. The conversion from Ct value to viral load

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	LY-CoV555 (N=309)	Placebo (N=143)
Age		
Median (range) — yr	45 (18–86)	46 (18–77)
65 Yr or older — no. (%)	33 (10.7)	20 (14.0)
Female sex — no. (%)	171 (55.3)	78 (54.5)
Race or ethnic group — no./total no. (%)†		
White	269/305 (88.2)	120/138 (87.0)
Hispanic or Latino	135/309 (43.7)	63/143 (44.1)
Black	22/305 (7.2)	7/138 (5.1)
Body-mass index‡		
Median	29.4	29.1
≥30 to <40 — no./total no. (%)	112/304 (36.8)	56/139 (40.3)
≥40 — no./total no. (%)	24/304 (7.9)	9/139 (6.5)
Risk factors for severe Covid-19 — no. (%)§	215 (69.6)	95 (66.4)
Disease status — no. (%)		
Mild	232 (75.1)	113 (79.0)
Moderate	77 (24.9)	30 (21.0)
Median no. of days since onset of symptoms	4.0	4.0
Mean viral load — Ct value¶	23.9	23.8

* Covid-19 denotes coronavirus disease 2019.
† Race or ethnic group was reported by the patients, who could choose more than one category.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Risk factors were an age of 65 years or older, a body-mass index of 35 or more, or at least one coexisting illness in certain prespecified categories.
¶ Ct denotes the cycle threshold of the reverse-transcriptase–polymerase-chain-reaction assay.

is described in Section 6.10 of the statistical analysis plan.

PRIMARY OUTCOME

By day 11, the majority of patients had a substantial trend toward viral clearance, including those in the placebo group. The observed mean decrease from baseline in the log viral load for the entire population was −3.81 (baseline mean, 6.36; day 11 mean, 2.56); this value corresponded to a decrease by more than a factor of 4300 in the SARS-CoV-2 burden, for an elimination of more than 99.97% of viral RNA. For patients who received the 2800-mg dose of LY-CoV555, the difference from placebo in the decrease from baseline was −0.53 (95% confidence interval [CI], −0.98 to −0.08; P=0.02), for a lower viral load by a factor of 3.4 (Table 2). However, smaller differences from placebo in the decrease from baseline were observed among the patients who received the 700-mg dose (−0.20; 95% CI, −0.66 to 0.25; P=0.38) and the 7000-mg dose (0.09; 95% CI, −0.37 to 0.55; P=0.70).

SECONDARY VIRAL OUTCOMES

On day 3, among the patients who received the 2800-mg dose of LY-CoV555, the observed difference from placebo in the decrease from baseline in the mean log viral load was −0.64 (95% CI, −1.11 to −0.17) (Table 2). The other two doses of LY-CoV555 showed similar improvements in viral clearance at day 3, with a difference from placebo in the change from baseline of −0.42 (95% CI, −0.89 to 0.06) for the 700-mg dose and −0.42 (95% CI, −0.90 to 0.06) for the 7000-mg dose. The difference from placebo in the change from baseline for the pooled doses of LY-CoV555 was −0.49 (95% CI, −0.87 to −0.11).

EXPLORATORY MEASURES OF VIRAL CLEARANCE

In the pooled trial population, an association was observed between slower viral clearance and more hospitalization events. Figure 2A presents the absolute viral load among hospitalized patients (pooled across randomization strata) as well as a box plot of viral loads among nonhospitalized patients. On day 7, all the available measures of viral load among hospitalized patients were higher than the median values among the nonhospitalized patients. Among the patients with a higher viral load on day 7, the frequency of hospitalization was 12% (7 of 56 patients) among those who had a Ct value of less than 27.5, as compared with a frequency of 0.9% (3 of 340 patients) among those with a lower viral load. (The SARS-CoV-2 N1 gene primer determines a Ct value that is equivalent to approximately 570,000 nucleic acid–based amplification tests per milliliter with the use of the SARS-CoV-2 reference panel of the Food and Drug Administration.) Since this difference was not anticipated and emerged from post hoc exploratory analysis, it is unclear whether it would be applicable to other populations. Figure 2B shows the cumulative probability that patients in each trial group would have the indicated cycle threshold of viral load on day 7.

Table 2. Change from Baseline in Viral Load.

Variable	LY-CoV555 (N=309)	Placebo (N=143)	Difference (95% CI)
Primary outcome			
Mean change from baseline in viral load at day 11		–3.47	
	700 mg, –3.67		–0.20 (–0.66 to 0.25)
	2800 mg, –4.00		–0.53 (–0.98 to –0.08)
	7000 mg, –3.38		0.09 (–0.37 to 0.55)
	Pooled doses, –3.70		–0.22 (–0.60 to 0.15)
Secondary outcomes*			
Mean change from baseline in viral load at day 3		–0.85	
	700 mg, –1.27		–0.42 (–0.89 to 0.06)
	2800 mg, –1.50		–0.64 (–1.11 to –0.17)
	7000 mg, –1.27		–0.42 (–0.90 to 0.06)
	Pooled doses, –1.35		–0.49 (–0.87 to –0.11)
Mean change from baseline in viral load at day 7		–2.56	
	700 mg, –2.82		–0.25 (–0.73 to 0.23)
	2800 mg, –3.01		–0.45 (–0.92 to 0.03)
	7000 mg, –2.85		–0.28 (–0.77 to 0.20)
	Pooled doses, –2.90		–0.33 (–0.72 to 0.06)

* Data regarding hospitalization, another key secondary outcome, are provided in Table 3.

COVID-19–RELATED HOSPITALIZATION

At day 29, the percentage of patients who were hospitalized with Covid-19 was 1.6% (5 of 309 patients) in the LY-CoV555 group and 6.3% (9 of 143 patients) in the placebo group (Table 3). The percentage of patients according to the LY-CoV555 dose who were hospitalized was similar to the overall percentage, with 1.0% (1 of 101) in the 700-mg subgroup, 1.9% (2 of 107) in the 2800-mg subgroup, and 2.0% (2 of 101) in the 7000-mg subgroup. In a post hoc analysis examining hospitalization among patients who were 65 years of age or older and among those with a BMI of 35 or more, the percentage who were hospitalized was 4% (4 of 95) in the LY-CoV555 group and 15% (7 of 48) in the placebo group. Only 1 patient in the trial (in the placebo group) was admitted to an intensive care unit.

SYMPTOM SCORE

To assess the effect of treatment on Covid-19 symptoms, we compared the change from baseline in symptom scores between the LY-CoV555 group and the placebo group (Fig. 3 and Fig. S1 in the Supplementary Appendix). The symptom score ranged from 0 to 24 and included eight domains that were graded from 0 (no symptoms) to 3 (severe symptoms). From day 2 to day 6, the change in the symptom score from baseline was better in the LY-CoV555 group than in the placebo group, with values of –0.79 (95% CI, –1.35 to –0.24) on day 2, –0.57 (95% CI, –1.12 to –0.01) on day 3, –1.04 (95% CI, –1.60 to –0.49) on day 4, –0.73 (95% CI, –1.28 to –0.17) on day 5, and –0.79 (95% CI, –1.35 to –0.23) on day 6. The change from baseline in the symptom score continued to be better in the LY-CoV555 group than in the placebo group from day 7 to day 11, although by these time points most of the patients in the two groups had fully recovered or had only very mild symptoms.

SAFETY

Serious adverse events occurred in none of the 309 patients in LY-CoV555 group and in 0.7% (1 of 143 patients) in the placebo group (Table 4). The percentage of patients who had an adverse event during treatment was 22.3% (69 of 309) in the LY-CoV555 group and 24.5% (35 of 143) in the placebo group. Diarrhea was reported in 3.2% of the patients (10 of 309) in the LY-CoV555 group and in 4.9% (7 of 143) in the placebo

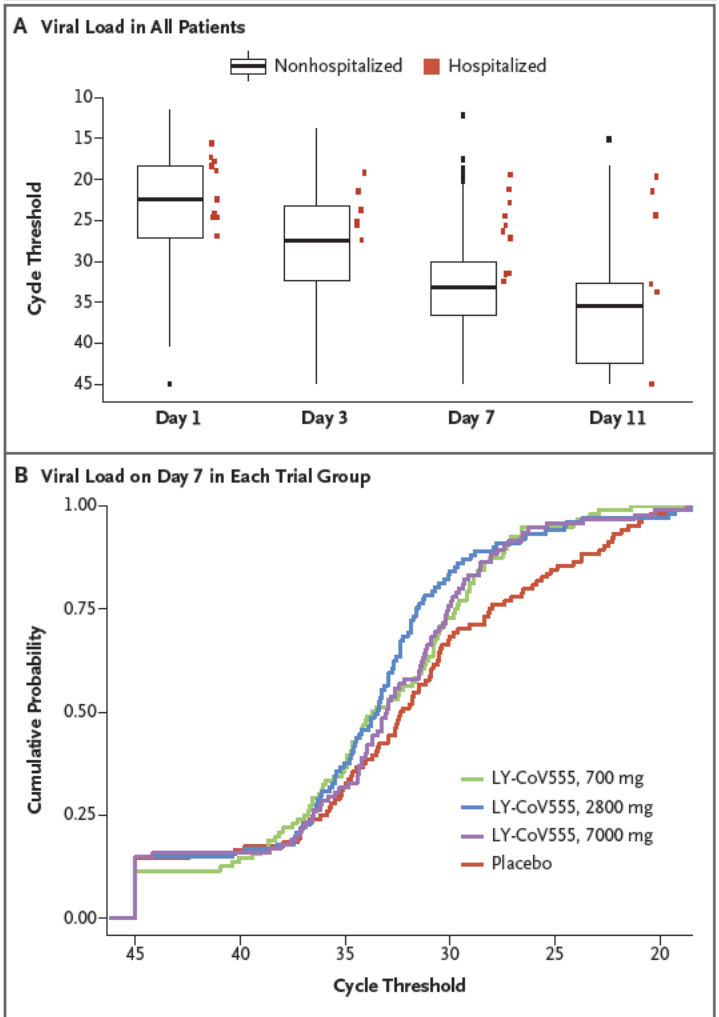

Figure 2. SARS-CoV-2 Viral Load in All Patients and According to Trial Group on Day 7.

Panel A shows the SARS-CoV-2 viral load (as measured by the cycle threshold on reverse-transcriptase–polymerase-chain-reaction assay) for all the patients who received either LY-CoV555 or placebo and for whom viral-load data were available at the time of the interim analysis. The box plots indicate the patients who were not hospitalized, and the red squares indicate those who were hospitalized. Such hospital contact was found to be associated with a high viral load on day 7. The boxes represent interquartile ranges, with the horizontal line in each box representing the median and the whiskers showing the minimum and maximum values (excluding outliers that were more than 1.5 times the values represented at each end of the box). Panel B shows the cumulative probability that patients in each trial group would have the indicated cycle threshold of viral load on day 7.

group; vomiting was reported in 1.6% (5 of 309) and 2.8% (4 of 143), respectively. The most frequently reported adverse event in the LY-CoV555 group was nausea (3.9%), whereas diarrhea (4.9%) was the most frequent adverse event in the placebo group. Infusion-related reactions were reported in 2.3% of the patients (7 of 309) in the LY-CoV555 group and in 1.4% (2 of 143) in the placebo group. Most of these events — which included pruritus, flushing, rash, and facial swelling — occurred during the infusion and were reported as mild in severity. No changes in vital signs were noted during these reactions, and the infusions were completed in all instances. In some patients, antihistamines were administered to help resolve symptoms.

We used standard methods to sequence all viral samples to determine the potential for resistance-associated treatment failure. Accordingly, we assessed the prevalence of variants with resistance to LY-CoV555 that were predicted in preclinical studies. Such variants were present with an allele fraction of more than 20% in at least one sample at any time point in 8.2% of the patients in the LY-CoV555 group (6.3% in the 700-mg subgroup, 8.4% in the 2800-mg subgroup, and 9.9% in the 7000-mg subgroup) and in 6.1% of those in the placebo group. The clinical importance of the presence of these variants is not known.

DISCUSSION

In this preplanned interim analysis of the BLAZE-1 trial, we examined the efficacy of LY-CoV555 in the treatment of mild or moderate Covid-19. The trial was designed to enroll patients with a recent disease onset to evaluate the effect of early intervention with antibody therapy on viral-load biomarkers, symptoms, and severe clinical outcomes, such as hospitalization and death.

Among the patients who received LY-CoV555, the viral load at day 11 (the primary outcome) was lower than that in the placebo group only among those who received the 2800-mg dose. However, a decreased viral load at day 11 did not appear to be a clinically meaningful end point, since the viral load was substantially reduced from baseline for the majority of patients, including those in the placebo group, a finding that was consistent with the natural course of the disease.[20,21] However, the evaluation of the effect of LY-CoV555 therapy on patients' symptoms at earlier time points during treatment (e.g., on day 3) showed a possible treatment effect, with no substantial differences observed among the three doses. It is unclear whether RT-PCR is an accurate

measure of viral neutralization, since viral RNA may persist for some time even in the absence of replication-competent virus. Since the severity of illness is primarily driven by lung injury from SARS-CoV-2 infection in the lower respiratory tract, the viral load in the air spaces would be a better reflection of the injury response than the viral load in nasopharyngeal secretions. However, assessments of the lower respiratory tract were not practical owing to precautions that were required in treating these highly infectious patients. Therefore, the nasopharyngeal viral swab was the most pragmatic way of getting a sense of viral load as a surrogate marker of the viral load in the lungs and to correlate with clinical outcomes. However, the nasopharyngeal viral load has not been validated as a predictor of clinical disease course.

An unanticipated observation in this trial was that patients with a higher viral load on day 7 had a higher rate of hospitalization than those with better clearance of viral RNA on day 7, a finding that was consistent with the delayed viral clearance that was observed in patients with more severe disease.[20,22,23] On day 7, no hospitalized patient had a viral load that was below the median value of the population. If this observation is prospectively confirmed in future studies, it would suggest the potential for an agent that lowers the viral load to reduce the rate of hospitalization.

To examine the potential of LY-CoV555 to improve Covid-19 clinical outcomes, we evaluated the effect of LY-CoV555 therapy on the frequency of hospitalization, an important outcome given the association between hospitalization and subsequent mortality in patients with Covid-19.[23,24] On day 29, the percentage of patients who were hospitalized was 1.6% in the LY-CoV555 group and 6.3% in the placebo group. In a post hoc analysis that was focused on high-risk subgroups (an age of ≥65 years or a BMI of ≥35), the percentage of hospitalization was 4.2% in the LY-CoV555 group and 14.6% in the placebo group.

The data regarding symptoms (as measured by the change from baseline in the symptom score) were also consistent with the hospitalization results, with findings that supported a possible reduction in symptom severity as early as day 2 in the LY-CoV555 group. This effect was maintained over time and across doses, which further supports the validity of a treatment effect on symptoms and suggests a mechanistic link between a lower viral load and a lower frequency of hospitalization. Although the differences in the effects of the three doses of LY-CoV555 were not clear, the 2800-mg dose was the only one to show evidence of accelerated viral clearance. Nevertheless, further studies should continue to assess the efficacy of lower doses.

The safety profile of patients who received LY-CoV555 was similar to that of placebo-treated patients. These data indicate that the treatment is safe. In this interim analysis, the patients who received LY-CoV555 had fewer hospitalizations

Table 3. Hospitalization.*

Key Secondary Outcome	LY-CoV555	Placebo	Incidence
	no. of patients/total no.		%
Hospitalization		9/143	6.3
	700 mg, 1/101		1.0
	2800 mg, 2/107		1.9
	7000 mg, 2/101		2.0
	Pooled doses, 5/309		1.6

* Data for patients who presented to the emergency department are included in this category.

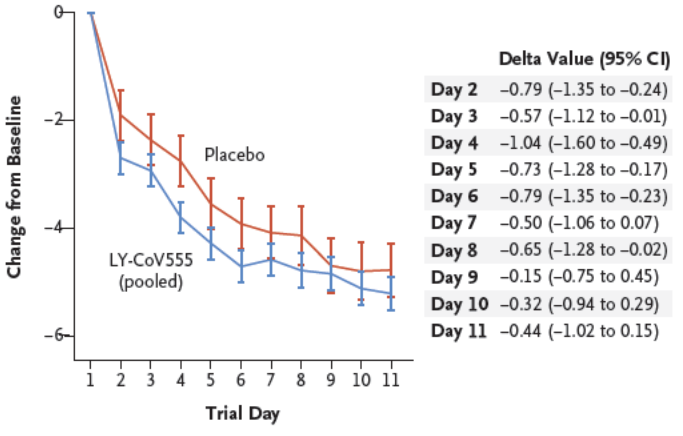

Figure 3. Symptom Scores from Day 2 to Day 11.

Shown is the difference in the change from baseline (delta value) in symptom scores between the LY-CoV555 group and the placebo group from day 2 to day 11. The symptom scores ranged from 0 to 24 and included eight domains, each of which was graded on a scale of 0 (no symptoms) to 3 (severe symptoms). The I bars represent 95% confidence intervals. Details about the symptom-scoring methods are provided in the Supplementary Appendix.

Table 4. Adverse Events.

Adverse Events	LY-CoV555 (N=309)				Placebo (N=143)
	700 mg (N=101)	2800 mg (N=107)	7000 mg (N=101)	Pooled Doses (N=309)	
	number of patients (percent)				
Serious adverse events*	0	0	0	0	1 (0.7)
Adverse events					
Any	24 (23.8)	23 (21.5)	22 (21.8)	69 (22.3)	35 (24.5)
Mild	16 (15.8)	18 (16.8)	10 (9.9)	44 (14.2)	18 (12.6)
Moderate	7 (6.9)	3 (2.8)	8 (7.9)	18 (5.8)	16 (11.2)
Severe	0	2 (1.9)	3 (3.0)	5 (1.6)	1 (0.7)
Missing data	1 (1.0)	0	1 (1.0)	2 (0.6)	0
Adverse events according to preferred term†					
Nausea	3 (3.0)	4 (3.7)	5 (5.0)	12 (3.9)	5 (3.5)
Diarrhea	1 (1.0)	2 (1.9)	7 (6.9)	10 (3.2)	7 (4.9)
Dizziness	4 (4.0)	3 (2.8)	3 (3.0)	10 (3.2)	3 (2.1)
Headache	3 (3.0)	2 (1.9)	0	5 (1.6)	3 (2.1)
Pruritus	2 (2.0)	3 (2.8)	0	5 (1.6)	1 (0.7)
Vomiting	1 (1.0)	3 (2.8)	1 (1.0)	5 (1.6)	4 (2.8)
Chills	0	1 (0.9)	3 (3.0)	4 (1.3)	0
Pyrexia	1 (1.0)	2 (1.9)	1 (1.0)	4 (1.3)	1 (0.7)
Chest discomfort	1 (1.0)	1 (0.9)	1 (1.0)	3 (1.0)	1 (0.7)
Fatigue	0	1 (0.9)	2 (2.0)	3 (1.0)	0
Hypertension	1 (1.0)	0	2 (2.0)	3 (1.0)	0
Lipase increased	1 (1.0)	0	2 (2.0)	3 (1.0)	0
Thrombocytosis	1 (1.0)	2 (1.9)	0	3 (1.0)	0
Blood pressure increased	2 (2.0)	0	0	2 (0.6)	0
Chest pain	1 (1.0)	1 (0.9)	0	2 (0.6)	0
Dyspepsia	1 (1.0)	0	1 (1.0)	2 (0.6)	0
Hypersensitivity	1 (1.0)	1 (0.9)	0	2 (0.6)	1 (0.7)
Insomnia	0	1 (0.9)	1 (1.0)	2 (0.6)	0
Nasal congestion	1 (1.0)	1 (0.9)	0	2 (0.6)	1 (0.7)
Rash	1 (1.0)	0	1 (1.0)	2 (0.6)	1 (0.7)
Syncope	0	1 (0.9)	1 (1.0)	2 (0.6)	1 (0.7)

* The serious adverse event in the placebo group was upper abdominal pain. There were no deaths during the trial.
† The preferred terms were defined according to the *Medical Dictionary for Regulatory Activities*, version 23.0.

and a lower symptom burden than those who received placebo, with the most pronounced effects observed in high-risk cohorts. If these results are confirmed in additional analyses in this trial, LY-CoV555 could become a useful treatment for emergency use in patients with recently diagnosed Covid-19.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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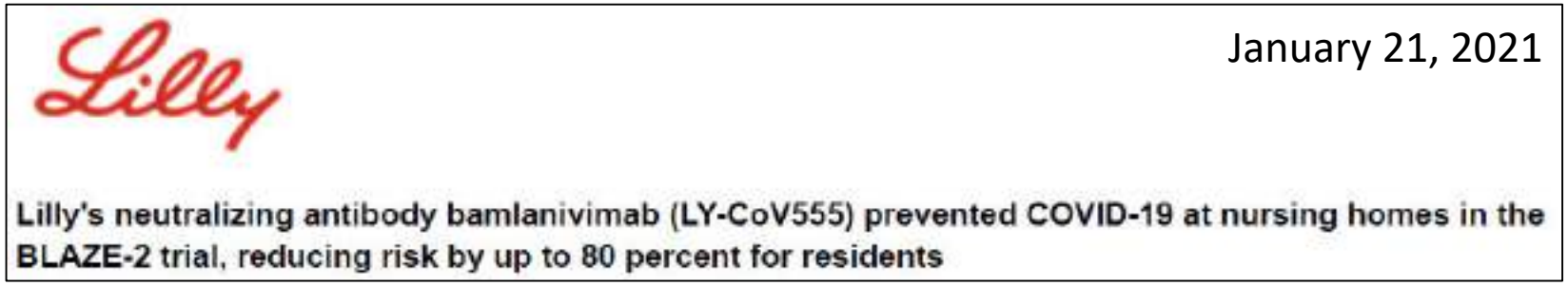
BLAZE-2: Press Release



Phase 3 multi-centre, double-blinded RCT (Part 1 exploratory analysis**)**	
Clinical Question	Does administration of bamlanivimab reduce the rate of symptomatic COVID-19 infections amongst all staff and residents in nursing homes with a high risk of COVID-19 exposure?
Participants	Residents or staff aged 18+ in a nursing home with at least 1 confirmed SARS-CoV-2 detection in previous 7 days • n = 965 participants with negative baseline COVID-19 test (299 residents, 666 staff) • n = 132 participants with positive baseline COVID-19 tests (41 residents, 91 staff)
Intervention	• Bamlanivimab 4200 mg IV x 1
Comparator	• Placebo IV x 1
Outcomes	[1º] Percentage of participants with COVID-19 within 21 days of detection (at 8 weeks) • **OR 0.43; p = 0.00021** • Pre-specified subgroup of nursing home residents **OR 0.20; p = 0.00026** • Serious adverse events: similar frequency to placebo

COVID-attributed deaths: 4, all in placebo

COVID-attributed deaths: 4, all in placebo

https://clinicaltrials.gov/ct2/show/NCT04497987

https://www.prnewswire.com/news-releases/lillys-neutralizing-antibody-bamlanivimab-ly-cov555-prevented-covid-19-at-nursing-homes-in-the-blaze-2-trial-reducing-risk-by-up-to-80-percent-for-residents-301212159.html

BLAZE-2: Press Release

Limitations:

- Preliminary reporting of exploratory analysis – no pre-print
  - Estimated study completion June 2021

Practical considerations:

- Administration to all staff/residents of a facility not aligned with NS procedures for LTC resident with COVID-19
  - RCU admission, vaccination of staff
  - Limited availability of pandemic supply of bamlanivimab

Suggest: no change to current bamlanivimab recommendation:

Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health-affiliated Regional Care Units.

BLAZE-1: Phase 3 Press Release

January 26, 2021

New data show treatment with Lilly's neutralizing antibodies bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016) together reduced risk of COVID-19 hospitalizations and death by 70 percent

Phase 3 multi-centre, double-blinded RCT	
Clinical Question	Does administration of bamlanivimab in combination with etesevimab in high-risk, recently diagnosed mild-mod COVID-19 prevent COVDI-19-related hospitalizations and death?
Participants	n = 1035 outpatients age ≥ 18, COVID-19 positive in past ≤ 3 days, 1 or more mild-moderate COVID-19 symptom AND have at least one high-risk factor
Intervention	• Bamlanivimab 2800 mg IV and etesevimab 2800 mg IV x 1
Comparator	• Placebo IV x 1
Outcomes	[1º] Percentage of participants with COVID-19-related hospitalization or all-cause death (by day 29) • **Intervention: 2.1% vs Placebo: 7.0%, p = 0.0004** • "Statistically significant key secondary endpoints" – symptom resolution, viral clearance, composite of hospitalization + ER visit + death

BLAZE-4: initial PK/PD results suggest lower bamlanivimab 700 mg /etesevimab 1400 mg doses together similar to 2800 mg doses

https://clinicaltrials.gov/ct2/show/NCT04427501

https://investor.lilly.com/news-releases/news-release-details/new-data-show-treatment-lillys-neutralizing-antibodies

BLAZE-1: Phase 3 Press Release

Limitations:

- Preliminary reporting – no pre-print
  - Results available for combination arm only

Practical considerations:

- Results suggest patient-important benefit similar to Phase 2 results

Suggest: no change to current bamlanivimab recommendation:

Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health-affiliated Regional Care Units.

FOR IMMEDIATE RELEASE

Eli Lilly Canada Inc.

P.O. Box 73, Exchange Tower
130 King Street West, Suite 900
Toronto, Ontario M5X 1B1
1.416.694.3221 | 1.800.268.4446
www.lilly.ca

January 26, 2021

New data show treatment with Lilly's neutralizing antibodies bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016) together reduced risk of COVID-19 hospitalizations and death by 70 per cent

- *BLAZE-1 trial met primary endpoint and key secondary endpoints with high statistical significance*
- *Results from more than 1,000 high-risk patients were consistent with previous data*
- *Findings from BLAZE-4 trial provide data on lower doses of bamlanivimab and etesevimab together*
- *Media and investor call "SARS-CoV-2 Neutralizing Antibody Program Update" to be held at noon EST January 26; link for joining live or for subsequent replay available here*

TORONTO, ON, Jan. 26, 2021 – Bamlanivimab (LY-CoV555) 2800 mg and etesevimab (LY-CoV016) 2800 mg together significantly reduced COVID-19-related hospitalizations and deaths (collectively, "events") in high-risk patients recently diagnosed with COVID-19, meeting the primary endpoint of the Phase 3 BLAZE-1 trial, Eli Lilly and Company (NYSE: LLY) announced. Across 1,035 patients, there were 11 events (2.1 percent) in patients taking therapy and 36 events (7.0 percent) in patients taking placebo, representing a 70 per cent risk reduction (p= 0.0004). There were 10 deaths total, all of which occurred in patients taking placebo, and no deaths in patients taking bamlanivimab and etesevimab together.

Bamlanivimab and etesevimab together also demonstrated statistically significant improvements on all key secondary endpoints, providing strong evidence that the therapy reduced viral load and accelerated symptom resolution.

"These data show that treatment with bamlanivimab and etesevimab together may be effective in reducing symptoms, reducing viral load, and decreasing the risk of hospitalization and death in patients recently diagnosed with mild to moderate COVID-19," said Doron Sagman, M.D., FRCPC, Lilly Canada's senior medical director and vice president of R & D and medical affairs. "These data, which replicate the positive Phase 2 data, increase our confidence in the use of neutralizing antibodies as an important treatment to help fight the rapidly increasing burden of this global pandemic, and we look forward to seeing them put to use for Canadian patients in need."

"Notably, the 70 per cent decrease in risk of hospitalizations or death seen in this Phase 3 trial of bamlanivimab and etesevimab together is consistent with the reduction in risk of hospitalization or ER visits seen with bamlanivimab alone in the Phase 2 trial," said Daniel Skovronsky, M.D., Ph.D., Lilly's chief scientific officer and president of Lilly Research Laboratories.

In the trial, the safety profile of bamlanivimab and etesevimab together was consistent with observations from other Phase 1, Phase 2 and Phase 3 trials evaluating these antibodies. Serious adverse events were reported at a similar frequency in the group receiving bamlanivimab and etesevimab together and the group receiving placebo. Across multiple clinical trials, Lilly has collected safety and efficacy data in more than 4,000 participants treated with Lilly's neutralizing antibodies, either bamlanivimab alone or bamlanivimab and etesevimab together.

Bamlanivimab is authorized for use in the treatment of mild- to moderate COVID-19 in high-risk patients under Health Canada's Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19, and it has also been authorized for use in several other countries.

BLAZE-4

Additionally, initial results from the ongoing BLAZE-4 trial provide viral load and pharmacodynamic/pharmacokinetic data which demonstrated lower doses, including bamlanivimab 700 mg and etesevimab 1400 mg together, are similar to bamlanivimab 2800 mg and etesevimab 2800 mg together. Lilly plans to explore even lower doses of bamlanivimab and etesevimab together, as lower doses can maximize available supply to treat more patients, allow potential for subcutaneous dosing, and potentially reduce the burden on healthcare system and patients through reduced infusion times.

Lilly has a robust global supply chain in place to produce its neutralizing antibodies, with numerous manufacturing sites worldwide, and the supply is expected to increase substantially in 2021. Lilly continues to accelerate the manufacturing of etesevimab in collaboration with Amgen, to provide up to 1 million doses of etesevimab for administration with bamlanivimab by mid-2021 – including more than 250,000 doses in the first quarter – for use around the world.

Investors, media and the general public are invited to a conference call where Lilly will provide more data and discuss Lilly's SARS-CoV-2-neutralizing antibody program. The webcast information is available here. Participants may join live at noon EST on January 26 or, after that time may access a replay of the event at that same link.

Important Information about bamlanivimab

HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS COVID-19 DRUG BASED ON LIMITED CLINICAL TESTING IN HUMANS AND/OR QUALITY INFORMATION.

Bamlanivimab is indicated for: The treatment of adults and pediatric patients 12 years of age or older with mild to moderate COVID19 who weigh at least 40 kg and who are at high risk of progressing to severe COVID-19 illness and/or hospitalization.

The use of bamlanivimab is permitted under an interim authorization delivered in accordance with section 5 of the Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. The interim authorization is associated with Terms and Conditions that need to be met by the sponsor to ascertain the continued quality, safety and efficacy of the

product. For further information on authorization under this pathway, please refer to Health Canada's IO Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19.

Healthcare providers should review the product monograph for bamlanivimab, the Patient Medication Information on bamlanivimab, and the Dear HCP Letter on the use of bamlanivimab with English-only labels. Also available is the Bamlanivimab Playbook: information for provincial, territorial and local public health programs in planning and implementing the use of bamlanivimab in response to COVID-19 (December 2020).

About bamlanivimab

Bamlanivimab is a recombinant, neutralizing human IgG1 monoclonal antibody (mAb) directed against the spike protein of SARS-CoV-2. It is designed to block viral attachment and entry into human cells, thus neutralizing the virus, potentially treating COVID-19. Bamlanivimab emerged from the collaboration between Lilly and AbCellera to create antibody therapies for the prevention and treatment of COVID-19. Lilly scientists rapidly developed the antibody in less than three months after it was discovered by AbCellera and the scientists at the National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center. It was identified from a blood sample taken from one of the first U.S. patients who recovered from COVID-19.

Lilly has successfully completed a Phase 1 study of bamlanivimab in hospitalized patients with COVID-19 (NCT04411628). A Phase 2/3 study in people recently diagnosed with COVID-19 in the ambulatory setting (BLAZE-1, NCT04427501) is ongoing. A Phase 3 study of bamlanivimab for the prevention of COVID-19 in residents and staff at long-term care facilities (BLAZE-2, NCT04497987) is ongoing. In addition, bamlanivimab is being tested in the National Institutes of Health-led ACTIV-2 study in ambulatory COVID-19 patients.

About etesevimab

Etesevimab (LY-CoV016, also known as JS016) is a recombinant fully human monoclonal neutralizing antibody, which specifically binds to the SARS-CoV-2 surface spike protein receptor binding domain with high affinity and can block the binding of the virus to the ACE2 host cell surface receptor. Point mutations were introduced into the native human IgG1 antibody to mitigate effector function. Lilly licensed etesevimab from Junshi Biosciences after it was jointly developed by Junshi Biosciences and Institute of Microbiology, Chinese Academy of Science (IMCAS). Junshi Biosciences leads development in Greater China, while Lilly leads development in the rest of the world.

Lilly has successfully completed a Phase 1 study (NCT04441931) of etesevimab in healthy U.S. volunteers to evaluate the safety, tolerability, pharmacokinetics and immunogenicity. A Phase 2/3 study in people recently diagnosed with COVID-19 in the ambulatory setting (BLAZE-1, NCT04427501) is ongoing. Junshi Biosciences has completed a similar Phase 1 study in healthy volunteers in China and has initiated Phase 1b/2 trials in COVID-19 patients globally.

About BLAZE-1

BLAZE-1 (NCT04427501) is a randomized, double-blind, placebo-controlled Phase 2/3 study designed to assess the efficacy and safety of bamlanivimab alone or bamlanivimab and etesevimab together for the

treatment of symptomatic COVID-19 in the outpatient setting. To be eligible, patients were required to have mild or moderate symptoms of COVID-19 as well as a positive SARS-CoV-2 test based on a sample collected no more than three days prior to drug infusion.

In the Phase 2 portion of BLAZE-1, cohorts of mild to moderate recently diagnosed COVID-19 patients, were randomized to one of three doses of bamlanivimab (700 mg, 2800 mg, and 7000 mg), bamlanivimab 2800 mg plus etesevimab 2800 mg, or placebo. Results from the Phase 2 cohorts of BLAZE-1 were published in the *New England Journal of Medicine* and *The Journal of the American Medical Association*.

In the Phase 3 portion of BLAZE-1, the combination therapy arms enrolled mild to moderate, recently diagnosed COVID-19 patients who are at high risk for progressing to severe COVID-19 and/or hospitalization, studying bamlanivimab 2800 mg plus etesevimab 2800 mg versus placebo. The primary outcome measure for the Phase 3 portion of the BLAZE-1 trial was the percentage of participants who experience COVID-related hospitalizations or death from any cause by day 29. The key secondary endpoints were change from baseline to day 7 in SARS-CoV-2 viral load, persistently high SARS-CoV2 viral load on day 7, time to sustained symptom resolution, and COVID-related hospitalization, ER visit or death from any cause from baseline by day 29. Additional endpoints include change from baseline in viral load at other time points, symptom improvement, symptom resolution, as well as safety.

The study is ongoing with additional treatment arms. Across all treatment arms, the trial will enroll up to 3,300 participants.

About BLAZE-4

BLAZE-4 (NCT04634409) is a randomized, double-blind, placebo-controlled trial designed to assess the efficacy and safety of bamlanivimab alone, and bamlanivimab and etesevimab together, at various doses, versus placebo for the treatment of symptomatic COVID-19 in the outpatient setting. Across all treatment arms, the trial will enroll an estimated 1,000 participants in the United States and Puerto Rico.

The primary outcome measure is percentage of participants who have a viral load greater than 5.27 at day 7. Additional endpoints include change from baseline to Day 7 in SARS-CoV-2 viral load, percentage of participants who experience COVID-related hospitalization, ER visit or death from baseline through Day 29, as well as safety.

About Lilly's COVID-19 Efforts

Lilly is bringing the full force of its scientific and medical expertise to attack the coronavirus pandemic around the world. Existing Lilly medicines are being studied to understand their potential in treating complications of COVID-19, and the company is collaborating with partner companies to discover novel antibody treatments for COVID-19. Lilly is testing both single antibody therapy as well as combinations of antibodies as potential therapeutics for COVID-19.

About Lilly Canada

Eli Lilly and Company is a global healthcare leader that unites caring with discovery to make life better for people around the world. We were founded more than a century ago by Colonel Eli Lilly, who was

committed to creating high quality medicines that meet people's needs, and today we remain true to that mission in all our work. Lilly employees work to discover and bring life-changing medicines to people who need them, improve the understanding and management of disease, and contribute to our communities through philanthropy and volunteerism.

Eli Lilly Canada was established in 1938, the result of a research collaboration with scientists at the University of Toronto which eventually produced the world's first commercially available insulin. Our work focuses on oncology, diabetes, autoimmunity, neurodegeneration, and pain. To learn more about Lilly Canada, please visit us at www.lilly.ca.

For our perspective on issues in healthcare and innovation, follow us on twitter @LillyPadCA

Lilly Cautionary Statement Regarding Forward-Looking Statements

This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about bamlanivimab (LY-CoV555) as a potential treatment for patients with or at risk of infection from COVID-19, as well as its supply, and reflects Lilly's current beliefs. However, as with any such undertaking, there are substantial risks and uncertainties in the process of drug development and commercialization. Among other things, there can be no guarantee that future study results will be consistent with the results to date, that bamlanivimab will prove to be a safe and effective treatment or preventative for COVID-19, that bamlanivimab will receive regulatory approvals or additional authorizations, or that we can provide an adequate supply of bamlanivimab in all circumstances. For a further discussion of these and other risks and uncertainties that could cause actual results to differ from Lilly's expectations, please see Lilly's most recent Forms 10-K and 10-Q filed with the U.S. Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

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Media Contact:
Michael McDougall
mcdougall_michael@lilly.com
647-226-3066

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group Recommendations

COVID Network request: suggestions about how bamlanivimab could potentially be implemented.

Bamlanivimab Recommendation: use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 aged 65 and older in NS Health-affiliated RCU facilities.

Rationale:

- **Health Canada indication**: Bamlanivimab is authorized for use under an interim order for patients ≥ 12 years of age (≥40 kg) with mild to moderate COVID-19 at high risk of progressing to severe COVID-19 illness and/or hospitalization
- **Evidence**: BLAZE-1 (interim analysis of a phase 2 trial)
    - Non-hospitalized patients (≥ 18 years of age) with recently diagnosed mild to moderate COVID-19. Approximately 69% of patients had risk factors for severe COVID-19.
    - **Efficacy:** Reduced hospital admissions (signal of increased benefit in those >/= 65 and BMI >/= 35). Note: lack of statistical backing for clinical outcomes.
    - **Safety**: No signal of serious harm
- **Role in therapy**:
    - **Pragmatic research**
    - Cannot be endorsed for use in routine care based on the published evidence to date
- **Population:**
    - ***Non-severe COVID-19 aged 65 and older***
    - Bamlanivimab is an neutralizing monoclonal antibody and is ideal for early disease in non-severe patients as it targets pre-cellular viral entry
    - Blaze-1 supports use in non-severe COVID-19 population, but evidence from BLAZE-1 not clear in terms of which patients with risk factors benefit most. Signals of increased benefit for older population aged 65 and greater and BMI greater than 35.
    - Individuals 65 years of age and up are at highest risk for progression to severe disease and death and mount less of an immune response
- **Setting:**
    - **Regional care units**
    - Health Canada provides several indications that are not feasible to implement in the context of pragmatic research relying on existing NS Health infrastructure
    - One NS Health affiliated setting that could incorporate the provision of bamlanivimab to non-severe outpatients are the RCUs.
- **Public health/IPAC considerations**:
    - Discussed inherent infection-control issues with infusing COVID-19 positive outpatients in existing healthcare facilities or infusion centers. Regional Care Units (RCUs) were suggested as a practical setting to administer bamlanivimab without having to introduce patients into a new healthcare environment, and aligns with the pragmatic research method of using existing systems. Also would not require an infusion center and could administer to patients in their bed. Would require an order set, IV monograph, pre medications, anaphylaxis kit, and nurse to infuse bamlanivimab and monitor for infusion reactions.

unrelated [redacted]

[redacted]

[redacted]

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Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	December 17, 2020	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Gabrielle Richard, Emma Reid, Barbara Goodall, Glenn Cox, Lisa Grandy Allen		

Items	Discussion
- **Review Minutes**	unrelated [redacted]
- **Bamlanivimab: role in therapy and implementation strategies**	Reviewed COVID Network request from Therapeutics and Prophylactics Advisory Group: provide the Network with information on each agent (i.e., unrelated [redacted], bamlanivimab) and suggestions about how they could potentially be implemented. Confirmed with Kathleen: Province of Nova Scotia has plans to receive 50 doses of bamlanivimab. For formal bamlanivimab review, slides presented: - Lisa presented on the progression of COVID-19 viral illness and the role of different treatments within the different stages. Discussed that targeting the pre-cellular entry stage of the virus may have effect beyond just the individual with infection, as it can impact infectivity and transmission risk. - Emma presented on the BLAZE-1 trial including a focus on methods and generalizability in the context of the Health Canada Interim Order authorization of bamlanivimab. Discussion followed around interpretation of BLAZE-1 results [redacted], s.14(1) [redacted] Discussed public health considerations around administration, s.14(1) [redacted] s.14(1) [redacted]. Other thoughts: s.14(1) [redacted] In interest of providing sufficient time toward the discussion, have scheduled an additional one-hour meeting with this as an agenda item for December 18.
- **CO-VIC and [redacted] discussion**	Barb presented slides with background information on the pragmatic CO-VIC study. Presentation and discussion will continue Dec 18 meeting. **Action item: B. Goodall to provide slides to Tasha for distribution before Dec 18 meeting.**
- [redacted]	[redacted]

OVID-19 Drugs and Biologics Clinical Practice Guidelines Working Group

crobial and Immunomodulatory Therapy in Adult Patients with COVID-19

mendations in this document apply to patients ars of age. Click the medication names in the table the associated science briefs.

Recommendations are based on the best available data and may change as additional data becomes available.

Infectious diseases consultation (where available) is recommended before any investigational treatment is offered to a patient with COVID-19 outside of a clinical trial.

Click for dosing and pharmacologic for medications approved or under management of COVID-19.

F ILLNESS	RECOMMENDATIONS
Patients ventilatory support, nasal oxygen, ation, invasive tion, or ECMO. usually ensive care	unrelated unrelated Bamlanivimab is not recommended outside of clinical trials.
Ill Patients uiring low-flow gen. These y managed in	unrelated Bamlanivimab is not recommended outside of clinical trials.
tients ot require supplemental baseline status, or other ort. These y managed in an tient setting.	unrelated Bamlanivimab is not recommended outside of clinical trials. unrelated

IENDED for any patient severity: Hydroxychloroquine or chloroquine Lopinavir/ritonavir

Version 2.0 | Upd
https://doi.org/10.4732

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]Bamlanivimab for injection

Solution for infusion, 700 mg/20 mL (35 mg/mL)

Anti-SARS-CoV-2 spike protein monoclonal antibody

HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS COVID-19 DRUG BASED ON LIMITED CLINICAL TESTING IN HUMANS AND/OR QUALITY INFORMATION

Bamlanivimab is indicated for:

The treatment of adults and pediatric patients 12 years of age or older with mild to moderate COVID-19 who weigh at least 40 kg and who are at high risk of progressing to severe COVID-19 illness and/or hospitalization.

The use of bamlanivimab is permitted under an interim authorization delivered in accordance with section 5 of the COVID-19 Interim order (IO)[*], pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. The interim authorization is associated with Terms and Conditions that need to be met by the sponsor to ascertain the continued quality, safety and efficacy of the product. For further information on authorization under this pathway, please refer to Health Canada's IO Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19.

[*] https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/interim-order-import-sale-advertising-drugs.html#a2.8

Eli Lilly Canada Inc.
Exchange Tower
130 King Street West, Suite 900
PO Box 73
Toronto, Ontario
M5X 1B1
1-888-545-5972
www.lilly.ca

Date of Initial Authorization:
November 20, 2020

Submission Control Number: 244947

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Bamlanivimab is indicated for the treatment of adults and pediatric patients 12 years of age or older with mild to moderate coronavirus disease 2019 (COVID-19), who weigh at least 40 kg and who are at high risk of progressing to severe COVID-19 illness and/or hospitalization.

High risk is defined as patients who meet at least one of the following criteria:

- Are ≥ 65 years of age
- Have a body mass index (BMI) ≥ 35 for patients ≥ 18 years of age
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥ 55 years of age **AND have**
  - cardiovascular disease, OR
  - hypertension, OR
  - chronic obstructive pulmonary disease/other chronic respiratory disease
- Are 12-17 years of age **AND have**
  - BMI ≥ 85th percentile for their age and gender, OR
  - Sickle cell disease, OR
  - Congenital or acquired heart disease, OR
  - Neurodevelopmental disorders, for example, cerebral palsy, OR
  - A medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
  - Asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

Bamlanivimab should not be used in patients hospitalized with severe COVID-19 respiratory disease as benefit of treatment has not been observed in this setting. Bamlanivimab, a monoclonal antibody, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Interim authorization is supported by a numerical reduction in hospitalization or emergency room visits in high risk patients treated with bamlanivimab compared to high risk patients treated with placebo (see **14 CLINICAL TRIALS**).

1.1 Pediatrics

Pediatrics: Based on the data submitted in this interim authorization and reviewed by Health Canada, the safety and efficacy of bamlanivimab in pediatric patients has not been established. However, because the mechanism of action of bamlanivimab, as a neutralizing IgG1 mAb against the spike (S) protein of SARS-CoV-2, is directed against the virus and not the host response to the viral infection, it is reasonable to anticipate similar function in adolescents compared to adults. In addition, considering the acceptable safety profile observed from the adult population who weigh at least 40 kg, treating physicians may consider the use of bamlanivimab for adolescents 12 years of age or older who weigh ≥ 40 kg with high risk factors. Close monitoring in this patient population is highly recommended.

2 CONTRAINDICATIONS

Bamlanivimab is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Bamlanivimab should only be administered in settings in which health care providers have immediate access to medications to treat a severe reaction, such as severe infusion reaction or anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

Bamlanivimab should be administered to patients as soon as possible after a positive test for COVID-19 using a direct SARS-CoV-2 validated testing method. The drug should be administered within 10 days following the onset of clinical signs and symptoms of infection.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of bamlanivimab is a single intravenous infusion of 700 mg bamlanivimab.

Use in Specific Populations

- Bamlanivimab is not recommended for patients weighing less than 40 kg.

4.3 Reconstitution

No reconstitution of bamlanivimab is required.

4.4 Administration

Preparation

Bamlanivimab for injection should be prepared by a qualified healthcare professional using aseptic technique:

- Remove the bamlanivimab vial from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat.**
- Inspect bamlanivimab visually for particulate matter and discoloration.
  - Bamlanivimab is a clear to opalescent and colorless to slightly yellow to slightly brown solution.
- Gently invert vial by hand approximately 10 times. **Do not shake.**

There are two options for preparation of the diluted solution (see Table 1):

Option 1: dilution using PREFILLED infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP.

- Withdraw and discard required volume of 0.9% Sodium Chloride Injection from infusion bag.
- Withdraw required volume of bamlanivimab from the vial using an appropriately sized syringe.

- Transfer bamlanivimab to the 0.9% Sodium Chloride Injection infusion bag.

OR

Option 2: dilution using an EMPTY, sterile, infusion bag able to accommodate 200 mL solution.

- Add required volume of 0.9% Sodium Chloride Injection to an empty, sterile infusion bag.
- Withdraw required volume of bamlanivimab from the vial using an appropriately sized syringe.
- Transfer bamlanivimab to the sterile infusion bag.

Following completion of Option 1 **OR** Option 2:

- Discard any product remaining in the vial.
- Gently invert IV bag by hand approximately 10 times to mix. **Do not shake.**
- This product is preservative-free and therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted bamlanivimab infusion solution for up to 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) or up to 14 hours at room temperature (20°C to 25°C [68°F to 77°F]) including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 20 minutes prior to administration.

Table 1: Recommended Dilution and Administration Instructions for Bamlanivimab

Drug	Number of Vials	Total Dose	Volume of 0.9% sodium chloride	Final Volume for IV Infusion	Maximum Infusion Rate	Minimum Infusion Time
Option 1: dilution using a PREFILLED infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP						
Bamlanivimab (700 mg/20 mL)	1 Vial	700 mg/20 mL	Discard 70 mL 0.9% Sodium Chloride	200 mL	200 mL/hr	60 minutes
Option 2: dilution using an EMPTY, sterile infusion bag						
Bamlanivimab (700 mg/20 mL)	1 Vial	700 mg/20 mL	Add 180 mL 0.9% Sodium Chloride	200 mL	200 mL/hr	60 minutes

Administration

Bamlanivimab for injection should be administered by a qualified healthcare professional.

- Gather the recommended materials for infusion:
  - Polyvinylchloride (PVC) infusion set containing a 0.20/0.22 micron in-line polyethersulfone (PES) filter.
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer the infusion solution via pump or gravity over at least 60 minutes (see **Table 1**).

- Once infusion is complete, flush the infusion line to ensure delivery of the required dose.
- Discard unused product.
- Clinically monitor patients during administration and observe patients after infusion is complete according to standard practice.

5 OVERDOSAGE

In the case of overdose, use supportive therapy. There is no known antidote to bamlanivimab.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
intravenous infusion	Solution, 700 mg/20 mL (35 mg/mL)	• L-histidine • L-histidine hydrochloride monohydrate • sodium chloride • sucrose • polysorbate 80 • water for injection

7 WARNINGS AND PRECAUTIONS

General

The limited clinical data available for bamlanivimab are derived from single intravenous doses administered in the ongoing Phase 2 randomized, double-blind, placebo-controlled clinical study, BLAZE-1 (Study PYAB). Serious and unexpected adverse events may occur that have not been previously reported with bamlanivimab use.

Sensitivity

Hypersensitivity and Anaphylaxis

There is a potential for serious hypersensitivity and/or anaphylactic reactions with administration of bamlanivimab. If signs and symptoms of a clinically significant hypersensitivity or anaphylactic reaction occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related Reactions

Infusion-related reactions have been observed with administration of bamlanivimab.

- Signs and symptoms of infusion related reactions may include: dyspnea, fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and dizziness.

If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.

7.1 Special Populations

7.1.1 Pregnant Women

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Bamlanivimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

Nonclinical reproductive toxicity studies have not been performed with bamlanivimab. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, bamlanivimab has the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of bamlanivimab provides any treatment benefit or risk to the developing fetus.

7.1.2 Breast-feeding

There are no available data on the presence of bamlanivimab in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bamlanivimab and any potential adverse effects on the breastfed child from bamlanivimab or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

7.1.3 Pediatrics

The safety and efficacy of bamlanivimab in children have not been established, although as per above (see **1 INDICATIONS**) it is reasonable to consider a single intravenous dose of bamlanivimab in adolescents 12 years of age or older who weigh ≥ 40 kg and who are high risk of developing severe COVID-19 symptoms and/or hospitalization.

7.1.4 Geriatrics

Of the 309 patients receiving bamlanivimab in BLAZE-1, 11% were 65 years of age and older and 3% were 75 years of age and older. Based on preliminary population PK analyses, there is no difference in PK in geriatric patients compared to younger patients (see **10.3 Pharmacokinetics, Special Populations and Conditions**).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Clinical studies evaluating the safety of bamlanivimab are ongoing. See Warnings and Precautions for potential risks associated with bamlanivimab.

An acceptable safety profile of bamlanivimab was reported in patients with mild to moderate COVID-19 illness (N = 309) following single intravenous doses of bamlanivimab in the BLAZE-1 Phase II study (700 mg, 2800 mg and 7000 mg). Based on the data, after treatment, adverse events occurred in 23% bamlanivimab-treated patients and 26% of placebo-treated patients who were followed for at least 28

days. Serious adverse events occurred in 1 placebo-treated subject (1%) and in no bamlanivimab-treated subjects.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

TEAEs reported in ≥ 1% of all participants in the BLAZE-1 Phase 2 study, following a single intravenous dose of placebo or 700 mg bamlanivimab are summarized in Table 3.

Table 3 - Treatment-emergent Adverse Events Reported in BLAZE-1

Adverse Event	Placebo N=156 n (%)	Bamlanivimab - 700 mg N=101 n (%)
Nausea	6 (3.8)	3 (3.0)
Dizziness	3 (1.9)	3 (3.0)
Headache	3 (1.9)	3 (3.0)
Pruritus	1 (0.6)	2 (2.0)
Diarrhoea	8 (5.1)	1 (1.0)
Vomiting	4 (2.6)	1 (1.0)

Hypersensitivity Including Anaphylaxis and Infusion-related Reactions:

One anaphylaxis reaction and one serious infusion-related reaction were reported during infusion of bamlanivimab in ongoing, blinded trials. The infusions were stopped. Both reactions required treatment, one required epinephrine. Both events resolved.

Immediate non-serious hypersensitivity events were noted for 2% of bamlanivimab treated subjects and 1% of placebo-treated subjects in BLAZE-1. Reported events of pruritus, flushing and hypersensitivity were mild with one case of face swelling which was moderate. All events resolved (see **7 WARNINGS AND PRECAUTIONS**).

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

The BLAZE-1 Phase 2 study did not include patients who were less than 18 years of age.

8.3 Less Common Clinical Trial Adverse Reactions

There were no significant adverse reactions reported at < 1% in patients treated with bamlanivimab.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial Findings

There were no clinically significant abnormal laboratory findings with bamlanivimab.

8.5 Post-Market Adverse Reactions

There are no post-market adverse drug reactions reported for bamlanivimab.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

No serious drug interactions have been reported for bamlanivimab.

9.2 Drug Interactions Overview

No drug interaction studies have been performed. Bamlanivimab is not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

9.3 Drug-Behavioural Interactions

Interactions with behaviour have not been established.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Bamlanivimab is a neutralizing IgG1 monoclonal antibody (mAb) to the spike protein of SARS-CoV-2, which can block the spike protein attachment to human ACE2 receptors, thus preventing subsequent viral entry into human cells and viral replication.

10.2 Pharmacodynamics

A Phase 2 trial evaluated bamlanivimab over a dose range of 1 to 10 times the recommended dose (700 to 7000 mg) of bamlanivimab in patients with mild to moderate COVID-19. Based on preliminary population pharmacokinetic/pharmacodynamic modelling and simulation, a flat exposure-response relationship for viral load reduction was identified for bamlanivimab within this dose range. In addition, body weight had no clinically meaningful effect on viral load reduction in adults with COVID-19 over the body weight range of 41 kg to 173 kg.

10.3 Pharmacokinetics

The pharmacokinetic (PK) profile of bamlanivimab is expected to be consistent with the profile of other IgG1 monoclonal antibodies.

Special Populations and Conditions

The PK of bamlanivimab was not affected by age (18 to 86), sex, race, or disease severity based on a preliminary population PK analysis.

Hepatic Insufficiency:
No clinical studies have been conducted to evaluate the effect of hepatic impairment on the PK of bamlanivimab.

Renal Insufficiency:
No clinical studies have been conducted to evaluate the effect of renal impairment on the PK of bamlanivimab. Bamlanivimab is not expected to be eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of bamlanivimab.

11 STORAGE, STABILITY AND DISPOSAL

Refrigerate unopened vials at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or expose to direct heat.

This product is preservative free and therefore, the prepared solution should be administered immediately. If immediate administration is not possible, store diluted bamlanivimab solution for up to 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) or 14 hours at room temperature (20°C to 25°C [68°F to 77°F]).

12 SPECIAL HANDLING INSTRUCTIONS

Protect from direct heat and light. Do not shake.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: bamlanivimab for injection

Chemical name: bamlanivimab

Molecular mass: 146439 Da

Structural formula:

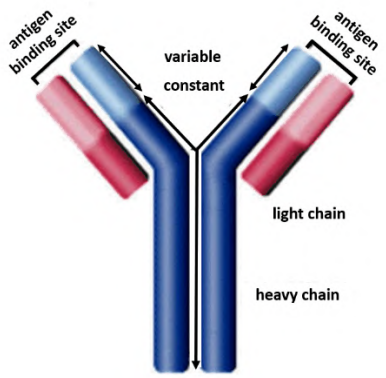

Figure 1: Structure of bamlanivimab

Product Characteristics:

Bamlanivimab is a fully human immunoglobulin G (IgG1 variant) mAb consisting of 2 identical light chain polypeptides composed of 214 amino acids each and 2 identical heavy chain polypeptides composed of 455 amino acids produced by a CHO cell line.

Bamlanivimab for injection is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution in a single-dose vial for intravenous infusion after dilution.

Each mL contains 35 mg of bamlanivimab, and L-histidine (0.4 mg), L-histidine hydrochloride monohydrate (0.6 mg), sodium chloride (2.9 mg), sucrose (60 mg), polysorbate 80 (0.5 mg), and Water for Injection. The bamlanivimab solution has a pH range of 5.5-6.5.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Mild to Moderate COVID-19 (BLAZE-1)

The data supporting this interim authorization are based on an interim analysis from Part A of BLAZE-1 that occurred after all enrolled subjects completed at least Day 29 of the trial. BLAZE-1 Part A is a Phase 2 randomized, double-blind, placebo-controlled clinical trial studying bamlanivimab for the treatment

of subjects with mild to moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). BLAZE-1 enrolled adult subjects who were not hospitalized and had at least 1 or more COVID-19 symptoms that were at least mild in severity. Treatment with bamlanivimab was initiated within 3 days of obtaining the clinical sample for the first positive SARS-CoV-2 viral infection determination. Subjects were treated with a single infusion of bamlanivimab (at doses of 700 mg [N=101], 2,800 mg [N=107], or 7,000 mg [N=101]) or placebo (N=156).

At baseline, median age was 45 years (with 12% of subjects aged 65 or older); 55% of subjects were female, 88% were White, 44% were Hispanic or Latino, and 6% were Black; 44% of subjects were considered high risk (as defined in Section 1, see **INDICATIONS**). Subjects had mild (76%) to moderate COVID-19 (24%); the mean duration of symptoms was 5 days; mean viral load by cycle threshold (CT) was 24 at baseline. The baseline demographics and disease characteristics were well balanced across bamlanivimab and placebo treatment groups.

14.2 Study Results

The pre-specified primary endpoint in the BLAZE-1 Phase 2 trial was change in viral load from baseline to Day 11 for bamlanivimab versus placebo. However, most subjects, including those receiving placebo, effectively cleared virus by Day 11 (not shown); therefore, no statistically significant reduction in viral load, as detected by viral RNA, was observed in subjects treated with bamlanivimab compared to subjects treated with placebo.

Evidence of the efficacy of bamlanivimab in subjects with mild to moderate COVID-19 related illness is limited to the predefined secondary endpoint of COVID-19-related hospitalizations or emergency room visits within 28 days after treatment. Numerically, a lower proportion of bamlanivimab-treated subjects progressed to COVID-19-related hospitalization or emergency room visits compared to placebo-treated subjects (Table 4). Results for this endpoint were suggestive of a relatively flat dose-response relationship.

Table 4 - Proportion of Subjects with Events of Hospitalization or Emergency Room Visits within 28 Days After Treatment

Treatment	N[a]	Events	Proportion of Subjects %
Placebo	156	9	5.8%
bamlanivimab 700 mg	101	1	1.0%
bamlanivimab 2800 mg	107	2	1.9%
bamlanivimab 7000 mg	101	2	2.0%
All bamlanivimab doses	309	5	1.6%

[a] Abbreviations: N = number of treated patients in analysis.

The subgroup of subjects who met the risk criteria (see **1 INDICATIONS**) also experienced a numerical reduction in the proportion of subjects who required COVID-19 related hospitalisations or emergency room visits (Table 5).

Table 5 - Proportion of Subjects with Events of Hospitalization or Emergency Room Visits for Subjects at Higher Risk of Progression to Severe COVID-19 Illness[a]

Treatment	N[b]	Events	Proportion of Subjects %
Placebo	69	7	10.1%
bamlanivimab 700 mg	46	1	2.2%
bamlanivimab 2800 mg	46	1	2.2%
bamlanivimab 7000 mg	44	2	4.5%
All bamlanivimab doses	136	4	2.9%

[a] Higher risk for progression to severe COVID-19 illness as defined in section 1 **INDICATIONS**.

[b] Abbreviations: N = number of treated patients in analysis.

The median time to symptom improvement as recorded in a trial specific daily symptom diary was 6 days for bamlanivimab-treated subjects, as compared with 8 days for placebo-treated subjects. Symptoms assessed were cough, shortness of breath, feeling feverish, fatigue, body aches and pains, sore throat, chills, and headache. Symptom improvement was defined as symptoms scored as moderate or severe at baseline being scored as mild or absent, and symptoms scored as mild or absent at baseline being scored as absent.

14.3 Immunogenicity

Immunogenicity has not yet been investigated. Samples for immunogenicity assessments have been collected and stored. Analysis will occur once validated anti-drug antibody assays are available.

15 MICROBIOLOGY

Antiviral Activity

The cell culture neutralization activity of bamlanivimab against SARS-CoV-2 was measured in a dose-response model using cultured Vero E6 cells. Bamlanivimab neutralized SARS-CoV-2 with an estimated EC50 value = 0.03 µg/mL and an estimated EC90 value = 0.09 µg/mL.

Bamlanivimab demonstrated antibody-dependent cell-mediated cytotoxicity on reporter Jurkat cells expressing FcγRIIIa following engagement with target cells expressing spike protein. Bamlanivimab did not elicit complement-dependent cytotoxicity activity in cell-based assays.

In Vivo Efficacy Pharmacology

Prophylactic administration of bamlanivimab to female Rhesus macaques (n=3 or 4 per group) resulted in 1 to 4 $\log_{10}$ decreases in viral load (genomic RNA) and viral replication (sub-genomic RNA) in bronchoalveolar lavage samples relative to control animals, but less of an impact on viral RNA in throat and nasal swabs following SARS-CoV-2 inoculation. The applicability of these findings to a prophylaxis or treatment setting is not known.

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to bamlanivimab.

Non-clinical studies using serial passage of SARS-CoV-2 and directed evolution of the spike protein identified E484K, F490S, Q493R and S494P, amino acid substitutions in the spike protein receptor binding domain, which had reduced susceptibility to bamlanivimab as determined in neutralization assays using SARS-CoV-2 (F490S and S494P: > 485-fold and > 71-fold reduction, respectively) and/or vesicular stomatitis virus-based pseudovirus (all variants > 100-fold reduction).

In a preliminary genotypic analysis of a subset of patients with mild or moderate COVID-19 who were considered high risk for severe illness and/or hospitalization, SARS-CoV-2 variants, at positions associated with bamlanivimab resistance, were identified more frequently at ≥ 15% and ≥ 50% allele fractions in bamlanivimab treated patients (14% and 9.3%, respectively) compared to placebo treated patients (2.4% and 0%, respectively). Phenotypic analysis of the identified variations is in progress. The clinical relevance of these findings is not known.

Immune Response Attenuation

There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

16 NON-CLINICAL TOXICOLOGY

Carcinogenicity, Genotoxicity and Reproductive and Developmental Toxicology:

Not conducted.

General Toxicology:

Toxicology studies in the rat uncovered no adverse effects when bamlanivimab was administered intravenously. Non-adverse increases in neutrophils were observed.

Special Toxicology:

Antibody Dependent Enhancement (ADE) of Infection

The risk that bamlanivimab could mediate viral uptake and replication by immune cells was studied in THP-1 and Raji cell lines and primary human macrophages. This experiment did not demonstrate productive viral infection in immune cells exposed to SARS-CoV-2 at concentrations of bamlanivimab down to 100-fold below the EC50 value.

Tissue Cross-Reactivity

In tissue cross reactivity studies using human adult and fetal tissues, no binding of clinical concern was detected.

PATIENT MEDICATION INFORMATION

HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS COVID-19 DRUG BASED ON LIMITED CLINICAL TESTING IN HUMANS AND/OR QUALITY INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]Bamlanivimab

Bamlanivimab for injection

Read this carefully before you start taking **bamlanivimab**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **bamlanivimab**.

What is bamlanivimab used for?

Bamlanivimab is a medicine being studied for the treatment of COVID-19. Bamlanivimab may help limit the amount of virus in your body; this may help you get better faster. Bamlanivimab may be given if you or your child are 12 years of age or older who weigh at least 40 kg (kilograms) and are not already in the hospital. Bamlanivimab is only given to patients at high-risk of having the disease get worse. Your healthcare professional will decide if you or your child should take bamlanivimab.

How does bamlanivimab work?

COVID-19 is caused by a virus called a coronavirus. Bamlanivimab may help limit the amount of virus in your body, which may help you get better faster.

What are the ingredients in bamlanivimab?

Medicinal ingredients: bamlanivimab

Non-medicinal ingredients: L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sodium chloride, sucrose, water for injection

Bamlanivimab comes in the following dosage forms:

Bamlanivimab solution, 700 mg/20 mL (35 mg/mL)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take bamlanivimab. Talk about any health conditions or problems you may have, including if you:

- Have any allergies
- Are pregnant or plan to become pregnant
- Are breast-feeding a child

- Have any serious illnesses
- Are taking any medications (prescription, over-the-counter, vitamins, or herbal products)
- Have reactions during or after the infusion. Symptoms of a possible allergic reaction include:
  - Changes to blood pressure or heart rate, low oxygen level in the blood, high temperature, shortness of breath, wheezing, swelling of the face, lips, tongue, or throat, rash/hives/itching, feeling sick or nauseous, sweating, shivering, muscle soreness, dizziness, headache

  Tell your doctor if you get any of these signs or symptoms.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take bamlanivimab:

- Bamlanivimab will be given to you by a healthcare professional through a vein (intravenous or IV) for at least 1 hour.

Usual dose:

Bamlanivimab is given once. The recommended dose is 700 mg.

Overdose:

If you think you, or a person you are caring for, have taken too much bamlanivimab, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using bamlanivimab?

Possible side effects of bamlanivimab are:
• Allergic reactions. Allergic reactions can happen during and after infusion with bamlanivimab. Tell your healthcare provider right away if you get any of the following signs and symptoms of allergic reactions: fever, chills, nausea, headache, shortness of breath, low blood pressure, wheezing, swelling of your lips, face, or throat, rash including hives, itching, muscle aches, and dizziness.

The side effects of getting any medicine by vein may include brief pain, bleeding, bruising of the skin, soreness, swelling, and possible infection at the infusion site.

These are not all the possible side effects of bamlanivimab. Not a lot of people have been given bamlanivimab. Serious and unexpected side effects may happen. Bamlanivimab is still being studied so it is possible that all of the risks are not known at this time.

It is possible that bamlanivimab could interfere with your body's own ability to fight off a future infection of SARS-CoV-2. Similarly, bamlanivimab may reduce your body’s immune response to a vaccine for SARS-CoV-2.

Specific studies have not been conducted to address these possible risks. Talk to your healthcare provider if you have any questions.

If you experience any side effects not listed here, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

If you want more information about bamlanivimab:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.lilly.ca, or by calling 1-888-545-5972.

This leaflet was prepared by Eli Lilly Canada, Inc.

Last Revised November 20, 2020

BAM-0001-EUA-CA-PM-20201120

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	December 17, 2020	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Gabrielle Richard, Emma Reid, Barbara Goodall, Glenn Cox, Lisa Grandy Allen		

Items	Discussion
- **Review Minutes**	unrelated [redacted] [redacted].
- **Bamlanivimab: role in therapy and implementation strategies**	Reviewed the COVID Network request for the Therapeutics and Prophylactics Advisory Group to provide information on unrelated [redacted], and bamlanivimab and suggestions about how bamlanivimab could potentially be implemented. Kathleen confirmed the province of Nova Scotia will receive 50 doses of bamlanivimab at the end of the month. Bamlanivimab discussion: - Lisa presented information on the progression of COVID-19 and the role of different treatments within the different stages. Targeting the pre-cellular entry stage may have effect beyond just the individual with infection, as it can impact infectivity and transmission risk. - Emma presented on the BLAZE-1 trial including a focus on methods and generalizability in the context of the Health Canada Interim Order authorization of bamlanivimab. Discussion followed around interpretation of BLAZE-1 results: s.14(1) [redacted]. Discussed public health considerations around administration, s.14(1) [redacted] Other thoughts: s.14(1) [redacted] To provide sufficient time for the bamlanivimab discussion, an additional one-hour meeting for December 18 was scheduled.
- **CO-VIC [redacted] discussion**	Barb presented initial slides with background information on the pragmatic CO-VIC study. Presentation and discussion will continue Dec 18 meeting. **Action item: B. Goodall to provide slides to Tasha for distribution before Dec 18 meeting.**
- unrelated [redacted]	[redacted].

From: Coleman, Kathleen
To: Gray, Thomas; Grandy Allen, Lisa; Ramsey, Tasha
Subject: FW: Nova Scotia - Request for Assistance for Bamlanivimab
Date: Friday, April 23, 2021 1:06:21 PM
Attachments: image001.png
image002.png
19.318 NS Ban.pdf
RFA form (003).pdf
Importance: High

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third party [redacted]

K

[redacted]

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	December 3, 2020	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Lisa Grandy Allen, Glenn Cox, Gabrielle Richard, Emma Reid		

Items	Discussion
[redacted]	unrelated [redacted]
- **Therapeutic agents being considered at Nova Scotia Health**	unrelated [redacted] Briefly discussed [redacted] agents accessible for COVID-19 treatment in the context of a clinical trial: unrelated, unrelated bamlanivimab. - unrelated [redacted], bamlanivimab: through enrollment in CO-VIC Trial. Overarching pragmatic trial is CO-VIC. unrelated [redacted] Concern voiced from Pharmacare perspective – expect allocation decisions for bamlanivimab soon, and many logistical issues to work out on a tight timeline thereafter. This concern has been brought to COVID Network by Tasha – and is on agenda for Tuesday (Dec 8) evening agenda. Discussed our group's role in accepting/rolling out emerging COVID-19 therapies – act as medication advisors to COVID Network on evidence (bearing in mind the quality of all COVID-related evidence at this time) and to provide implementation strategies. **Action Items: E. Reid/T. Ramsey to update bamlanivimab summary document to include practical guidance/talking points on administration/efficacy/safety, distribute to group and during meeting Dec 9.**

Items	Discussion
- **Bamlanivimab administration logistics**	Tabled – will discuss next week.
- **Round Table**	

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	December 10, 2020	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Gabrielle Richard, Emma Reid, Barbara Goodall, Glenn Cox, Lisa Grandy Allen		

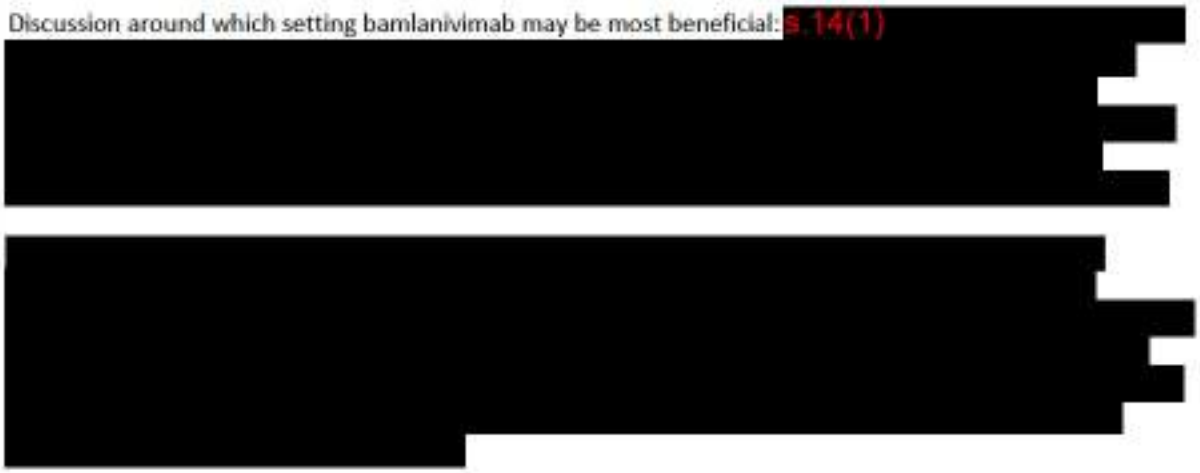
Items	Discussion
- [redacted]	unrelated [redacted]
- **Bamlanivimab**	Tasha presented a review of our current COVID-19 therapeutic options at the NS Health COVID Network meeting earlier this week, including bamlanivimab. The Therapeutics and Prophylaxis Advisory Group was asked to provide the COVID Network with information on unrelated bamlanivimab, unrelated [redacted] nd suggestions of how bamlanivimab could potentially be implemented. Discussed the bamlanivimab Health Canada indication - overall quite broad and inclusive compared with the inclusion criteria for the BLAZE-1 study. Briefly reviewed some challenges with applying the BLAZE-1 published literature, including lack of statistical comparisons. Discussed that this will likely be a recurring theme as more COVID-19 therapeutics come down the pipeline and we are tasked with using the available evidence to inform our recommendations. Consensus was that we should try a more formal process of reviewing the literature and discuss the fine details of bamlanivimab as a group next week before making formal recommendations to the COVID Network. Tasha to arrange to have the bamlanivimab agenda item deferred until the December 22nd COVID Network meeting Kathleen confirmed that NS will receive their allotment of 50 vials next week. There will also be a 50 vial stock in Ottawa that can be requested and shipped with a turnaround time of about 3 days. Discussed the potential for media and other groups inquiring about the drug and our plans in the interim before we have formulated our recommendations - Lisa willing to respond. **Action items: Emma to prepare short slide set to organize bamlanivimab discussion next week, Lisa to inform about virology component. Slides, the BLAZE-1 trial, and the bamlanivimab summary sheet will be distributed prior to next meeting.**
- **Introduction of Barbara Goodall**	Barb is the research coordinator who runs the ongoing pragmatic CO-VIC study and will run CATCO in NS Health. This is the first large pragmatic study in Nova Scotia, and pragmatic studies are unique in nature. Discussed that it would be beneficial for Barb to speak more to her role and how the studies work. **Action items: Barb to discuss CO-VIC unrelated next meeting.**
- [redacted]	unrelated [redacted]

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	December 17, 2020	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Gabrielle Richard, Emma Reid, Barbara Goodall, Glenn Cox, Lisa Grandy Allen		

Items	Discussion
- unrelated	[redacted]
- **Bamlanivimab: role in therapy and implementation strategies**	Reviewed the COVID Network request for the Therapeutics and Prophylactics Advisory Group to provide information on unrelated [redacted] bamlanivimab and suggestions about how bamlanivimab could potentially be implemented. Kathleen confirmed the province of Nova Scotia will receive 50 doses of bamlanivimab at the end of the month. Bamlanivimab discussion: - Lisa presented information on the progression of COVID-19 and the role of different treatments within the different stages. Targeting the pre-cellular entry stage may have effect beyond just the individual with infection, as it can impact infectivity and transmission risk. - Emma presented on the BLAZE-1 trial including a focus on methods and generalizability in the context of the Health Canada Interim Order authorization of bamlanivimab. Discussion followed around interpretation of BLAZE-1 results: s.14(1) [redacted] Discussed public health considerations around administration, s.14(1) [redacted] Other thoughts: s.14(1) [redacted] To provide sufficient time for the bamlanivimab discussion, an additional one-hour meeting for December 18 was scheduled.
- **CO-VIC [redacted] discussion**	Barb presented initial slides with background information on the pragmatic CO-VIC study. Presentation and discussion will continue Dec 18 meeting. **Action item: B. Goodall to provide slides to Tasha for distribution before Dec 18 meeting.**
- unrelated	unrelated [redacted]

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	December 18, 2020	**Meeting Time**	0830-0930
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Gabrielle Richard, Emma Reid, Barbara Goodall, Glenn Cox, Lisa Grandy Allen		

Items	Discussion
- **Review of CO-VIC,** [redacted]	Barb summarized the CO-VIC study highlighting the unique features of pragmatic research. Pragmatic research relies on existing systems and is adaptable, flexible, iterative. Eligibility criteria are intended to be inclusive to allow for a diverse study population. Results are therefore generalizable at local level. More applicable for stakeholders involved like patients, policy makers. Drug is sequentially assigned – e.g., if hospital doesn't have it, next intervention is offered. Reviewed the clinical (phase 2) main study and immune sub study in CO-VIC. Everyone enrolling has option to enroll in sub study (involves some extra bloodwork). unrelated [redacted]
- **Bamlanivimab: role in therapy and implementation strategies**	Resumed COVID Network recommendation discussion, from Dec 17 recognizing the province will acquire a supply from the federal government at the end of the month. Had previously determined the role of bamlanivimab would fall into the pragmatic research setting. Revisited discussion about what the Therapeutics and Prophylactics Advisory Group's role is – providing a recommendation to COVID Network about evidence-based treatment option with practical lens regarding implementation. In anticipation of additional discussions in future regarding other novel therapeutic agents for COVID-19 treatment/prevention with Health Canada conditional approval or interim orders, applied the following framework: • Do we believe the therapy will not cause harm? • Do we think there might be benefit? ○ If yes: In whom or what setting, and how can we implement use? Brief discussion around safety: no signal of serious harm in BLAZE-1 and Health Canada has authorized for use under an Interim Order. Discussion around which setting bamlanivimab may be most beneficial: s.14(1) [redacted]



	Discussion around the model of RCUs – most sites across the province will be NS Health-affiliated but some will be private, such as Ocean View or Shannex. We believe the private sites will use NS Heath staff, guidelines, and order sets, so the same access to the drug would be available for individuals in these RCU sites. Agreed that all RCU patients regardless of site should qualify for inclusion in pragmatic research. If there is delay in staffing these private sites with NS Health staff, reasonable to start enrolling in NS Health-affiliated sites first with a goal to include all RCUs when infrastructure is in place. Attendees asked if anyone had opposition to the recommendation to use bamlanivimab in NS Health-affiliated RCUs for patients with non-severe illness aged 65 and older in the context of pragmatic research. Discussion around needing to be practical about decision, and that in general the higher age group is at highest risk of death. No member voiced opposition. The bamlanivimab recommendation, and all advisory group recommendations, will be revisited as evidence evolves. ***Bamlanivimab Recommendation: use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units***
[redacted]	unrelated [redacted]
[redacted]	unrelated [redacted]
[redacted]	unrelated [redacted]
- **Next meeting**	Resume meetings January 7, 2021.

To:	NS Health COVID Network
Date:	22 December 2020
From:	Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group
Subject:	Bamlanivimab, unrelated [redacted] interim recommendation

Bamlanivimab Recommendation: use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units.

Rationale:

- **Health Canada indication**:
  - Bamlanivimab is authorized for use under an interim order for patients ≥ 12 years of age (≥40 kg) with mild to moderate COVID-19 at high risk of progressing to severe COVID-19 illness and/or hospitalization
- **Evidence**: BLAZE-1 (interim analysis of a Phase II trial)
  - Non-hospitalized patients (≥ 18 years of age) with recently diagnosed mild to moderate COVID-19. Approximately 69% of patients had risk factors for severe COVID-19.
  - **Efficacy:** Numerically reduced hospital admissions (signal of increased benefit in those >/= 65 and BMI >/= 35), however statistical analysis of this clinical outcome not provided
  - **Safety**: No signal of serious harm
- **Role in therapy**: **Pragmatic research**
  - Bamlanivimab cannot be endorsed for use in routine care based on the published evidence to date
  - Until further efficacy and safety data are published to support bamlanivimab in routine care, the advisory group recommends use in the context of pragmatic research to evaluate real-world clinical safety and effectiveness in NS Health
- **Population:**
  - **Non-severe COVID-19 aged 65 and older**
  - Bamlanivimab is a neutralizing monoclonal antibody and is ideal for early disease in non-severe patients as it targets pre-cellular viral entry
  - Blaze-1 supports use in non-severe COVID-19 population, however evidence from BLAZE-1 is not clear in terms of which patients with risk factors benefit most. There was increased benefit for those aged 65 and greater and BMI greater than 35.
  - Individuals 65 years of age and up are at highest risk for progression to severe disease and death and mount less of an immune response
- **Setting:**
  - **Regional care units (RCU)**
  - Health Canada approved a relatively broad indication that is not feasible to implement in the context of pragmatic research using our existing NS Health infrastructure
  - One NS Health affiliated setting that may be able to incorporate bamlanivimab administration in non-severe outpatients are the RCUs
  - Use of RCUs would allow patients who are very vulnerable to COVID-19 to receive bamlanivimab and allow data collection in individuals at high risk of disease progression
  - Other settings to be considered after initial roll out in NS Health affiliated RCUs
- **Public health/IPAC considerations**:
  - Advisory group discussed inherent infection-control issues if community-based COVID-19 positive patients were directed to existing healthcare facilities or infusion centers. RCUs were suggested as a practical setting to administer bamlanivimab without having to introduce COVID-19 positive patients into a new healthcare environment, and aligns with the pragmatic research method of using existing systems. Would not require an infusion center and would administer to patients in their RCU bed. An order set, IV monograph, pre medications, anaphylaxis kit, and nurse to infuse bamlanivimab and monitor for infusion reactions will be needed.

unrelated [redacted]

[redacted]

Note: Recommendations will be reviewed on a monthly basis by the NS Therapeutics and Prophylactics Advisory Group (review date: January 21, 2021)

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	January 7, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Gabrielle Richard, Emma Reid, Barbara Goodall, Glenn Cox, Lisa Grandy Allen		

Items	Discussion
- unrelated [redacted]	unrelated [redacted]
- unrelated [redacted]	unrelated [redacted]
- **Bamlanivimab, unrelated [redacted]: outcome of COVID Network recommendations**	Tasha discussed COVID Network meeting that took place Dec 22. Our Advisory Group's recommendations were made into a memo, and Lisa and Tasha presented supporting evidence and put recommendations forward. Recommendations were accepted. Recap of recommendations: - Bamlanivimab: use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units. - unrelated [redacted] Advisory Group to revisit these therapeutic recommendations on a monthly basis. Discussed next steps for bamlanivimab. Drug has been received in NS. CO-VIC research team revising study protocol to incorporate changes required for use of bamlanivimab in eligible RCU population. RCUs must be up and running with appropriate staffing and staff must be trained before drug can be used.
- unrelated [redacted]	[redacted]

	unrelated [redacted]
- **Next meeting**	Jan 21st – next week cancelled.

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	January 21, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, Barbara Goodall, Glenn Cox, Amanda Porter, Kenneth Rockwood, Lisa Grandy Allen, Gabrielle Richard		

Items	Discussion
- unrelated	[redacted]
[redacted]	[redacted]
- unrelated	[redacted]
[redacted]	[redacted]

	unrelated [redacted]
- unrelated [redacted]	unrelated [redacted]
[redacted]	[redacted].
- unrelated [redacted] **Bamlanivimab**	Deferred.

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	January 28, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, Barbara Goodall, Glenn Cox, Amanda Porter, Kenneth Rockwood, Lisa Grandy Allen		

Items	Discussion
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
- unrelated [redacted]	unrelated [redacted]
[redacted]	[redacted]

	unrelated [redacted]
- unrelated [redacted]	[redacted]
- unrelated [redacted]	unrelated [redacted]

	unrelated [redacted]
- unrelated [redacted] **Bamlanivimab: Review previous recommendation**	Reviewed the process for reviewing previous recommendations at the planned four-week interval. MSSU has been engaged to provide new evidence reviews for unrelated [redacted] bamlanivimab prior to next meeting. Summarized the previous recommendations which were all accepted by COVID Network for unrelated [redacted] bamlanivimab. unrelated [redacted] Note that RCUs are newly up and running as of earlier in the week (setting for recommended bamlanivimab use).
- **Other**	Pandemic supply procurement update from Kathleen: procurement for unrelated [redacted] bamlanivimab both end at end of March. unrelated [redacted]. Will need to ensure federal procurement is considered for future recommendations and reviews of past recommendations.

To:	NS Health COVID Network
Date:	9 February 2021
From:	Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group
Subject:	Recommendations

unrelated [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

The following recommendations were approved by the COVID Network on December 22, 2020. The Advisory Group reviewed them as part of our monthly review of previous recommendations. We have no revisions to the recommendations at this time.

Bamlanivimab: Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units.

unrelated [redacted]

[redacted]

Note: Recommendations will be reviewed on a monthly basis by the NS Therapeutics and Prophylactics Advisory Group

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	February 4, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, Barbara Goodall, Glenn Cox, Amanda Porter, Kenneth Rockwood, Lisa Grandy Allen, Gabrielle Richard		

Items	Discussion
- unrelated	[redacted]
- unrelated	unrelated [redacted]
- unrelated	[redacted]
- unrelated	[redacted]
- unrelated	unrelated [redacted]
- unrelated	[redacted]

	unrelated [redacted]
- unrelated [redacted] **bamlanivimab: Review previous recommendations**	unrelated [redacted] bamlanivimab. MSSU summaries had been distributed with meeting agenda. unrelated [redacted] Discussed bamlanivimab in more detail in context of two press releases from the manufacturer that addressed its use in populations different from what we had previously discussed. - BLAZE-2 (ongoing – investigating bamlanivimab monotherapy and bamlanivimab + etesevimab) has suggested a role for bamlanivimab in the reduction of COVID-19 infection in nursing home staff and residents with recent evidence of infection within the site. Despite high doses of bamlanivimab (4200 mg infusion x 1) administered, side effects were similar to placebo. Discussed potential use of bamlanivimab for prophylaxis in congregate living facilities. Acknowledged current plan for RCU care for COVID-19 positive LTC patients and that there is still potential for this system to become overwhelmed, in which case prophylaxis would be important. Currently province has access to 50 doses and can receive more. Discussed role for combination monoclonal antibodies as protection against viral mutation. Also noted that an add-on substudy to CATCO, "CATCO-NOS," plans to investigate bamlanivimab. Still in protocol draft stage and not yet approved by ethics. - BLAZE-1 is ongoing in Phase 3 and press release suggests reduction in hospitalization + death in outpatients aged 12 and older with mild-mod disease and a high-risk factor to progressing to severe disease receiving combination bamlanivimab + etesevimab. Discussed that this combination may be useful in pediatrics with hypogammaglobinemia. Agreement amongst meeting attendees that our *current bamlanivimab recommendation does not require a change at this time, but that we should be prepared to update* based on evolving evidence in these other populations, and keep on top of evidence for combination treatment. Suggested that further conversation about congregate living facilities and potential role for bamlanivimab can be continued as a future side discussion. - **Action items: L. Barrett, T. Ramsey, K. Rockwood and others to connect for offline discussion about potential bamlanivimab role in prophylaxis.**
- unrelated [redacted]	[redacted]
[redacted]	[redacted]

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	February 25, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, Amanda Porter, Gabrielle Richard, Lisa Grandy Allen		

Items	Discussion
- unrelated	[redacted]
- unrelated [redacted]	unrelated [redacted]
- **Review recommendations** - unrelated [redacted] **bamlanivimab**	unrelated [redacted] Addressed bamlanivimab: the prophylaxis in long term care discussion planned with stakeholders like Dr. Johnston, Dr. Rockwood, will occur March 9th. s.14(1) [redacted]. Will revisit this discussion after the meeting.

	- [redacted]
- **Pandemic supply update**	unrelated [redacted]. Expect that we may want to order more bamlanivimab, especially if we wouldn't be pulling from the resources of other provinces (some provinces have not recommended its use). We have 50 bamlanivimab vials. Expect we may want to order more bamlanivimab – especially if it is not pulling from other resources. Note that the supply is refrigerated so we have to confirm they have room to store it. - **Action item: T. Ramsey, K. Coleman, and L. Barrett to confirm desired amount of bamlanivimab for provincial supply.**
- **Next meeting**	Will cancel next week (March 4) unless extenuating circumstances arise. Next meeting: March 11, 2021.

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	March 11, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, Amanda Porter, Gabrielle Richard, Lisa Grandy Allen, Barbara Goodall, Kenneth Rockwood		

Items	Discussion
- [redacted]	[redacted]
unrelated [redacted]	[redacted] Gabrielle provided a list of agents that are currently under discussion and being followed by PHAC: 1. Bamlanivimab + etesevimab [redacted]
[redacted] **Review recommendations:** - **Bamlanivimab** - unrelated [redacted]	unrelated [redacted] Discussed current recommendations for bamlanivimab, unrelated [redacted] in light of most recent MSSU summaries. No evidence that we haven't previously reviewed and considered. There was agreement to continue with current recommendations. Briefly discussed bamlanivimab for prophylaxis – stakeholder meeting to discuss role in congregate living facilities such as long-term care happened earlier this week. s.14(1) [redacted] Group agreed that there was no need to update the current recommendation for bamlanivimab at this time.

	Revisited incorporating Advisory Group recommendations into research protocols so that recommendations can be actioned in a reasonable and realistic timeframe. Discussed a recent scenario where a patient was a candidate for study enrollment and possible drug therapy from our research category but not all agents were available through the study route. Lisa B provided an update: unrelated - Bamlanivimab: CO-VIC sub study, CATCO-NOS, paperwork under review by Barb and to be returned to ethics. s.14(1) current plan is for use in CO-VIC-NOS. unrelated Discussed that a reasonable protocol update turnaround time is 4 weeks. Also discussed that if drugs are to be pursued in addition to standard of care prior to full study protocol incorporation, a non-formulary approval avenue may be used up to three times per medication.
- **Pandemic supply update**	Kathleen provided update on federal pandemic supply: unrelated - Bamlanivimab: have requested 100 doses in addition to the 50 doses we currently have. The above unrelated drugs are planned to be maintained as federal supply, unrelated There has not been a conversation about discontinuation of federal procurement - expect pandemic response to be ongoing and durable. There is now a website that addresses the Critical Drug Reserve: https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/critical-drug-reserve.html
- **Next meeting**	Will start scheduling meetings for every two weeks, with the option to host additional meetings or cancel meetings if needed. Next meeting: March 25.

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	April 8, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Kathleen Coleman, Emma Reid, Amanda Porter, Gabrielle Richard, Lisa Grandy Allen, Barbara Goodall, Kenneth Rockwood		

Items	Discussion
- [redacted]	[redacted]
unrelated [redacted]	[redacted]
Review recommendations: - **Bamlanivimab** - unrelated [redacted]	Bamlanivimab review: Emma reviewed brief update on bamlanivimab as monotherapy including recommendations from the USA (distribution for monotherapy has stopped given efficacy concerns for variants of concern) and current status in Canada. Tasha informed that variant strains are confirmed through National Micro Lab in Winnipeg which takes 7-10 days, but we do have an in-house preliminary screening test for 501y to identify variants. Barb provided update on a prospective study through which Nova Scotian bamlanivimab supply could be used, CATCO-NOS. It is a pragmatic trial that is the Canadian arm of Solidarity (Phase 4 study). Patients are still being enrolled in Calgary, and Ontario and BC have also recently received ethics approval. NS has received the CATCO-NOS protocol and we have been asked to move forward with ethics submission. Barb will take part in collaborator call next week and is hoping more information around bamlanivimab role as monotherapy will be shared. Noted that the Ontario clinical guidelines and BC recommendations do not include bamlanivimab outside of clinical trials. Discussion about updating our recommendation – until we have more information available and recognizing that no use of bamlanivimab will happen locally without the setting of a clinical trial, decision to leave recommendation as is. *Bamlanivimab recommendation: Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health-affiliated Regional Care Units.* unrelated [redacted] [redacted]

	unrelated [redacted]
- **Pandemic supply update**	- Bamlanivimab – we have 50 vials. Never received the 100 additional requested. Kathleen had not heard that distribution was being stopped. Will follow up with Thomas Gray. - unrelated [redacted] - **Action item: T. Ramsey will** unrelated [redacted] **contact Thomas Gray regarding bamlanivimab supply.**
- **Next meeting**	Will occur in two weeks on April 22.

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	April 22, 2021	**Meeting Time**	0800-0900
Present	**Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, , Gabrielle Richard, Lisa Grandy Allen, Kenneth Rockwood**		

Items	Discussion
- unrelated	[redacted]
Review recommendations: - **Bamlanivimab** - unrelated [redacted]	**Bamlanivimab** – s.14(1) [redacted], Note that CATCO-NOS was the study intended to operationalize bamlanivimab use here locally – population in protocol is people who acquire COVID-19 in hospital. - Lisa led discussion: CATCO is changing rapidly all the time. Challenges with CATCO-NOS which looks like nosocomial in-hospital population, but intended population was instead people needing hospitalization. s.14(1) [redacted] Meeting attendees agreed that our current recommendation should be updated to reflect offering bamlanivimab as an option for those who are at high risk for clinical deterioration due to previous risk factors. Current recommendation: *Bamlanivimab to be used in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units.* **Updated recommendation: *Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19:*** • ***65 years of age and older in NS Health affiliated Regional Care Units OR*** • ***18 years of age and older hospitalized for other reasons at high risk for progression (e.g.: early transplant)*** unrelated [redacted]

Pandemic supply update	Reviewed current available quantities of unrelated bamlanivimab unrelated [redacted]
unrelated [redacted]	[redacted]
- **Next meeting**	Will occur in two weeks on May 6.

To:	NS Health COVID Network
Date:	26 April 2021
From:	Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group
Subject:	Bamlanivimab unrelated [redacted]: Revised Recommendations

The Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group has the following revised recommendations for the COVID Network to consider for approval:

1. Bamlanivimab: use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19:

- **65 years of age and older in NS Health affiliated Regional Care Units OR**
- **18 years of age and older hospitalized for other reasons at high risk for progression (e.g.: early transplant)**

The current NS Health bamlanivimab recommendation is: use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units.

Bamlanivimab is approved by Health Canada under an Interim Order for those with mild to moderate COVID-19 at high risk of progressing to severe COVID-19. Heath Canada examples of factors that are high risk for progression to severe disease include:

- ≥ 65 years of age
- BMI ≥ 35
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or receiving immunosuppressive treatment
- ≥ 55 years old AND any of: cardiovascular disease, hypertension, or chronic respiratory disease

NS Health affiliated Regional Care Units were initially selected as a study location for administration convenience. Individuals with non-severe COVID-19 hospitalized for another reason represent a second setting that is convenient to infuse bamlanivimab.

unrelated [redacted]

[redacted]

[redacted]

Note: Recommendations will be reviewed on a monthly basis by the NS Therapeutics and Prophylactics Advisory Group

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	May 6, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, Amanda Porter, Gabrielle Richard, Lisa Grandy Allen, Kenneth Rockwood, Kathryn Slayter, Glenn Cox		

Items	Discussion
- unrelated	[redacted]
[redacted]	[redacted]
Review recommendations: - Bamlanivimab - unrelated [redacted]	unrelated [redacted]. Other recommendations to remain the same. unrelated unrelated [redacted]

	unrelated [redacted]
Pandemic supply update	Reviewed current supply in NS: - 50 vials bamlanivimab unrelated [redacted] unrelated [redacted].
- **Next meeting**	Will occur in two weeks on May 20.

From:	Barrett, Lisa L
To:	Ramsey, Tasha; Grandy Allen, Lisa; Coleman, Kathleen; Neale, Siony; Cox, Glenn; Richard, Gabrielle; Reid, Emma K
Subject:	RE: COVID-19 therapeutics and prophylactics advisory group
Date:	Wednesday, December 2, 2020 3:56:43 PM

thanks Tasha

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Ramsey, Tasha
Sent: Wednesday, December 2, 2020 2:26 PM
To: Barrett, Lisa L; Grandy Allen, Lisa; Coleman, Kathleen; Neale, Siony; Cox, Glenn; Richard, Gabrielle; Reid, Emma K
Subject: COVID-19 therapeutics and prophylactics advisory group

Hi,

I have also attached a bamlanivimab info sheet Emma created that may help tomorrow.

Tasha

From: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Date: Wednesday, December 2, 2020 at 10:42 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics advisory group

Hi everyone,

I am hoping we can discuss the following during our meeting tomorrow:

1. unrelated [redacted]
2. Therapeutic agents being considered at NSH (including: bamlanivimab, unrelated [redacted])
3. Bamlanivimab administration logistics

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

From: tasha.ramsey@nshealth.ca
To: Grandy Allen, Lisa
Subject: Re: COVID-19 therapeutics and prophylactics advisory group
Date: Wednesday, December 2, 2020 9:11:35 PM

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unrelated [redacted]

Tasha

From: "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
Date: Wednesday, December 2, 2020 at 12:01 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics advisory group

unrelated [redacted].

Lisa

Lisa R Grandy Allen , B.Sc.(Pharm), ACPR
Drug Information Pharmacist
(902)473-6233; Fax (902)473-8612

From: Ramsey, Tasha
Sent: Wednesday, December 02, 2020 10:43 AM
To: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics advisory group

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Tasha

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Mi'kma'ki—Unceded Mi'kmaq Territory
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Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

From:	Coleman, Kathleen
To:	Ramsey, Tasha; Ramsey, Tasha; Barrett, Lisa L; Grandy Allen, Lisa; Neale, Siony; Cox, Glenn; Richard, Gabrielle; Reid, Emma K
Subject:	RE: COVID-19 therapeutics and prophylactics advisory group
Date:	Wednesday, December 2, 2020 10:17:37 PM
Attachments:	NS COVID-19 Therapeutics and Prophylactics Advisory Group TOR DRAFT kc comments.docx

Thanks Tasha

unrelated [redacted]

K

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: December 2, 2020 10:43 AM
To: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics advisory group

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1. unrelated [redacted]
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3. Bamlanivimab administration logistics

Tasha

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Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

From: tasha.ramsey@nshealth.ca
To: Coleman, Kathleen
Subject: Re: COVID-19 therapeutics and prophylactics advisory group
Date: Wednesday, December 2, 2020 10:20:26 PM

Thank you!
Tasha

From: "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>
Date: Wednesday, December 2, 2020 at 10:17 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics advisory group

Thanks Tasha
unrelated [redacted]

K

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: December 2, 2020 10:43 AM
To: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics advisory group

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1. unrelated [redacted]
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3. Bamlanivimab administration logistics

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine

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Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

From: tasha.ramsey@nshealth.ca
To: McNeil, Shelly; Milligan, Samantha
Cc: Barrett, Lisa L
Subject: Re: COVID-19 therapeutics and prophylactics
Date: Friday, January 29, 2021 8:41:28 AM

---

unrelated [redacted]

[redacted].

Tasha

From: "McNeil, Shelly" <Shelly.McNeil@nshealth.ca>
Date: Thursday, January 28, 2021 at 11:22 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Cc: "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Reid, Emma K" <EmmaK.Reid@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Rockwood, Kenneth" <Kenneth.Rockwood@nshealth.ca>, Amanda Porter <Amanda.Porter@dal.ca>, "Milligan, Samantha" <Samantha.Milligan@nshealth.ca>
Subject: Re: COVID-19 therapeutics and prophylactics

unrelated [redacted]

S

Sent from my iPhone

> On Jan 26, 2021, at 9:49 PM, Ramsey, Tasha <Tasha.Ramsey@nshealth.ca> wrote:
>
> Hi everyone,
>
> Here is the agenda for our Jan 28th meeting:
>
> - Minutes

- unrelated
- unrelated
- unrelated
- [redacted]
- [redacted]
- [redacted]
- [redacted] Bamlanivimab: Review previous recommendation

Please review the attached items in advance of the meeting and feel free to let me know if you have any questions,
Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
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Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

From: tasha.ramsey@nshealth.ca
To: Coleman, Kathleen
Subject: Re: For Thursday's agenda
Date: Wednesday, January 13, 2021 8:18:34 AM

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unrelated [redacted]!
Tasha

From: "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>
Date: Tuesday, January 12, 2021 at 10:46 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: Re: For Thursday's agenda

unrelated [redacted].

Sent from my iPhone

> On Jan 12, 2021, at 9:09 PM, Ramsey, Tasha <Tasha.Ramsey@nshealth.ca> wrote:
>
> unrelated [redacted]
>
> [redacted].
>
> Tasha
>
> ---
>
> **From:** "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
> **Date:** Tuesday, January 12, 2021 at 6:04 PM
> **To:** "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Coleman, Katie" <Katie.Coleman@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
> **Subject:** RE: For Thursday's agenda
>
> [redacted]
>
> Lisa

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Ramsey, Tasha
Sent: Tuesday, January 12, 2021 5:51 PM
To: Richard, Gabrielle; Neale, Siony; Barrett, Lisa L; Coleman, Kathleen; Coleman, Katie; Cox, Glenn; Goodall, Barbara; Grandy Allen, Lisa
Subject: Re: For Thursday's agenda

Hi Gabrielle,

Thanks for this update.

unrelated [redacted]

third party [redacted]

unrelated [redacted]

[redacted].

Tasha

From: "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>
Date: Tuesday, January 12, 2021 at 4:49 PM
To: "Neale, Siony" <Siony.Neale@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Coleman, Katie" <Katie.Coleman@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Grandy Allen, Lisa"

<Lisa.GrandyAllen@nshealth.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: For Thursday's agenda

Hi everyone

unrelated [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Gabrielle

<image001.gif>

Health and Wellness

Dr. Gabrielle Richard BSc (Pharm), Pharm D
Pharmacist Consultant
Pharmaceutical Services and Extended Health Benefits
T: 902.424.0059
gabrielle.richard@novascotia.ca

From:	Barrett, Lisa L
To:	Ramsey, Tasha; Coleman, Kathleen; Richard, Gabrielle; Neale, Siony; Cox, Glenn; Goodall, Barbara; Grandy Allen, Lisa
Subject:	RE: For Thursday"s agenda
Date:	Thursday, January 14, 2021 9:45:59 AM

Hi folks
unrelated [redacted]

Lisa

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Ramsey, Tasha
Sent: Wednesday, January 13, 2021 11:29 AM
To: Coleman, Kathleen; Barrett, Lisa L; Richard, Gabrielle; Neale, Siony; Cox, Glenn; Goodall, Barbara; Grandy Allen, Lisa
Subject: Re: For Thursday's agenda

unrelated [redacted]

[redacted]

Tasha

From: "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>
Date: Wednesday, January 13, 2021 at 9:49 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
Subject: RE: For Thursday's agenda

unrelated [redacted]

unrelated [redacted]

[redacted]

Kathleen

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: January 12, 2021 9:09 PM
To: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Coleman, Katie <Katie.Coleman@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Subject: Re: For Thursday's agenda

unrelated [redacted]

[redacted]

Tasha

From: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Date: Tuesday, January 12, 2021 at 6:04 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Coleman, Katie" <Katie.Coleman@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
Subject: RE: For Thursday's agenda

Hello
unrelated [redacted]

Lisa

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
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From: Ramsey, Tasha
Sent: Tuesday, January 12, 2021 5:51 PM
To: Richard, Gabrielle; Neale, Siony; Barrett, Lisa L; Coleman, Kathleen; Coleman, Katie; Cox, Glenn; Goodall, Barbara; Grandy Allen, Lisa
Subject: Re: For Thursday's agenda

Hi Gabrielle,

Thanks for this update.

unrelated [redacted].

third party [redacted]

unrelated [redacted]

[redacted].

Tasha

From: "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>
Date: Tuesday, January 12, 2021 at 4:49 PM
To: "Neale, Siony" <Siony.Neale@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Coleman, Katie" <Katie.Coleman@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: For Thursday's agenda

Hi everyone

unrelated [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

Gabrielle

NOVA SCOTIA
Health and Wellness

Dr. Gabrielle Richard BSc (Pharm),
Pharm D
Pharmacist Consultant
Pharmaceutical Services and Extended
Health Benefits
T: 902.424.0059
gabrielle.richard@novascotia.ca

From: tasha.ramsey@nshealth.ca
To: Coleman, Kathleen; Barrett, Lisa L; Richard, Gabrielle; Neale, Siony; Cox, Glenn; Goodall, Barbara; Grandy Allen, Lisa
Subject: Re: For Thursday"s agenda
Date: Wednesday, January 13, 2021 11:29:14 AM

---

unrelated [redacted]

[redacted]

Tasha

From: "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>
Date: Wednesday, January 13, 2021 at 9:49 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
Subject: RE: For Thursday's agenda

unrelated [redacted]

[redacted]

[redacted]

Kathleen

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: January 12, 2021 9:09 PM
To: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Richard, Gabrielle

<Gabrielle.Richard@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Coleman, Katie <Katie.Coleman@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Subject: Re: For Thursday's agenda

unrelated
[redacted]

[redacted]

Tasha

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Date: Tuesday, January 12, 2021 at 6:04 PM
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Subject: RE: For Thursday's agenda

[redacted]

Lisa

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
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Subject: Re: For Thursday's agenda

Hi Gabrielle,

Thanks for this update.

unrelated [redacted]

third party [redacted]

unrelated [redacted]

[redacted]

Tasha

From: "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>
Date: Tuesday, January 12, 2021 at 4:49 PM
To: "Neale, Siony" <Siony.Neale@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Coleman, Katie" <Katie.Coleman@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: For Thursday's agenda

Hi everyone

unrelated [redacted]

[redacted]

[redacted]

- unrelated [redacted]

[redacted]

[redacted]

[redacted]

Gabrielle

NOVA SCOTIA
Health and Wellness

Dr. Gabrielle Richard BSc (Pharm), Pharm D
Pharmacist Consultant
Pharmaceutical Services and Extended Health Benefits
T: 902.424.0059
gabrielle.richard@novascotia.ca

From: tasha.ramsey@nshealth.ca
To: Barrett, Lisa L; Coleman, Kathleen; Richard, Gabrielle; Neale, Siony; Cox, Glenn; Goodall, Barbara; Grandy Allen, Lisa
Subject: Re: For Thursday"s agenda
Date: Friday, January 15, 2021 11:11:56 AM

---

third party [redacted]

Tasha

From: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Date: Friday, January 15, 2021 at 9:27 AM
To: "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
Subject: RE: For Thursday's agenda

third party [redacted].

unrelated [redacted]

Lisa

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
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Rm. 5076, Dickson Building
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From: Coleman, Kathleen [Kathleen.Coleman@novascotia.ca]
Sent: Wednesday, January 13, 2021 9:49 AM
To: Ramsey, Tasha; Barrett, Lisa L; Richard, Gabrielle; Neale, Siony; Cox, Glenn; Goodall, Barbara; Grandy Allen, Lisa
Subject: RE: For Thursday's agenda

unrelated [redacted]

[redacted]

unrelated [redacted]

[redacted]

Kathleen

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: January 12, 2021 9:09 PM
To: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Coleman, Katie <Katie.Coleman@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Subject: Re: For Thursday's agenda

unrelated [redacted]

[redacted]

Tasha

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Date: Tuesday, January 12, 2021 at 6:04 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Coleman, Katie" <Katie.Coleman@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
Subject: RE: For Thursday's agenda

[redacted]

Lisa

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
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Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Ramsey, Tasha
Sent: Tuesday, January 12, 2021 5:51 PM
To: Richard, Gabrielle; Neale, Siony; Barrett, Lisa L; Coleman, Kathleen; Coleman, Katie; Cox, Glenn; Goodall, Barbara; Grandy Allen, Lisa
Subject: Re: For Thursday's agenda

Hi Gabrielle,

Thanks for this update.

unrelated [redacted].

third party [redacted]?

unrelated [redacted]

[redacted]

Tasha

From: "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>
Date: Tuesday, January 12, 2021 at 4:49 PM
To: "Neale, Siony" <Siony.Neale@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Coleman, Katie" <Katie.Coleman@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: For Thursday's agenda

Hi everyone

unrelated

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

Gabrielle

NOVA SCOTIA
Health and Wellness

Dr. Gabrielle Richard BSc (Pharm), Pharm D
Pharmacist Consultant
Pharmaceutical Services and Extended Health Benefits
T: 902.424.0059
gabrielle.richard@novascotia.ca

From: Coleman, Kathleen
To: Ramsey, Tasha; Barrett, Lisa L; Richard, Gabrielle; Neale, Siony; Cox, Glenn; Goodall, Barbara; Grandy Allen, Lisa
Subject: RE: For Thursday's agenda
Date: Friday, January 15, 2021 11:22:29 AM

Yes we have access to bamlan.

unrelated [redacted]

K

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: January 15, 2021 11:12 AM
To: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Subject: Re: For Thursday's agenda

third party [redacted]

Tasha

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Date: Friday, January 15, 2021 at 9:27 AM
To: "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
Subject: RE: For Thursday's agenda

third party [redacted].

unrelated [redacted]

Lisa

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases

NSHA/Dalhousie University
Rm. 5076, Dickson Building
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From: Coleman, Kathleen [Kathleen.Coleman@novascotia.ca]
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To: Ramsey, Tasha; Barrett, Lisa L; Richard, Gabrielle; Neale, Siony; Cox, Glenn; Goodall, Barbara; Grandy Allen, Lisa
Subject: RE: For Thursday's agenda

unrelated [redacted]

[redacted]

[redacted]

Kathleen

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: January 12, 2021 9:09 PM
To: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Coleman, Katie <Katie.Coleman@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Subject: Re: For Thursday's agenda

unrelated [redacted]

[redacted].

Tasha

From: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Date: Tuesday, January 12, 2021 at 6:04 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Coleman, Katie" <Katie.Coleman@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
Subject: RE: For Thursday's agenda

[redacted]

Lisa

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
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Subject: Re: For Thursday's agenda

Hi Gabrielle,

Thanks for this update.

unrelated [redacted]

third party [redacted] ?

unrelated [redacted]

unrelated
[redacted]
.

Tasha

From: "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>
Date: Tuesday, January 12, 2021 at 4:49 PM
To: "Neale, Siony" <Siony.Neale@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Coleman, Katie" <Katie.Coleman@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: For Thursday's agenda

Hi everyone

unrelated
[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

Gabrielle

NOVA SCOTIA
Health and Wellness

Dr. Gabrielle Richard BSc (Pharm), Pharm D
Pharmacist Consultant
Pharmaceutical Services and Extended Health Benefits
T: 902.424.0059
gabrielle.richard@novascotia.ca

From: Coleman, Kathleen
To: Ramsey, Tasha
Subject: Re: For Thursday's agenda
Date: Tuesday, January 12, 2021 10:46:08 PM

---

unrelated [redacted]

Sent from my iPhone

> On Jan 12, 2021, at 9:09 PM, Ramsey, Tasha <Tasha.Ramsey@nshealth.ca> wrote:
>
> unrelated [redacted]
>
> [redacted]
>
> Tasha
>
> ---
>
> **From:** "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
> **Date:** Tuesday, January 12, 2021 at 6:04 PM
> **To:** "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Coleman, Katie" <Katie.Coleman@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
> **Subject:** RE: For Thursday's agenda
>
> [redacted]
>
> Lisa
>
> ---
> Lisa Barrett MD PhD FRCPC
> Clinician Scientist, Infectious Diseases
> NSHA/Dalhousie University
> Rm. 5076, Dickson Building
> Halifax, NS
> Lisa.Barrett@nshealth.ca
> Ph. 902 473 8477
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To: Richard, Gabrielle; Neale, Siony; Barrett, Lisa L; Coleman, Kathleen; Coleman, Katie; Cox, Glenn; Goodall, Barbara; Grandy Allen, Lisa
Subject: Re: For Thursday's agenda

Hi Gabrielle,

Thanks for this update.

unrelated [redacted]

third party [redacted]

unrelated [redacted]

[redacted]

Tasha

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Date: Tuesday, January 12, 2021 at 4:49 PM
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Subject: For Thursday's agenda

Hi everyone

unrelated [redacted].

unrelated

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Gabrielle

Health and Wellness

Dr. Gabrielle Richard BSc (Pharm), Pharm D
Pharmacist Consultant
Pharmaceutical Services and Extended Health Benefits
T: 902.424.0059
gabrielle.richard@novascotia.ca

From: Gray, Thomas
To: "Coleman, Kathleen"; Grandy Allen, Lisa; Ramsey, Tasha
Subject: RE: Nova Scotia - Request for Assistance for Bamlanivimab
Date: Friday, April 23, 2021 1:13:05 PM
Attachments: image005.png
image006.png

---

third party [redacted]
Tom

Thomas Gray, BSc
Manager, Provincial Drug Distribution Program
Victoria Bldg West, Rm 5W250
1276 South Park Street Halifax NS B3H2Y9
Office: 902-473-8490 Cell: 902-471-7541
thomas.gray@nshealth.ca

From: Coleman, Kathleen [mailto:Kathleen.Coleman@novascotia.ca]
Sent: Friday, April 23, 2021 1:06 PM
To: Gray, Thomas <Thomas.Gray@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Subject: FW: Nova Scotia - Request for Assistance for Bamlanivimab
Importance: High

third party [redacted]

K

---

third party [redacted]

Subject: Re: COVID Drug Therapy Process
Date: Friday, May 7, 2021 at 11:26:51 AM Atlantic Daylight Time
From: Ramsey, Tasha
To: Toombs, Kent
Attachments: image001.jpg, image002.jpg

The pragmatic study is CO-VIC. Dr. Barrett is the PI

From: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Date: Friday, May 7, 2021 at 11:08 AM
To: "Toombs, Kent" <Kent.Toombs@nshealth.ca>
Subject: Re: COVID Drug Therapy Process

You can forward the following link that will be kept up to date with our NS Health COVID Medication recommendations from the Hub:

Medication Recommendations – COVID-19 Therapeutics and Prophylactics Advisory Group

unrelated [redacted]

I clarified all patients in NS health will receive standard of care (dexamethasone, oxygen, etc) but the study medications are only available at the study sites.

There is a study site in each zone (HI, DGH, CBRH, CEHHC, VRH, YRH). We are open to helping to support transfer to the zonal study site if a patient is interested in a study medication.

It is important to emphasize unrelated [redacted], and bamlanivimab are study medications and not considered standard of care in NS Health.

Tasha

From: "Toombs, Kent" <Kent.Toombs@nshealth.ca>
Date: Friday, May 7, 2021 at 10:53 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: COVID Drug Therapy Process

Just wanting to ensure I forward along accurate information/process with this s.20(1) [redacted]

KT

From: Scott-Davidson, Helen
Sent: Friday, May 7, 2021 10:42 AM
To: Toombs, Kent <Kent.Toombs@nshealth.ca>
Subject: COVID Drug Therapy Process
Importance: High

Hi Kent,

Wondering if you are able to provide 1-2 bullet points about the COVID drug therapy process that we reviewed last week (if you recall we addressed with as per South Shore issue)

s.20(1) [redacted] is going to the media and Lisa Barrett directly regarding why these are not available – Jake has that there is a process in place, but could you outline the process that we would follow if someone required these drugs in Amherst what the process would be.

Thanks!

Helen Scott-Davidson, PDt. CFE
Director, Nutrition and Food Services, Northern Zone
Nova Scotia Health Authority
Room C1521 Colchester East Hants Health Center
600 Abenaki Rd
Truro, NS B2N 5A1
Office: 902-893-5554 ext. 42172
Mobile: 902-890-9244
www.nshealth.ca
Helen.Scott-Davidson@nshealth.ca

Subject: Re: Results for Submit Content to the COVID-19 Hub.
Date: Friday, May 7, 2021 at 8:24:50 AM Atlantic Daylight Time
From: Ramsey, Tasha
To: Millen, Chelsey
CC: COVID-19 Hub

Thank you!! It was brought to my attention when I was reviewing COVID patients late last night with the docs that the recommendations were not up to date.

Tasha

From: "Millen, Chelsey" <Chelsey.Millen@nshealth.ca>
Date: Friday, May 7, 2021 at 8:03 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Cc: COVID-19 Hub <COVID-19Hub@nshealth.ca>
Subject: RE: Results for Submit Content to the COVID-19 Hub.

Hi Tasha,

I see this submission came in after our on-call hours, so wanted to let you know it's been updated this morning: Medication Recommendations – COVID-19 Therapeutics and Prophylactics Advisory Group

Thanks!
Chelsey

From: donotreply@libwizard.com [mailto:donotreply@libwizard.com]
Sent: May-06-21 10:27 PM
To: Millen, Chelsey <Chelsey.Millen@nshealth.ca>
Subject: Results for Submit Content to the COVID-19 Hub.

Form Name: Submit Content to the COVID-19 Hub
Submitted: May 06, 2021 10:26 PM
Report link: https://cdha-nshealth-ca libwizard com/forms/reports/5004b718c3a01a24046fed2adfc786a1

Your name::
Tasha Ramsey

Your Department::
Pharmacy

Your email::

tasha.ramsey@nshealth.ca

Your phone number::
(902)441-8181

Your content is::
An update to an existing document

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Please provide a brief summary of the changes made (maximum 1000 characters). This will be posted on the Hub below the link to your document. We also recommend adding this summary to the beginning of your document. See our template for a sample format.(Not required for forms or order sets/PPOs.):
Bamlanivimab recommendation updated to include those with non-severe COVID-19 that are 18 years of age and older hospitalized for other reasons at high risk for progression (e.g.: early transplant). unrelated [redacted]

Please paste the name of the document you are revising (use the name from the Hub itself to ensure we revise the correct document)::
Medication Recommendations – COVID-19 Therapeutics and Prophylactics Advisory Group

Please provide the link to your document from the Hub (open the document, and paste the web address into the line below)::
http://policy.nshealth.ca/Site_Published/covid19/document_render.aspx?documentRender.IdType=6&documentRender.GenericField=&documentRender.Id=85287

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medication, recommendation, unrelated, bamlanivimab, unrelated [redacted]

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Urgent and must be posted as soon as possible, i.e.,

- changes in operations, patient care to such a degree that following existing document is no longer true;
- fixing errors or making changes that, if left untouched, will cause a level of harm moderate or higher (as per CSPI definitions)

Subject: Results for Submit Content to the COVID-19 Hub.
Date: Thursday, May 6, 2021 at 10:27:08 PM Atlantic Daylight Time
From: donotreply@libwizard.com
To: Ramsey, Tasha

Form Name: Submit Content to the COVID-19 Hub
Submitted: May 06, 2021 10:27 PM

Your name::
Tasha Ramsey

Your Department::
Pharmacy

Your email::
tasha.ramsey@nshealth.ca

Your phone number::
(902)441-8181

Your content is::
An update to an existing document

Are you the original author of this content or a member of the working group that created the content?:
Yes

Your update is a:(See Updated content: Approval and posting above for more information about editorial and content changes.):
Content change (i.e., contains new information)

Please provide a brief summary of the changes made (maximum 1000 characters). This will be posted on the Hub below the link to your document. We also recommend adding this summary to the beginning of your document. See our template for a sample format.(Not required for forms or order sets/PPOs.):
Bamlanivimab recommendation updated to include those with non-severe COVID-19 that are 18 years of age and older hospitalized for other reasons at high risk for progression (e.g.: early transplant). unrelated [redacted]

Please paste the name of the document you are revising (use the name from the Hub itself to ensure we revise the correct document)::
Medication Recommendations – COVID-19 Therapeutics and Prophylactics Advisory Group

Please provide the link to your document from the Hub (open the document, and paste the web address into the line below)::
http://policy.nshealth.ca/Site_Published/covid19/document_render.aspx?documentRender.IdType=6&documentRender.GenericField=&documentRender.Id=85287

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medication, recommendation, unrelated bamlanivimab, unrelated unrelated

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Subject: COVID-19 therapeutics and prophylactics
Date: Wednesday, May 5, 2021 at 11:17:04 AM Atlantic Daylight Time
From: Ramsey, Tasha
To: Richard, Gabrielle, Barrett, Lisa L, Grandy Allen, Lisa, Coleman, Kathleen, Neale, Siony, Cox, Glenn, Reid, Emma K, Goodall, Barbara, Rockwood, Kenneth, Amanda Porter, Slayter, Kathryn
CC: McNeil, Shelly
Attachments: 1. May 6 Full Slides.pdf, 2. April 22 NS COVID-19 Therapeutics and Prophylactics Minutes.pdf, 3. NS COVID-19 Therapeutics and Prophylactics Advisory Group TOR DRAFT.pdf, Barrett Ramsey_C-19 Therapeutics AG_Summary_Bamlanivimab_2021-05-03[1].pdf, [redacted]

Hi everyone,

Sorry for the delay in sending out our meeting materials, busy times right now!

Here is the agenda for our meeting tomorrow:

- Minutes
- [redacted]
- [redacted]ated
  - [redacted]
- Pandemic supply update

You will find slides for our meeting, minutes from our last meeting, our TOR, and MSSU reviews attached.

Feel free to let me know if you have any questions or if you do not have a meeting invite in your calendar for the meeting from 8-9 tomorrow.
Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: FW: This week's summaries
Date: Tuesday, May 4, 2021 at 10:17:36 AM Atlantic Daylight Time
From: Ramsey, Tasha
To: Reid, Emma K
Attachments: image001.png, image002.png, Barrett Ramsey_C-19 Therapeutics AG_Summary_Bamlanivimab_2021-05-03.pdf, unrelated [redacted]

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Tuesday, May 4, 2021 at 9:38 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: FW: This week's summaries

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Boulos, Leah M
Sent: Tuesday, May 4, 2021 9:14 AM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Cc: Farrell, Ashley M <Ashley.Farrell@nshealth.ca>
Subject: This week's summaries

Hi Barb,

Here are this week's summaries! I know you're buried with rapid testing, but could you confirm that this project is still going strong?

Thanks,
Leah

Leah Boulos, MLIS
Evidence Synthesis Coordinator
Maritime SPOR SUPPORT Unit
Email: LeahM.Boulos@nshealth.ca
s.20(1) [redacted]

s.20(1) [redacted]

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Subject: RE: Slides AND Nova Scotia COVID-19 Vaccine Program - Information for Health Care Professionals- update April 29, 2021
Date: Friday, April 30, 2021 at 1:43:51 PM Atlantic Daylight Time
From: McLaughlin, Nancy
To: Ramsey, Tasha
CC: Currie, Rochelle
Attachments: image001.jpg

Thanks Tasha for your response.
Rochelle let me know if you need anymore info.

Take care
Nancy

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: Thursday, April 29, 2021 9:49 PM
To: McLaughlin, Nancy <Nancy.McLaughlin@nshealth.ca>
Cc: Currie, Rochelle <Rochelle.Currie@nshealth.ca>
Subject: Re: Slides AND Nova Scotia COVID-19 Vaccine Program - Information for Health Care Professionals- update April 29, 2021

Hi,

I am not sure it is necessary to post the notice.

The local context is that we have not used bamlanivimab in NS Health yet. It is recommended for non-severe disease (it is more of an outpatient drug) and it does not have published phase 3 literature to support use. So we would only consider using it in the context of research.

Our current NS Health approved recommendation is to use bamlanivimab: in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non severe COVID-19:
- 65 years of age and older in NS Health affiliated Regional Care Units OR
- 18 years of age and older hospitalized for other reasons at high risk for progression (e.g.: early transplant)

It also maintains activity against the B.1.1.7 variant and that is our predominant variant at the moment.

Tasha

From: "McLaughlin, Nancy" <Nancy.McLaughlin@nshealth.ca>
Date: Thursday, April 29, 2021 at 1:49 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Cc: "Currie, Rochelle" <Rochelle.Currie@nshealth.ca>
Subject: RE: Slides AND Nova Scotia COVID-19 Vaccine Program - Information for Health Care Professionals- update April 29, 2021

Hi Tasha, (ccing Rochelle)

I was asked by a colleague in Quality today if the recent HC notice about Bamlanivimab (below) should be put on the COVID hub under drug info. What do you think? I thought it was appropriate but wanted to check with you to confirm (could be local context I am missing).

As a subscriber to Health Canada's MedEffect™ e-Notice, you are being informed of the latest Health Product Risk Communication.
http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2021/75503a-eng.php

Important Safety Information – Bamlanivimab – Potential Risk of Treatment Failure Due to Circulation of Resistant SARS-CoV-2 Variants - Eli Lilly Canada Inc.

A potential risk of treatment failure of bamlanivimab against certain severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants was identified through global surveillance. Bamlanivimab is expected to retain neutralizing activity against the United Kingdom (UK) origin B.1.1.7 variant.

You can report any suspected adverse reactions to drugs and other health products to the Canada Vigilance Program by visiting the Adverse Reaction and Medical Device Problem Reporting page.
https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html

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Thanks,
Nancy

From: Ramsey, Tasha
Sent: Thursday, April 29, 2021 1:15 PM
To: Allen, Steven <Steven.Allen@nshealth.ca>; Arsenault, Joanna <Joanna.Arsenault@nshealth.ca>; Athanasiou, Dimitri <Dimitri.Athanasiou@nshealth.ca>; Baker, Roberta <Roberta.Baker@nshealth.ca>; Barnhill, Deb <Deb.Barnhill@nshealth.ca>; Beaver, Stephanie <Stephanie.Beaver@nshealth.ca>; Belliveau, Julia E <JuliaE.Belliveau@nshealth.ca>; Berakos, Steven <Steven.Berakos@nshealth.ca>; Bezanson, Danielle <Danielle.Bezanson@nshealth.ca>; Boudreau, Stephanie <Stephanie.Boudreau@nshealth.ca>; Bowles, Susan

<Susan.Bowles@nshealth.ca>; Bowley, Deanna <Deanna.Bowley@nshealth.ca>; Boyd, Sherry <Sherry.Boyd@nshealth.ca>; Brennan, Meghan <Meghan.Brennan@nshealth.ca>; Brown, Megan <Megan.Brown@nshealth.ca>; Brown, Michael <Michael.Brown@nshealth.ca>; Brown, Morgan <Morgan.Brown@nshealth.ca>; Brunt, Diane <Diane.Brunt@nshealth.ca>; Buckland, Amy M <AmyM.Buckland@nshealth.ca>; Burdock, Joanne <Joanne.Burdock@nshealth.ca>; Burgess, Sarah <Sarah.Burgess@nshealth.ca>; Callaghan, Allison <Allison.Callaghan@nshealth.ca>; Callaghan, Michael <Michael.Callaghan@nshealth.ca>; Cameron, Ashley <AshleyH.Cameron@nshealth.ca>; Cardiff, Kaylee <Kaylee.Cardiff@nshealth.ca>; Carter, Krista <Krista.Carter@nshealth.ca>; Carver, Holly <Holly.Carver@nshealth.ca>; Champion, Janis <Janis.Champion@nshealth.ca>; Chaulk, Alanna <Alanna.Chaulk@nshealth.ca>; Chiasson, Rose <Rose.Chiasson@nshealth.ca>; Chipman, Jenna <Jenna.Chipman@nshealth.ca>; Clee, Ceilidh <Ceilidh.Clee@nshealth.ca>; Clements, Jenny <Jenny.Clements@nshealth.ca>; Clements, Jenny L <JennyL.Clements@nshealth.ca>; Clemenza-Wrigley, Lisa <Lisa.Clemenza-Wrigley@nshealth.ca>; Conrod, Paula <Paula.Conrod@nshealth.ca>; Corporon, Tara <Tara.Corporon@nshealth.ca>; Cousins, Staci <Staci.Cousins@nshealth.ca>; Cross, Jordin M <Jordin.Cross@nshealth.ca>; Daley, Christopher <Christopher.Daley@nshealth.ca>; Dalgarno, Penny <Penny.Dalgarno@nshealth.ca>; Daniels, Amanda <Amanda.Daniels@nshealth.ca>; Davis, Meghan <Meghan.Davis@nshealth.ca>; Dearing, Marci <Marci.Dearing@nshealth.ca>; Delorme, Adrienne <Adrienne.Delorme@nshealth.ca>; d'Entremont-Harris, Mackenzie <MacKenzie.dEntremont-Harris@nshealth.ca>; DeVan, Caroline <Caroline.DeVan@nshealth.ca>; Dickinson, Sydney <Sydney.Dickinson@nshealth.ca>; Dion, Catherine <Catherine.Dion@nshealth.ca>; Doherty, Catherine <Catherine.Doherty@nshealth.ca>; Donald, Gillian <Gillian.Donald@nshealth.ca>; Doull-McCaul, Kate <Kate.Doull-McCaul@nshealth.ca>; Elford, Courtney <Courtney.Elford@nshealth.ca>; Ewert, Elizabeth <Elizabeth.Ewert@nshealth.ca>; Faulkner, Christopher <Christopher.Faulkner@nshealth.ca>; Ferguson, Nicole <Nicole.Ferguson@nshealth.ca>; Fleming, Jennifer <Jennifer.Fleming@nshealth.ca>; Friis, Amanda M <Amanda.Friis@nshealth.ca>; Ferguson, Bryan <Bryan.Ferguson@nshealth.ca>; Galbraith, Patricia <Patricia.Galbraith@nshealth.ca>; Gallant, Patrice - R CH T/L May 1, 2017 <Patrice.Gallant@nshealth.ca>; Gavel, Sydney <Sydney.Gavel@nshealth.ca>; Gebre, Afomia <Afomia.Gebre@nshealth.ca>; Gehrig, Melissa <Melissa.Gehrig@nshealth.ca>; Girroir, Shanda <Shanda.Girroir@nshealth.ca>; Glawson, Glenda 2 <Glenda2.Glawson@nshealth.ca>; Godin, James <James.Godin@nshealth.ca>; Gosbee, Kristin <Kristin.Gosbee@nshealth.ca>; Graham, Nicole <Nicole.Graham@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Grant, Alex <Alex.Grant@nshealth.ca>; Gray, Carlette <Carlette.Gray@nshealth.ca>; Handspiker-Wade, Hailey <Hailey.Handspiker-Wade@nshealth.ca>; Harding, Claudia <Claudia.Harding@nshealth.ca>; Hart, Melissa M <MelissaM.Hart@nshealth.ca>; Hasler, Tracey <Tracey.Hasler@nshealth.ca>; Healy, Colleen <Colleen.Healy@nshealth.ca>; Hebb, Melisa <Melisa.Hebb@nshealth.ca>; Henley, Nathan <Nathan.Henley@nshealth.ca>; Henneberry, Mallory G. <Mallory.Henneberry@nshealth.ca>; Heukshorst, Shelley <Shelley.Heukshorst@nshealth.ca>; Hilchie, Brooke <Brooke.Hilchie@nshealth.ca>; Hillier, Katelyn M <KatelynM.Hillier@nshealth.ca>; Hoadley, Christina <Christina.Hoadley@nshealth.ca>; Hodder, June <June.Hodder@nshealth.ca>; Hodder, Winston <Winston.Hodder@nshealth.ca>; Horwood, Laura <Laura.Horwood@nshealth.ca>; Horwood, Scott <Scott.Horwood@nshealth.ca>; Houlihan, Joanne <Joanne.Houlihan@nshealth.ca>; Hubley, Rebecca <Rebecca.Hubley@nshealth.ca>; Hughes, Tabitha <Tabitha.Hughes@nshealth.ca>; Huo, Bright <Bright.Huo@nshealth.ca>; Hurley, Theresa <Theresa.Hurley@nshealth.ca>; Hutton, Lauren <Lauren.Hutton@nshealth.ca>; Jeffrey, Jocelyn M <JocelynM.Jeffrey@nshealth.ca>; Jennex, Amber <Amber.Jennex@nshealth.ca>; Jennex, Matthew <Matthew.Jennex@nshealth.ca>; Johnson, Beth <Beth.Johnson@nshealth.ca>; Johnson, Jamie <Jamie.Johnson@nshealth.ca>; Johnston, Emily <Emily.Johnston@nshealth.ca>; Kaupp, Kristin 2 <Kristin2.Kaupp@nshealth.ca>; Kearley, Dale <Dale.Kearley@nshealth.ca>; Kennedy, Sharon <Sharon.Kennedy@nshealth.ca>; Killen, Jessica 2 <Jessica2.Killen@nshealth.ca>; Killen, Katrina <Katrina.Killen@nshealth.ca>; Kingham, Michael <Michael.Kingham@nshealth.ca>; Kowalchuk, Michael <Michael.Kowalchuk@nshealth.ca>; Ladouceur, Lauren <Lauren.Ladouceur@nshealth.ca>; Latariya, Gali <Gali.Latariya@nshealth.ca>; Latham, Laura <Laura.Latham@nshealth.ca>; Lawless, Brittany A <BrittanyA.Lawless@nshealth.ca>; Leadbeater, Kelly

<Kelly.Leadbeater@nshealth.ca>; LeBlanc, Carly <Carly.LeBlanc@nshealth.ca>; Leblanc, Phillip <Phillip.Leblanc@nshealth.ca>; Legere, Kimberley <Kimberley.Legere@nshealth.ca>; Leyte, Karen <Karen.Leyte@nshealth.ca>; Lively, Allison A <AllisonA.Lively@nshealth.ca>; Locke, Michelle <Michelle.Locke@nshealth.ca>; Logan, Alan <Alan.Logan@nshealth.ca>; McGinnis, Andrea <Andrea.McGinnis@nshealth.ca>; Ma, Mae <Mae.Ma@nshealth.ca>; MacDiarmid, Bob <Bob.MacDiarmid@nshealth.ca>; MacDonald, Hannah S <HannahS.MacDonald@nshealth.ca>; MacDonald, Seanna <Seanna.MacDonald@nshealth.ca>; MacDonald, Taylor D <TaylorD.MacDonald@nshealth.ca>; MacDuff, Mong-Diep <Mong-Diep.MacDuff@nshealth.ca>; MacEachern, Nicole <Nicole.MacEachern@nshealth.ca>; MacIntyre, Debbie <Debbie.MacIntyre@nshealth.ca>; MacIsaac, Kaleigh <Kaleigh.MacIsaac@nshealth.ca>; MacIsaac, Kelly <Kelly.MacIsaac@nshealth.ca>; MacKay, Stephen <Stephen.MacKay@nshealth.ca>; MacKeen, Heather <Heather.MacKeen@nshealth.ca>; MacKenzie, Kim <Kim.MacKenzie@nshealth.ca>; Mackenzie, Meghan <Meghan.Mackenzie@nshealth.ca>; MacLean, Charles <Charles.MacLean@nshealth.ca>; MacLean, Gill <Gill.MacLean@nshealth.ca>; MacMillan, Peter <Peter.MacMillan@nshealth.ca>; MacNeil, Erin N2 <ErinN2.MacNeil@nshealth.ca>; MacNeil, Michael <Michael.MacNeil@nshealth.ca>; Mahar, Gordie <Gordie.Mahar@nshealth.ca>; Manalang, Miguel <Miguel.Manalang@nshealth.ca>; Manderville, John R <John.Manderville@nshealth.ca>; Mannala, Sherly <Sherly.Mannala@nshealth.ca>; Mannette, Stephen <Stephen.Mannette@nshealth.ca>; Marriott, Chantal <Chantal.Marriott@nshealth.ca>; Marriott, Kimberly A <KimberlyA.Marriott@nshealth.ca>; Mason, Paul <Paul.Mason@nshealth.ca>; Matchett, Tamara <Tamara.Matchett@nshealth.ca>; McCarthy, Vicki <Vicki.McCarthy@nshealth.ca>; McIntosh, Stephanie <Stephanie.McIntosh@nshealth.ca>; McIvor, Melanie A <MelanieA.McIvor@nshealth.ca>; McKay, Alexandria <Alexandria.McKay@nshealth.ca>; McLaughlin, Scott <Scott.McLaughlin@nshealth.ca>; McLean, Marla <Marla.McLean@nshealth.ca>; McLean-Veysey, Pam <Pam.McLean-Veysey@nshealth.ca>; McQuaid, Alanna <Alanna.McQuaid@nshealth.ca>; Meade, Andrea <Andrea.Meade@nshealth.ca>; Melnick, Carrie <Carrie.Melnick@nshealth.ca>; Meunier, Fallon <Fallon.Meunier@nshealth.ca>; Micallef, Tony <Tony.Micallef@nshealth.ca>; Miller, Alexa <Alexa.Miller@nshealth.ca>; Miller, Laura 2 <Laura2.Miller@nshealth.ca>; Millett, Jean <Jean.Millett@nshealth.ca>; Minard, Laura V <LauraV.Minard@nshealth.ca>; Mohammad, Zahra <Zahra.Mohammad@nshealth.ca>; Moore, Dee <Dee.Moore@nshealth.ca>; Moore, Erin A <ErinA.Moore@nshealth.ca>; Mortlock, Susan <Susan.Mortlock@nshealth.ca>; Morvan, Marc <Marc.Morvan@nshealth.ca>; Murphy, Valerie <Valerie.Murphy@nshealth.ca>; Murray, Emma <Emma.Murray@nshealth.ca>; Murray, Logan <Logan.Murray@nshealth.ca>; Nejat, Ramin <Ramin.Nejat@nshealth.ca>; Neville, Heather <Heather.Neville@nshealth.ca>; Nodwell, Lisa <Lisa.Nodwell@nshealth.ca>; Northup, Hannah <Hannah.Northup@nshealth.ca>; Nunn, Judy <Judy.Nunn@nshealth.ca>; O'Ball, Jenna <Jenna.OBall@nshealth.ca>; Oconnell, Alivia <Alivia.Oconnell@nshealth.ca>; O'Hanley, Leanne <Leanne.OHanley@nshealth.ca>; Oldfield, Stephanie <Stephanie.Oldfield@nshealth.ca>; Osmond, Chelsea <Chelsea.Osmond@nshealth.ca>; Otis, Jacqueline <Jacqueline.Otis@nshealth.ca>; Packwood, Lana <Lana.Packwood@nshealth.ca>; Paktarigh, Shila <Shila.Paktarigh@nshealth.ca>; Park, Hyun-Ae <Hyun-Ae.Park@nshealth.ca>; Parker, Bob <Bob.Parker@nshealth.ca>; Parker, Kelsey <Kelsey.Parker@nshealth.ca>; Parker, Thomas J <ThomasJ.Parker@nshealth.ca>; Peet, Sherri <Sherri.Peet@nshealth.ca>; Pennington, Donna <Donna.Pennington@nshealth.ca>; Perrodou, Marion <Marion.Perrodou@nshealth.ca>; Phinney, Alyssa <Alyssa.Phinney@nshealth.ca>; Phonchareon, Ny <Ny.Phonchareon@nshealth.ca>; Pickrem, Tracy <Tracy.Pickrem@nshealth.ca>; Poirier, Jennifer 3 <Jennifer3.Poirier@nshealth.ca>; Poirier, Sophie <Sophie.Poirier@nshealth.ca>; Randall, Jessica <Jessica.Randall@nshealth.ca>; Redmond, Ashley <Ashley.Redmond@nshealth.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>; Richard, Hannah <Hannah.Richard@nshealth.ca>; Rideout, Megan <Megan.Rideout@nshealth.ca>; Ring, Erin <Erin.Ring@nshealth.ca>; Rioux, Josee <Josee.Rioux@nshealth.ca>; Rodney, Natasha <Natasha.Rodney@nshealth.ca>; Rolle, Megan <Megan.Rolle@nshealth.ca>; Ross, Kayla <Kayla.Ross@nshealth.ca>; Saccary, Brittany M <BrittanyM.Saccary@nshealth.ca>; Salsbury, Lauren <Lauren.Salsbury@nshealth.ca>; Salter, Shannon N <ShannonN.Salter@nshealth.ca>; Sanford, Melissa R <Melissa.Sanford@nshealth.ca>; Saulnier, Debbie <Debbie.Saulnier@nshealth.ca>; Savary, Ryan

<Ryan.Savary@nshealth.ca>; Scott, Kady <Kady.Scott@nshealth.ca>; Scott, Samantha N <SamanthaN.Scott@nshealth.ca>; Seif El Nasr, Krista <Krista.SeifElNasr@nshealth.ca>; Sharpe, Rebecca <Rebecca.Sharpe@nshealth.ca>; Sheffield, Maneka <maneka.sheffield@nshealth.ca>; Shepherd, Kristi <Kristi.Shepherd@nshealth.ca>; Sheppard, Annette <Annette.Sheppard@nshealth.ca>; Sherman, Kelsey <Kelsey.Sherman@nshealth.ca>; Simmons, Trevor <Trevor.Simmons@nshealth.ca>; Simon, Katherine <Katherine.Simon@nshealth.ca>; Simpson, Michael <Michael.Simpson@nshealth.ca>; Skeard, June <June.Skeard@nshealth.ca>; Slade, Joanne <Joanne.Slade@nshealth.ca>; Smith, Susan <SusanD.Smith@nshealth.ca>; Somers, Ellen <Ellen.Somers@nshealth.ca>; Spencer, Krysta <Krysta.Spencer@nshealth.ca>; St Peters, Taylor <Taylor.StPeters@nshealth.ca>; Steele, Barbara <Barbara.Steele@nshealth.ca>; Stevenson, Natisha <Natisha.Stevenson@nshealth.ca>; Stewart, Hailey <Hailey.Stewart@nshealth.ca>; Sweetapple, Jennifer <Jennifer.Sweetapple@nshealth.ca>; Teimouri, Arezou <Arezou.Teimouri@nshealth.ca>; ten Brinke, Michelle <Michelle.tenBrinke@nshealth.ca>; Thorne-Humphrey, Lucas M <Lucas.Thorne-Humphrey@nshealth.ca>; Tomarelli, Alex <Alex.Tomarelli@nshealth.ca>; Toombs, Kent <Kent.Toombs@nshealth.ca>; Toulany, Nada <Nada.Toulany@nshealth.ca>; Tozer-MacMillan, Tiffany <Tiffany.Tozer-MacMillan@nshealth.ca>; Tran, Jaclyn <Jaclyn.Tran@nshealth.ca>; Tran, Nga <Nga.Tran@nshealth.ca>; Trenaman, Shanna <Shanna.Trenaman@nshealth.ca>; Veith, Mary Annette <MaryAnnette.Veith@nshealth.ca>; Vickers, Jana <Jana.Vickers@nshealth.ca>; Vu, Tam <Tam.Vu@nshealth.ca>; Wadden, Angela <Angela.Wadden@nshealth.ca>; Walker, Kathleen <Kathleen.Walker@nshealth.ca>; Walters, Katrina <Katrina.Walters@nshealth.ca>; Wayte, Hazel <Hazel.Wayte@nshealth.ca>; Weagle, Amber <Amber.Weagle@nshealth.ca>; Wedlake, Bonnie <Bonnie.Wedlake@nshealth.ca>; Wentzell, Erin <Erin.Wentzell@nshealth.ca>; Wentzell, Violet <Violet.Wentzell@nshealth.ca>; White, Raymond A <RaymondA.White@nshealth.ca>; Wilson, Jo-Anne <Jo-Anne.Wilson@nshealth.ca>; Wride, Amy <Amy.Wride@nshealth.ca>; Wrighte, Sherri <Sherri.Wrighte@nshealth.ca>; Zinck, Terri <Terri.Zinck@nshealth.ca>; Zubair, Areebah <Areebah.Zubair@nshealth.ca>; Zunic, Josee <Josee.Zunic@nshealth.ca>; Abbass, Kimberley <Kimberley.Abbass@nshealth.ca>; Archibald, Ashley <Ashley.Archibald@nshealth.ca>; Barrett, Catherine <Catherine.Barrett@nshealth.ca>; Billard, Krista <Krista.Billard@nshealth.ca>; Boutilier, Karrah <Karrah.Boutilier@nshealth.ca>; Bray, Coleen <Coleen.Bray@nshealth.ca>; Cashin, Bernie <Bernie.Cashin@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Crowdis, Jeanne <Jeanne.Crowdis@nshealth.ca>; Cullen, Lois <Lois.Cullen@nshealth.ca>; Doyle, Leanne <Leanne.Doyle@nshealth.ca>; Facchin, Debora <Debora.Facchin@nshealth.ca>; Fitzgerald, Maureen <Maureen.Fitzgerald@nshealth.ca>; Flynn, Amanda <Amanda.Flynn@nshealth.ca>; Ford, Jacquelyn <Jacquelyn.Ford@nshealth.ca>; Ford, Wanda <Wanda.Ford@nshealth.ca>; Forrest, Tessa <Tessa.Forrest@nshealth.ca>; Gallagher, Adrienne <adrienne.gallagher@nshealth.ca>; Gervais, Manon <Manon.Gervais@nshealth.ca>; Giles, Shauna <Shauna.Giles@nshealth.ca>; Gillis, Heather <HeatherA.Gillis@nshealth.ca>; Gniewek, Holly <Holly.Gniewek@nshealth.ca>; Harrison, Joanne <Joanne.Harrison@nshealth.ca>; Hooper, Jennifer <Jennifer.Hooper@nshealth.ca>; Jardine, Paul <dwayne.jardine@nshealth.ca>; Jessome, Leslie <Leslie.Jessome@nshealth.ca>; Keith, Marjorie <Marjorie.Keith@nshealth.ca>; Kell, Gen <Gen.Kell@nshealth.ca>; Kelloway, Lauren <Lauren.Kelloway@nshealth.ca>; Kennedy, Elaine <Elaine.Kennedy@nshealth.ca>; Keough, Christina <Christina.Keough@nshealth.ca>; Keylor, Lauren <lauren.keylor@nshealth.ca>; Lamey, Hila <Hila.Lamey@nshealth.ca>; LeBlanc, Shannon <Shannon.LeBlanc@nshealth.ca>; Leblanc, Wendy <Wendy.LeBlanc@nshealth.ca>; Lemoine, Danielle <Danielle.Lemoine@nshealth.ca>; MacDonald, April <April.MacDonald@nshealth.ca>; MacDonald, Carolyn <CarolynJ.MacDonald@nshealth.ca>; MacDonald, Kari <Kari.MacDonald@nshealth.ca>; MacDonald, Myrna <Myrna.MacDonald@nshealth.ca>; MacDonald, Sheri <Sheri.MacDonald@nshealth.ca>; MacDougall, Rosemary <Rosemary.MacDougall@nshealth.ca>; MacFarlane, Ian <Ian.MacFarlane@nshealth.ca>; MacInnis, Marie <Marie.MacInnis@nshealth.ca>; MacInnis, Paul <Paul.MacInnis@nshealth.ca>; MacIntosh, Michelle <Michelle.MacIntosh@nshealth.ca>; MacIntyre, Lisa <Lisa.MacIntyre@nshealth.ca>; MacIntyre, Mona <Mona.MacIntyre@nshealth.ca>; MacIsaac, Amanda <Amanda.MacIsaac@nshealth.ca>; MacIsaac, Jill <Jill.MacIsaac@nshealth.ca>; MacLean, Courtney <Courtney.MacLean@nshealth.ca>; Marks, Andrew <Andrew.Marks@nshealth.ca>; Marois, Lise

<Lise.Marois@nshealth.ca>; Matthews, Michelle <Michelle.Matthews@nshealth.ca>; Moggach, Connor <Connor.Moggach@nshealth.ca>; Nathanson, Robin <Robin.Nathanson@nshealth.ca>; Neville, Jamie <Jamie.Neville@nshealth.ca>; O'Keefe, Meghan <Meghan.O'Keefe@nshealth.ca>; OKeefe, Tanya <tanya.okeefe@nshealth.ca>; O'Neil, Tara <Tara.ONeil@nshealth.ca>; Parsons, Nichol <Nichol.Parsons@nshealth.ca>; Pastuck, Joanne <Joanne.Pastuck@nshealth.ca>; Penny, Ellen <Ellen.Penny@nshealth.ca>; Perks, Amber <Amber.Perks@nshealth.ca>; Pilling, Norita <Norita.Pilling@nshealth.ca>; Ramsey, Terrence <Terrence.Ramsey@nshealth.ca>; Ransome, Anita <Anita.Ransome@nshealth.ca>; Rizzato, Julie <Julie.Rizzato@nshealth.ca>; Rowe, Cheryl <Cheryl.Rowe@nshealth.ca>; Seville, Julie <Julie.Seville@nshealth.ca>; Shaheen, Philip <Philip.Shaheen@nshealth.ca>; Shea, Ruth <Ruth.Shea@nshealth.ca>; Sullivan, Samantha <Samantha.Sullivan@nshealth.ca>; Sutherland, Judith <Judith.Sutherland@nshealth.ca>; Tibbo, Lee <Lee.Tibbo@nshealth.ca>; Travers, Nancy <Nancy.Travers@nshealth.ca>; Troke, Tara <Tara.Troke@nshealth.ca>; Worthington, Martha <Martha.Worthington@nshealth.ca>; Zakeriabeiazni, Azadeh <Azadeh.Zakeriabeiazni@nshealth.ca>; Zinck, Leanne <Leanne.Zinck@nshealth.ca>; Adams, Jennifer <Jennifer.Adams@nshealth.ca>; Atwater, Lori <Lori.Atwater@nshealth.ca>; Baillie, Danielle <Danielle.Baillie@nshealth.ca>; Benjamin, Carla <Carla.Benjamin@nshealth.ca>; Bigney, Jessica <Jessica.Bigney@nshealth.ca>; Blackwood, Robyn <Robyn.Blackwood@nshealth.ca>; Blank, Coleen <Coleen.Blank@nshealth.ca>; Burgess, Niki <Niki.Burgess@nshealth.ca>; Buske, Bethany <Bethany.Buske@nshealth.ca>; Cameron, Samantha <Samantha.Cameron@nshealth.ca>; Clyburne, Allie <Allie.Clyburne@nshealth.ca>; Comeau, Rejean <Rejean.Comeau@nshealth.ca>; Crouse, Sheila <Sheila.Crouse@nshealth.ca>; Denton, Vera <Vera.Denton@nshealth.ca>; Fraser, Karen <Karen.Fraser@nshealth.ca>; Gallagher, Gloria <Gloria.Gallagher@nshealth.ca>; Goldrich, Shannon <Shannon.Goldrich@nshealth.ca>; Green, Dennise <Dennise.Green@nshealth.ca>; Grosvold, Denise <Denise.Grosvold@nshealth.ca>; Haley, Jessie <Jessie.Haley@nshealth.ca>; Hayter, Rosemary <Rosemary.Hayter@nshealth.ca>; Horechuk, Michael <Michael.Horechuk@nshealth.ca>; Hunter, Cindy <Cindy.Hunter@nshealth.ca>; Ingraham, Katlin <Katlin.Ingraham@nshealth.ca>; Jobes, Tanya <Tanya.Jobes@nshealth.ca>; Joudrie, Ben <Ben.Joudrie@nshealth.ca>; Kent, Andrea <Andrea.Kent@nshealth.ca>; Kent, Glenda <Glenda.Kent@nshealth.ca>; Laureijs, Tessa <Tessa.Laureijs@nshealth.ca>; Long, Brianna <Brianna.Long@nshealth.ca>; Lush, Nicole <Nicole.Lush@nshealth.ca>; MacDonald, Elaine M <Elaine.MacDonald@nshealth.ca>; Macdonald, Ruby <Ruby.Macdonald@nshealth.ca>; MacInnis, Kelly <Kelly.MacInnis@nshealth.ca>; MacKinnon, Kelly <Kelly.MacKinnon@nshealth.ca>; MacLean, Erica <Erica.MacLean@nshealth.ca>; Mikail, Krista <Krista.Mikail@nshealth.ca>; Mosher, Heather <Heather.Mosher@nshealth.ca>; Norden, Henny <Henny.Norden@nshealth.ca>; OBrien, Jennifer <Jennifer.OBrien@nshealth.ca>; OConnell, Trudi <Trudi.OConnell@nshealth.ca>; O'Laney, Patrice <Patrice.O'Laney@nshealth.ca>; Porter, Jennifer <JenniferA.Porter@nshealth.ca>; Reynolds, Jason <Jason.Reynolds@nshealth.ca>; Richard, Gabrielle <Gabrielle.Richard@nshealth.ca>; Roberts, Katelyn <Katelyn.Roberts@nshealth.ca>; Ross, Melissa <Melissa.Ross@nshealth.ca>; Seymour, Lisa <Lisa.Seymour@nshealth.ca>; Spicer, Nathan <Nathan.Spicer@nshealth.ca>; Stevens, Corrine <Corrine.Stevens@nshealth.ca>; Stevens, Tammy <Tammy.Stevens@nshealth.ca>; Stobo, Kim <Kim.Stobo@nshealth.ca>; Sudsbury, Rhonda <Rhonda.Sudsbury@nshealth.ca>; Totten, Abigaile <Abigaile.Totten@nshealth.ca>; Touesnard, Kaitlyn <Kaitlyn.Touesnard@nshealth.ca>; Tucker, Megan <Megan.Tucker@nshealth.ca>; Amero, Deanna <Deanna.Amero@nshealth.ca>; Arenburg, Maggie <Maggie.Arenburg@nshealth.ca>; Baettig, Sonja <Sonja.Baettig@nshealth.ca>; Beaton, Amanda <Amanda.Beaton@nshealth.ca>; Bishop, Shelley <Shelley.Bishop@nshealth.ca>; Boyer, Cheryl <Cheryl.Boyer@nshealth.ca>; Burgess, Kimberly <Kimberly.Burgess@nshealth.ca>; Campbell, Keisha <Keisha.Campbell@nshealth.ca>; Coleman, Katie <Katie.Coleman@nshealth.ca>; Conrad, Sharon J <Sharon.Conrad@nshealth.ca>; Corbin, Amanda <Amanda.Corbin@nshealth.ca>; Corkum, Lynn <Lynn.Corkum@nshealth.ca>; Crawshaw, Jennine <Jennine.Crawshaw@nshealth.ca>; Dagley-Vaughn, Angela <Angela.Dagley-Vaughn@nshealth.ca>; d'Entremont, Candace <Candace.d'Entremont@nshealth.ca>; d'Entremont, Stacey (Pharmacy) <StaceyA.dEntremont@nshealth.ca>; d'Entremont-MacVicar, Eden <Eden.d'Entremont-

MacVicar@nshealth.ca>; Dolan, Christopher <Christopher.Dolan@nshealth.ca>; Doubleday, Carlos <Carlos.Doubleday@nshealth.ca>; Doucette, Ashley <AshleyR.Doucette@nshealth.ca>; Drouin, Liana <Liana.Drouin@nshealth.ca>; Genge, Roland <Roland.Genge@nshealth.ca>; Gillis, Amie <Amie.Gillis@nshealth.ca>; Goodwin, Erin <Erin.Goodwin@nshealth.ca>; Goreham, Janena <Janena.Goreham@nshealth.ca>; Gorst, Karen <Karen.Gorst@nshealth.ca>; Griffiths, Braden <Braden.Griffiths@nshealth.ca>; Haase, Wanda <Wanda.Haase@nshealth.ca>; Haltner, Nicole <Nicole.Haltner@nshealth.ca>; Harry, Kristy <Kristy.Harry@nshealth.ca>; Hemming, Jennifer <Jennifer.Hemming@nshealth.ca>; Hiltz, Tyler <Tyler.Hiltz@nshealth.ca>; Joudrey, Michelle <Michelle.Joudrey@nshealth.ca>; Keddy, Jared <Jared.Keddy@nshealth.ca>; Kenny, Lindsey <Lindsey.Kenny@nshealth.ca>; Kokocki, Jennifer (Nikki) <Nikki.Kokocki@nshealth.ca>; LeBlanc, Joline <Joline.LeBlanc@nshealth.ca>; Lister, Karen <Karen.Lister@nshealth.ca>; Lohnes, Jessica <Jessica.Lohnes@nshealth.ca>; Lucas, Stephanie <Stephanie.Lucas@nshealth.ca>; MacQuarrie, Sharon <Sharon.MacQuarrie@nshealth.ca>; Madden, Emma <Emma.Madden@nshealth.ca>; Martin, Stephen <Stephen.Martin@nshealth.ca>; McDormand, Ian <Ian.McDormand@nshealth.ca>; McKinlay, Monique <Monique.McKinlay@nshealth.ca>; McLaughlin, Nancy <Nancy.McLaughlin@nshealth.ca>; Melanson, Dayna <Dayna.Melanson@nshealth.ca>; Milbury, Chrissy <Chrissy.Milbury@nshealth.ca>; Mills, Gerard <Gerard.Mills@nshealth.ca>; Misner, Sonya <Sonya.Misner@nshealth.ca>; Mood, Courtney <Courtney.Mood@nshealth.ca>; Morton, Davina <Davina.Morton@nshealth.ca>; Murphy, Amy <Amy.Murphy@nshealth.ca>; Nickerson, Ashley <AshleyR.Nickerson@nshealth.ca>; Nickerson, Victor <Victor.Nickerson@nshealth.ca>; Norris, Cynthia <Cynthia.Norris@nshealth.ca>; Page, Lauren <Lauren.Page@nshealth.ca>; Parks, Rebecca <Rebecca.Parks@nshealth.ca>; Rogers, Michelle <Michelle.Rogers@nshealth.ca>; Ryan, Nicole <Nicole.Ryan@nshealth.ca>; Sabean, Beverley <Beverley.Sabean@nshealth.ca>; Scott, Angele <Angele.Scott@nshealth.ca>; Seto, Cheryl <Cheryl.Seto@nshealth.ca>; Seto, Walter <Walter.Seto@nshealth.ca>; Silver, Jessica <Jessica.Silver@nshealth.ca>; Sine, Keith - Pharmacy <Keith.Sine@nshealth.ca>; Smith, Jennifer <JenniferM.Smith@nshealth.ca>; Smith, Kate <KateM.Smith@nshealth.ca>; Smith, Stephen <Stephen.Smith@nshealth.ca>; Soucie, Josee <Josee.Soucie@nshealth.ca>; Stanwood, Shaun <Shaun.Stanwood@nshealth.ca>; Surette, Marcel <Marcel.Surette@nshealth.ca>; Tanner, Kelsey <Kelsey.Tanner@nshealth.ca>; Veinott, Brittany <Brittany.Veinott@nshealth.ca>; Weihers, Monique <Monique.Weihers@nshealth.ca>; Whynot, Jessie <Jessie.Whynot@nshealth.ca>; Wilson, Scott <Scott.Wilson@nshealth.ca>; Worthing, Tiffany <Tiffany.Worthing@nshealth.ca>

Subject: unrelated [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

- unrelated
- [redacted]

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: Re: COVID Network-Updated COVID medication recommendations for approval
Date: Monday, April 26, 2021 at 11:10:55 AM Atlantic Daylight Time
From: McNeil, Shelly
To: Ramsey, Tasha
CC: Tracey, Angela, Barrett, Lisa L
Attachments: Memo 4 April 26 2021.pdf

Sure
Angela, pls add
Shelly

Sent from my iPhone

> On Apr 26, 2021, at 11:00 AM, Ramsey, Tasha <Tasha.Ramsey@nshealth.ca> wrote:
>
> Hi Angela and Shelly,
>
> I am wondering if Lisa and I can have 5 minutes on the agenda tomorrow to request approval of two small COVID medication recommendation updates from the advisory group. See memo for COVID Network membership attached.
>
> We have already reviewed the medications (bamlanivimab and unrelated), so I will just focus on the change in the recommendation and rationale.
>
> Tasha
>
> **Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD**
>
> Clinical Coordinator– Infectious Diseases and Internal Medicine
> Pharmacy Department | Nova Scotia Health Authority
> 1796 Summer Street, Halifax, NS | Canada | B3H 3A7
> Mi'kma'ki—Unceded Mi'kmaq Territory
> ☎902-473-6829
> ✉ Tasha.Ramsey@nshealth.ca
>
> Assistant Professor– College of Pharmacy
> Dalhousie University
> 5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
> ✉ Tramsey@dal.ca

third party [redacted]

[redacted]

[redacted]

[redacted]

third party [redacted]

[redacted]

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third party

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third party

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third party

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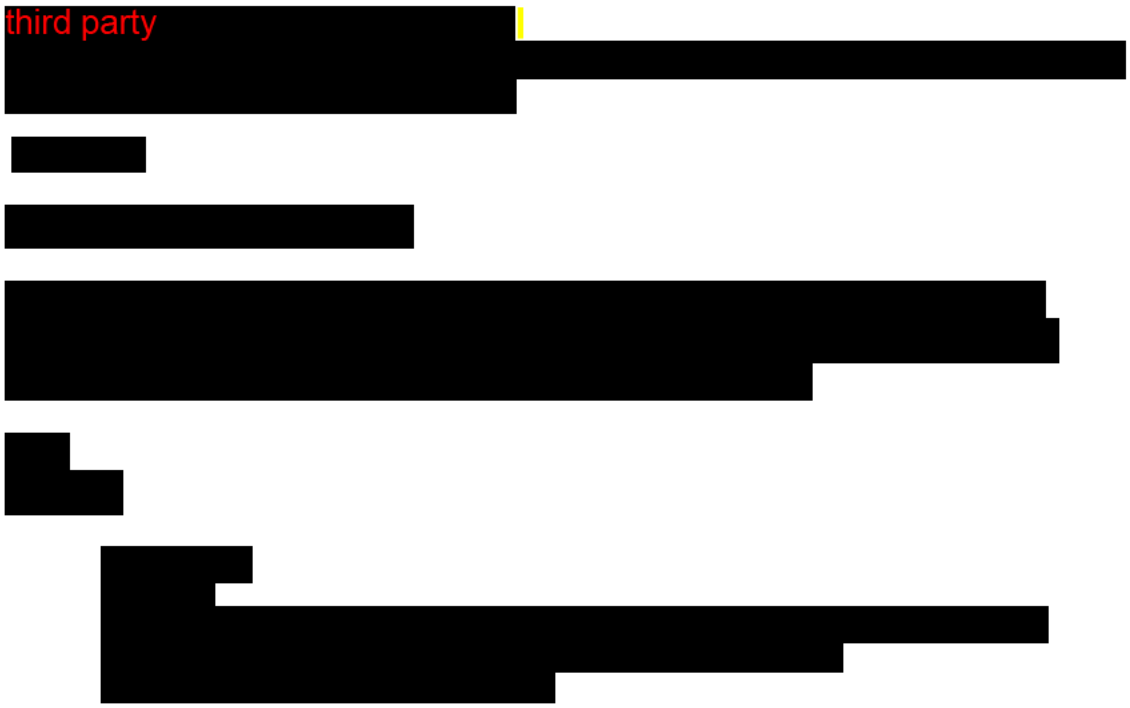
third party



Subject: COVID-19 therapeutics and prophylactics
Date: Tuesday, April 20, 2021 at 10:56:57 PM Atlantic Daylight Time
From: Ramsey, Tasha
To: Richard, Gabrielle, Barrett, Lisa L, Grandy Allen, Lisa, Coleman, Kathleen, Neale, Siony, Cox, Glenn, Reid, Emma K, Goodall, Barbara, Rockwood, Kenneth, Amanda Porter
CC: McNeil, Shelly
Attachments: 1. April 22 Full Slides.pdf, 2 April 8 NS COVID-19 Therapeutics and Prophylactics Minutes.pdf, Barrett Ramsey_C-19 Therapeutics AG_Summary_Bamlanivimab_2021-04-12.pdf, unrelated [redacted]

Hi everyone,

Here is the agenda for our April 22nd meeting:

- Minutes
- [redacted]
  - [redacted]
- Review recommendations:
  - Bamlanivimab
  - unrelated
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Pandemic supply update

You will find slides for our meeting, minutes from our last meeting, and MSSU reviews attached.

Feel free to let me know if you have any questions,
Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: FW: unrelated and bamlanivimab
Date: Monday, April 12, 2021 at 7:24:05 PM Atlantic Daylight Time
From: Ramsey, Tasha
To: Reid, Emma K
Attachments: image001.png, image002.png, Barrett Ramsey_C-19 Therapeutics AG_Summary_Bamlanivimab_2021-04-12.pdf, unrelated

FYI

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Monday, April 12, 2021 at 5:43 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Subject: FW: unrelated and bamlanivimab

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Boulos, Leah M
Sent: Monday, April 12, 2021 3:05 PM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Cc: Farrell, Ashley M <Ashley.Farrell@nshealth.ca>
Subject: unrelated and bamlanivimab

Hi Barb,

Here's this week's unrelated update, and the edited version of last week's bamlanivimab, which now features a "Variants of Concern" section.

I also wanted to highlight this article on bamlanivimab published about the ACTIV-3 trial (NEJM Mar 11), concluding that bamlanivimab + remdesivir was ineffective compared to placebo: https://www.nejm.org/doi/full/10.1056/NEJMoa2033130 - The bamlanivimab summary is already pretty lengthy and I didn't have time to incorporate this article, but thought I'd highlight it for the group nonetheless.

Have a good week!
Leah

Leah Boulos, MLIS
Evidence Synthesis Coordinator
Maritime SPOR SUPPORT Unit
Email: LeahM.Boulos@nshealth.ca

www.mssu.ca | @maritimespor
Sign up for our mailing list

Subject: Re: Ivermectin and bamlanivimab
Date: Monday, April 12, 2021 at 7:23:56 PM Atlantic Daylight Time
From: Ramsey, Tasha
To: Goodall, Barbara, Barrett, Lisa L
Attachments: image001.png, image002.png

Thanks!

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Monday, April 12, 2021 at 5:43 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Subject: FW: unrelated and bamlanivimab

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Boulos, Leah M
Sent: Monday, April 12, 2021 3:05 PM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Cc: Farrell, Ashley M <Ashley.Farrell@nshealth.ca>
Subject: Ivermectin and bamlanivimab

Hi Barb,

Here's this week's unrelated update, and the edited version of last week's bamlanivimab, which now features a "Variants of Concern" section.

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Have a good week!
Leah

Leah Boulos, MLIS
Evidence Synthesis Coordinator
Maritime SPOR SUPPORT Unit
Email: LeahM.Boulos@nshealth.ca

www.mssu.ca | @maritimespor

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Subject: FW: MSSU summaries
Date: Monday, April 12, 2021 at 10:06:23 AM Atlantic Daylight Time
From: Ramsey, Tasha
To: Reid, Emma K
Attachments: image001.png, unrelated [redacted]

FYI- updated versions

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Thursday, April 8, 2021 at 9:58 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: FW: MSSU summaries

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Boulos, Leah M
Sent: Thursday, April 8, 2021 9:40 AM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Subject: RE: MSSU summaries

Hi Barb,

unrelated [redacted]

We'll be in touch next week with the unrelated [redacted] updated bamlanivimab.

Cheers,
Leah

Subject: Re: MSSU summaries
Date: Monday, April 12, 2021 at 10:06:10 AM Atlantic Daylight Time
From: Ramsey, Tasha
To: Goodall, Barbara
Attachments: image001.png

Thanks!

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Thursday, April 8, 2021 at 9:58 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: FW: MSSU summaries

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Boulos, Leah M
Sent: Thursday, April 8, 2021 9:40 AM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Subject: RE: MSSU summaries

Hi Barb,

Here are the updated summaries unrelated [redacted]

We'll be in touch next week with the unrelated [redacted] updated bamlanivimab.

Cheers,
Leah

Subject: RE: COVID-19 therapeutics and prophylactics
Date: Thursday, April 8, 2021 at 8:57:55 AM Atlantic Daylight Time
From: Richard, Gabrielle
To: Ramsey, Tasha, Coleman, Kathleen, Barrett, Lisa L, Grandy Allen, Lisa, Neale, Siony, Cox, Glenn, Reid, Emma K, Goodall, Barbara, Rockwood, Kenneth, Amanda Porter
CC: McNeil, Shelly
Attachments: ON COVID tx guidelines April 6, 2021.jpg, image001.gif, image002.png

Hi all

In case you're interested, these are the ON guidelines for COVID-19 published April 6th, 2021.
Thanks
Gabrielle

[redacted]
Health and Wellness

Dr. Gabrielle Richard BSc (Pharm), Pharm D (she/her)
Pharmacist Consultant
Pharmaceutical Services and Extended Health Benefits
gabrielle.richard@novascotia.ca

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: April 7, 2021 8:38 PM
To: Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Rockwood, Kenneth <Kenneth.Rockwood@nshealth.ca>; Amanda Porter <Amanda.Porter@dal.ca>
Cc: McNeil, Shelly <Shelly.McNeil@nshealth.ca>
Subject: Re: COVID-19 therapeutics and prophylactics

Thank you!
Tasha

From: "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>
Date: Wednesday, April 7, 2021 at 4:47 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Reid, Emma K" <EmmaK.Reid@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Rockwood, Kenneth" <Kenneth.Rockwood@nshealth.ca>, Amanda Porter <Amanda.Porter@dal.ca>
Cc: "McNeil, Shelly" <Shelly.McNeil@nshealth.ca>

Subject: RE: COVID-19 therapeutics and prophylactics

Hi everyone,

Attached is a presentation on emerging therapies from an FPT Meeting held a couple of weeks ago. The focus is specifically on the monoclonal neutralizing antibodies. I thought it was well done so wanted to share. In particular I liked slide 10 that compares activity against specific variants.

Talk tomorrow,
Kathleen

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: April 6, 2021 10:14 PM
To: Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Rockwood, Kenneth <Kenneth.Rockwood@nshealth.ca>; Amanda Porter <Amanda.Porter@dal.ca>
Cc: McNeil, Shelly <Shelly.McNeil@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics

Hi everyone,

Here is the agenda for our April 8th meeting:

- Minutes
- unrelated [redacted]
  - [redacted]
- Review recommendations:
  - unrelated [redacted]
  - Bamlanivimab
  - unrelated [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Pandemic supply update

You will find the slides for our meeting, minutes from our last meeting, and MSSU reviews for the agents we are due to review attached.

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: Re: COVID-19 therapeutics and prophylactics
Date: Wednesday, April 7, 2021 at 8:37:38 PM Atlantic Daylight Time
From: Ramsey, Tasha
To: Coleman, Kathleen, Richard, Gabrielle, Barrett, Lisa L, Grandy Allen, Lisa, Neale, Siony, Cox, Glenn, Reid, Emma K, Goodall, Barbara, Rockwood, Kenneth, Amanda Porter
CC: McNeil, Shelly

Thank you!
Tasha

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Date: Wednesday, April 7, 2021 at 4:47 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Reid, Emma K" <EmmaK.Reid@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Rockwood, Kenneth" <Kenneth.Rockwood@nshealth.ca>, Amanda Porter <Amanda.Porter@dal.ca>
Cc: "McNeil, Shelly" <Shelly.McNeil@nshealth.ca>
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To: Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Rockwood, Kenneth <Kenneth.Rockwood@nshealth.ca>; Amanda Porter <Amanda.Porter@dal.ca>
Cc: McNeil, Shelly <Shelly.McNeil@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics

Hi everyone,

Here is the agenda for our April 8th meeting:

- Minutes
- unrelated [redacted]
  - [redacted]

- Review recommendations:
  - unrelated
  - Bamlanivimab
  - unrelated
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- Pandemic supply update

You will find the slides for our meeting, minutes from our last meeting, and MSSU reviews for the agents we are due to review attached.

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

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Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: RE: COVID-19 therapeutics and prophylactics
Date: Wednesday, April 7, 2021 at 4:47:39 PM Atlantic Daylight Time
From: Coleman, Kathleen
To: Ramsey, Tasha, Richard, Gabrielle, Barrett, Lisa L, Grandy Allen, Lisa, Neale, Siony, Cox, Glenn, Reid, Emma K, Goodall, Barbara, Rockwood, Kenneth, Amanda Porter
CC: McNeil, Shelly
Attachments: third party [redacted].pptx

Hi everyone,

Attached is a presentation on emerging therapies from an FPT Meeting held a couple of weeks ago. The focus is specifically on the monoclonal neutralizing antibodies. I thought it was well done so wanted to share. In particular I liked slide 10 that compares activity against specific variants.

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Kathleen

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To: Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Rockwood, Kenneth <Kenneth.Rockwood@nshealth.ca>; Amanda Porter <Amanda.Porter@dal.ca>
Cc: McNeil, Shelly <Shelly.McNeil@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics

Hi everyone,

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- Minutes
- unrelated [redacted]
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- Review recommendations:
  - unrelated [redacted]
  - Bamlanivimab
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  - [redacted]
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  - [redacted]
  - [redacted]
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5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: COVID-19 therapeutics and prophylactics
Date: Tuesday, April 6, 2021 at 10:13:49 PM Atlantic Daylight Time
From: Ramsey, Tasha
To: Richard, Gabrielle, Barrett, Lisa L, Grandy Allen, Lisa, Coleman, Kathleen, Neale, Siony, Cox, Glenn, Reid, Emma K, Goodall, Barbara, Rockwood, Kenneth, Amanda Porter
CC: McNeil, Shelly
Attachments: 1. April 8 Full Slides.pdf, 2. Mar 11 Minutes.pdf, Barrett Ramsey_C-19 Therapeutics AG_Summary_Bamlanivimab_2021-04-06.pdf, unrelated [redacted]

Hi everyone,

Here is the agenda for our April 8th meeting:

- Minutes
- unrelated [redacted]
  - [redacted]
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  - unrelated [redacted]
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✉ Tramsey@dal.ca

Subject: Re: Bamlanivimab update slides
Date: Tuesday, April 6, 2021 at 8:21:06 PM Atlantic Daylight Time
From: Ramsey, Tasha
To: Reid, Emma K

Have not sent it yet- will add it.

T

From: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Date: Tuesday, April 6, 2021 at 8:18 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: Bamlanivimab update slides

Actually I added one more bullet to the final slide in this version if I slip in before you send!!

From: Ramsey, Tasha
Sent: Tuesday, April 6, 2021 8:09 PM
To: Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: Re: Bamlanivimab update slides

Thanks- I will include this in the meeting materials. unrelated [redacted].

Tasha

From: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Date: Tuesday, April 6, 2021 at 8:02 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: Bamlanivimab update slides

These should help facilitate a bit of discussion on monotherapy. Couldn't find much info aside from the study MSSU located.

Emma

From: Ramsey, Tasha
Sent: Tuesday, April 6, 2021 1:31 PM
To: Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: Re: unrelated [redacted] updated

Just sent the MSSU summaries. The only thing I feel would be helpful for Thursday is if you can scan, even the grey literature, for VOC info for bam.

Tasha

From: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Date: Tuesday, April 6, 2021 at 1:13 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: unrelated updated

Hi! Don't think I ever passed this one along to you – updated since the last working group meeting. Will upload to Sharepoint.

I've been wanting to update the bamlanivimab one-pager as well, but I think I need to wait until we discuss as a group on Thursday. So far no official word about removing the recommendation for monotherapy in Canada that I've seen. Bam + etesevimab is still "under review" on HC authorization website and bam + VIR7831 not listed at all... Did a facepalm when I realized VOCs = variants of concern!!

s.20(3)(a)

Emma

Subject: RE: Bamlanivimab update slides
Date: Tuesday, April 6, 2021 at 8:18:35 PM Atlantic Daylight Time
From: Reid, Emma K
To: Ramsey, Tasha
Attachments: Update on bamlanivimab monotherapy.pptx

Actually I added one more bullet to the final slide in this version if I slip in before you send!!

From: Ramsey, Tasha
Sent: Tuesday, April 6, 2021 8:09 PM
To: Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: Re: Bamlanivimab update slides

Thanks- I will include this in the meeting materials. We can also chat about the CATCO materials (without slides).

Tasha

From: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Date: Tuesday, April 6, 2021 at 8:02 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: Bamlanivimab update slides

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Date: Tuesday, April 6, 2021 at 1:13 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: unrelated updated

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s.20(3)(a)

Emma

Subject: FW: SARS-CoV-2 variant's resistance to therapeutics tracker
Date: Tuesday, April 6, 2021 at 2:24:29 PM Atlantic Daylight Time
From: Ramsey, Tasha
To: Reid, Emma K
Attachments: image001.png, image002.png, image003.png, image004.png, Barrett Ramsey_C-19 Therapeutics AG_Summary_Bamlanivimab_2021-04-06.pdf, unrelated [redacted]

FYI- updates

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Tuesday, April 6, 2021 at 2:19 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: FW: SARS-CoV-2 variant's resistance to therapeutics tracker

Updated for those two

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Farrell, Ashley M
Sent: Tuesday, April 6, 2021 2:18 PM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Cc: Boulos, Leah M <LeahM.Boulos@nshealth.ca>
Subject: RE: SARS-CoV-2 variant's resistance to therapeutics tracker

Hi Barb,

Thank you for forwarding that along and flagging these pieces of missed information.

Upon an additional search, there was published evidence to no longer use bamlanivimab as monotherapy for variants of concern due to resistance. However, there were no updates made yet to Health Canada of Government of Canada statements. For now, I've just added the evidence articles to the review.

unrelated [redacted]

Let me know if you need any additional information on my search.

Ashley Crawford

Research Assistant
Maritime SPOR SUPPORT Unit
Phone: (902) 473-7642
Email: Ashley.Crawford@nshealth.ca

Centre for Clinical Research
5790 University Avenue, Halifax, NS B3H 1V7

www.mssu.ca | @maritimespor

MSSU · USSM

From: Goodall, Barbara
Sent: Tuesday, April 06, 2021 11:51 AM
To: Farrell, Ashley M <Ashley.Farrell@nshealth.ca>
Subject: FW: SARS-CoV-2 variant's resistance to therapeutics tracker

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Goodall, Barbara
Sent: Tuesday, April 6, 2021 11:50 AM
To: Boulos, Leah M <LeahM.Boulos@nshealth.ca>; 'Ashley.Crawford@nshealth.ca' <Ashley.Crawford@nshealth.ca>
Subject: FW: SARS-CoV-2 variant's resistance to therapeutics tracker

unrelated [redacted]

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

---

third party [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Subject: RE: unrelated updated
Date: Tuesday, April 6, 2021 at 1:44:38 PM Atlantic Daylight Time
From: Reid, Emma K
To: Ramsey, Tasha

Thanks!

I'll see what I can come up with for bam.

From: Ramsey, Tasha
Sent: Tuesday, April 6, 2021 1:31 PM
To: Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: Re: unrelated updated

Just sent the MSSU summaries. The only thing I feel would be helpful for Thursday is if you can scan, even the grey literature, for VOC info for bam.

Tasha

From: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Date: Tuesday, April 6, 2021 at 1:13 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: unrelated updated

Hi! Don't think I ever passed this one along to you – updated since the last working group meeting. Will upload to Sharepoint.

I've been wanting to update the bamlanivimab one-pager as well, but I think I need to wait until we discuss as a group on Thursday. So far no official word about removing the recommendation for monotherapy in Canada that I've seen. Bam + etesevimab is still "under review" on HC authorization website and bam + VIR7831 not listed at all... Did a facepalm when I realized VOCs = variants of concern!!

s 20(3)(a)

Emma

Subject: FW: Bamlanivimab, unrelated [redacted]
Date: Tuesday, April 6, 2021 at 1:30:42 PM Atlantic Daylight Time
From: Ramsey, Tasha
To: Reid, Emma K
Attachments: image001.png, image002.png, Barrett Ramsey_C-19 Therapeutics AG_Summary_Bamlanivimab_2021-04-06.pdf, unrelated [redacted]

FYI- barb is following up to see if they can find anything on VOCs for bam

---

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Tuesday, April 6, 2021 at 10:51 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: FW: Bamlanivimab, unrelated [redacted]

I am following up with them about Bam .. I think they are missing new information particularly with variants

Barbara Goodall
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From: Farrell, Ashley M
Sent: Tuesday, April 6, 2021 10:47 AM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Cc: Boulos, Leah M <LeahM.Boulos@nshealth.ca>
Subject: Bamlanivimab, unrelated [redacted]

Hi Barb,

I hope you had a good long weekend! Here are this week's summaries.

Best,

Ashley Crawford
Research Assistant
Maritime SPOR SUPPORT Unit
Phone: (902) 473-7642
Email: Ashley.Crawford@nshealth.ca

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Subject: Re: Bamlanivimab, unrelated
Date: Tuesday, April 6, 2021 at 12:19:05 PM Atlantic Daylight Time
From: Ramsey, Tasha
To: Goodall, Barbara
Attachments: image001.png, image002.png

Thanks Barb!

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Tuesday, April 6, 2021 at 10:51 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: FW: Bamlanivimab, unrelated

I am following up with them about Bam .. I think they are missing new information particularly with variants

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Cc: Boulos, Leah M <LeahM.Boulos@nshealth.ca>
Subject: Bamlanivimab, unrelated

Hi Barb,

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Maritime SPOR SUPPORT Unit

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Email: Ashley.Crawford@nshealth.ca

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MSSU · USSM

Subject: Re: unrelated
Date: Tuesday, April 6, 2021 at 11:40:08 AM Atlantic Daylight Time
From: Ramsey, Tasha
To: Barrett, Lisa L, McNeil, Shelly, Angus, Margaret
Attachments: unrelated

[redacted]

From: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Date: Tuesday, April 6, 2021 at 9:33 AM
To: "McNeil, Shelly" <Shelly.McNeil@nshealth.ca>, "Angus, Margaret"

<Margaret.Angus@nshealth.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: unrelated

[redacted]

From: McNeil, Shelly
Sent: Tuesday, April 6, 2021 9:25 AM
To: Angus, Margaret; Barrett, Lisa L; Ramsey, Tasha
Subject: unrelated

[redacted]

Thanks
S

Sent from my iPhone

> On Apr 6, 2021, at 7:59 AM, Angus, Margaret <Margaret.Angus@nshealth.ca> wrote:
>
> unrelated
>
> Thanks,
> Margaret
>
> -----Original Message-----
> From: COVID19INFO [mailto:COVID19INFO@novascotia.ca]
> Sent: Monday, April 5, 2021 1:45 PM
> To: Angus, Margaret <Margaret.Angus@nshealth.ca>; Heroux Rhymes, Clara <Clara.HerouxRhymes@nshealth.ca>
> Subject: unrelated
>
>
> -----Original Message-----
> From: s.20(1) @gmail.com>
> Sent: April 5, 2021 8:43 AM
> To: COVID19INFO <COVID19INFO@novascotia.ca>
> Subject: unrelated
>
> unrelated
>
>
> Sent from my iPhone
>

Subject: unrelated Bamlanivimab Recommendation Review
Date: Friday, April 2, 2021 at 1:35:53 PM Atlantic Daylight Time
From: Ramsey, Tasha
To: Goodall, Barbara, Reid, Emma K, Barrett, Lisa L
Attachments: image001.png, image002.jpg, image003.png

Thanks for the updates Barb- I was trying to decide how much time we should spend on our view of bam and unrelated at our next advisory group meeting.

Sounds like bamlanivimab is no longer recommended as monotherapy for variants of concern due to resistance ...so I am wondering how this will impact CATCO-NOS and if we want to participate in it? We do not know if we have VOCs until weeks later when the national lab confirms it. What are your thoughts Lisa?

unrelated

Tasha

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Thursday, April 1, 2021 at 2:50 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Reid, Emma K" <EmmaK.Reid@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Subject: unrelated

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barbara.goodall@nshealth.ca

From:

[redacted]

[redacted]

third party

[redacted]

Subject: RE: unrelated and bamlanivimab research questions
Date: Thursday, April 1, 2021 at 2:53:12 PM Atlantic Daylight Time
From: Goodall, Barbara
To: Ramsey, Tasha
Attachments: image002.png

I'm not sure about CATCO-NOS and bamlan ... so far they haven't said anything besides "Waiting for BC ethics approval and then will send to you" .. they have ontario ethics approval and started recruitment and enrollment in Calgary already.

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5790 University Ave., Halifax, NS B3H 1V7
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From: Ramsey, Tasha
Sent: Thursday, April 1, 2021 2:30 PM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>
Cc: Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: unrelated and bamlanivimab research questions

Hi Lisa and Barb,

unrelated

For bamlanivimab...Lisa had mentioned there are recommendations to no longer use it as monotherapy. Will this impact CATCO-NOS?
Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

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Tramsey@dal.ca

[redacted]

third party

third party [redacted]


third party
third party


third party

third party

[redacted]

d party

Subject: RE: monoclonal antibodies
Date: Friday, March 26, 2021 at 2:16:24 PM Atlantic Daylight Time
From: Poirier, Adele
To: Ramsey, Tasha, Barrett, Lisa L

Thanks very much, both of you.

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: March 26, 2021 1:15 PM
To: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Poirier, Adele <Adele.Poirier@novascotia.ca>
Subject: Re: monoclonal antibodies

Hi,

Our official NS Health recommendation for bamlanivimab is to: use in the context of pragmatic research in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units

Tasha

From: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Date: Friday, March 26, 2021 at 1:01 PM
To: "Poirier, Adele" <Adele.Poirier@novascotia.ca>
Cc: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: Re: monoclonal antibodies

Hi there

Bamlanivumab has early data that allowed it's approval in Canada. The data suggested the biggest positive impact on older adults and those with significant other medical issues. Because our most vulnerable are the older people in LTC and because this medication requires an intravenous infusion, it was decided that we would use it for those with mild COVID 19 transferred to RCUs from LTC. This medication is supplied through the federal pandemic supply and we have 150 doses available.

Many other provinces have decided not to use it due to the challenges of logistics for the IV infusion but we have said we would do so as part of pragmatic research.

Just call me if other information needed.

Lisa

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Poirier, Adele <Adele.Poirier@novascotia.ca>
Sent: Friday, March 26, 2021 12:39 PM
To: Barrett, Lisa L
Subject: FW: monoclonal antibodies

Hi Lisa…

Shelley pointed me to you…would you be able to help me with a very high level answer? I will respond through the covid19info account.

Thanks.

Adèle

From: COVID19INFO
Sent: March 26, 2021 11:39 AM
To: Deeks, Shelley <Shelley.Deeks@novascotia.ca>
Subject: FW: monoclonal antibodies

I don't even know where to start with this one…might you be able to help?

Adèle

From: s.20(1) [redacted] @eastlink.ca>
Sent: March 25, 2021 11:52 PM
To: COVID19INFO <COVID19INFO@novascotia.ca>
Subject: monoclonal antibodies

** EXTERNAL EMAIL / COURRIEL EXTERNE **

After watching the Rachel Maddow show on MSNBC Thursday evening March 25, I was intrigued by the efficacy of a monoclonal antibody, in this case LILLY's "bamlanivimab" in keeping people infected with Covid-19 out of hospitals. Reductions in admissions, where used, were reported in the 70 – 80+% ranges. When I tried to see if this drug/treatment was available in Nova Scotia, I found it was available in Canada, had in fact been approved by Health Canada for use under certain conditions, yet was not mentioned in any official NS website I could find.

QUESTION: is "bamlanivimab", or similar monoclonal antibody, available for use in Nova Scotia. or is being considered for use at authorized sites?

Thank you.

s.20(1)
[redacted]

Subject: RE: COVID-19 therapeutics and prophylactics
Date: Thursday, March 18, 2021 at 10:40:05 AM Atlantic Daylight Time
From: Amanda Porter
To: Ramsey, Tasha

Hi Tasha,

unrelated [redacted]

-Amanda

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: March 12, 2021 10:37 AM
To: Amanda Porter <Amanda.Porter@dal.ca>
Subject: Re: COVID-19 therapeutics and prophylactics

CAUTION: The Sender of th s ema s not from w th n Da hous e.

Hi,

d [redacted]

[redacted]

[redacted]

[redacted]

unrelated [redacted]

Tasha

From: Amanda Porter <Amanda.Porter@dal.ca>
Date: Thursday, March 11, 2021 at 9:21 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics

Hi Tasha,

[redacted]

unrelated [redacted]

[redacted]

-Amanda

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: March 10, 2021 9:06 PM
To: Amanda Porter <Amanda.Porter@dal.ca>
Subject: Re: COVID-19 therapeutics and prophylactics

unrelated [redacted]

[redacted]

unrelated [redacted]

[redacted]

[redacted]

Tasha

From: Amanda Porter <Amanda.Porter@dal.ca>
Date: Wednesday, March 10, 2021 at 4:25 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics

** EXTERNAL EMAIL / COURRIEL EXTERNE **
Exercise caution when opening attachments or clicking on links / Faites preuve de prudence si vous ouvrez une pièce jointe ou cliquez sur un lien

Hi Tasha,

unrelated [redacted]

-Amanda

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: March 10, 2021 10:45 AM
To: Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Barrett, Lisa L <lisa.barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Coleman, Kathleen <kathleen.coleman@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>; Goodall, Barbara <barbara.goodall@nshealth.ca>; Rockwood, Kenneth <Kenneth.Rockwood@nshealth.ca>; Amanda Porter <Amanda.Porter@dal.ca>
Cc: shelly.mcneil@nshealth.ca
Subject: COVID-19 therapeutics and prophylactics

CAUTION: The Sender of th s ema s not from w th n Da hous e.

Here is the agenda for our March 11th meeting:

- Minutes
- unrelated [redacted]
  - [redacted]

    - unrelated
- Review recommendations:
    - Bamlanivimab
    - unrelated
    - [redacted]
- Pandemic supply update

You will find the slides for our meeting, minutes from last week, and MSSU reviews for unrelated [redacted] bamlanivimab, unrelated [redacted] attached.

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: RE: drugs being tracked by [redacted] for COVID
Date: Friday, March 12, 2021 at 8:13:54 AM Atlantic Standard Time
From: Goodall, Barbara
To: Richard, Gabrielle, Coleman, Kathleen, Rockwood, Kenneth, Barrett, Lisa L, Ramsey, Tasha, Reid, Emma K, Porter, Amanda
Attachments: image001.png

Thank you Gabrielle, is there any interest in me engaging Leah at the MSSU to prepare evidence reviews for the below (for publically available information)?
Barb

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Richard, Gabrielle [mailto:Gabrielle.Richard@novascotia.ca]
Sent: Thursday, March 11, 2021 8:29 AM
To: Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Rockwood, Kenneth <Kenneth.Rockwood@nshealth.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Porter, Amanda <Amanda.Porter@nshealth.ca>
Subject: drugs being tracked by [redacted] for COVID

Good morning!

Here is the list I got from PHAC of drugs they are tracking. It is not a complete list.

1. Bamlanivimab + etesevimab combination monoclonal antibody therapy

unrelated [redacted]

If you have any that you are wondering about, please let me know. Tracking doesn't mean there is absolute evidence, but spidey senses are tingling…

Gabrielle

Subject: Re: drugs being tracked by [redacted] for COVID
Date: Thursday, March 11, 2021 at 8:34:59 AM Atlantic Standard Time
From: Barrett, Lisa L
To: Richard, Gabrielle, Coleman, Kathleen, Rockwood, Kenneth, Ramsey, Tasha, Reid, Emma K, Goodall, Barbara, Porter, Amanda

Merci! Very helpful!

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>
Sent: Thursday, March 11, 2021 8:28 AM
To: Coleman, Kathleen; Rockwood, Kenneth; Barrett, Lisa L; Ramsey, Tasha; Reid, Emma K; Goodall, Barbara; Porter, Amanda
Subject: drugs being tracked by [redacted] for COVID

Good morning!

Here is the list I got from PHAC of drugs they are tracking. It is not a complete list.

1. Bamlanivimab + etesevimab combination monoclonal antibody therapy

unrelated [redacted]

If you have any that you are wondering about, please let me know. Tracking doesn't mean there is absolute evidence, but spidey senses are tingling…

Gabrielle

Subject: drugs being tracked by [redacted] for COVID
Date: Thursday, March 11, 2021 at 8:28:54 AM Atlantic Standard Time
From: Richard, Gabrielle
To: Coleman, Kathleen, Rockwood, Kenneth, Barrett, Lisa L, Ramsey, Tasha, Reid, Emma K, Goodall, Barbara, Porter, Amanda

Good morning!

Here is the list I got from PHAC of drugs they are tracking. It is not a complete list.

1. Bamlanivimab + etesevimab combination monoclonal antibody therapy

[redacted]

If you have any that you are wondering about, please let me know. Tracking doesn't mean there is absolute evidence, but spidey senses are tingling...

Gabrielle

Subject: COVID-19 therapeutics and prophylactics
Date: Wednesday, March 10, 2021 at 10:44:51 AM Atlantic Standard Time
From: Ramsey, Tasha
To: Richard, Gabrielle, Barrett, Lisa L, Grandy Allen, Lisa, Coleman, Kathleen, Neale, Siony, Cox, Glenn, Reid, Emma K, Goodall, Barbara, Rockwood, Kenneth, Amanda Porter
CC: McNeil, Shelly
Attachments: 2. Feb 25 NS COVID-19 Therapeutics and Prophylactics Minutes.pdf, 3. Mar 11 Slides.pdf, Barrett Ramsey_C-19 Therapeutics AG_Summary_Bamlanivimab_2021-03-09.pdf, unrelated [redacted]

Hi everyone,

Here is the agenda for our March 11th meeting:

- Minutes
- unrelated [redacted]
  - [redacted]
  - [redacted]
- Review recommendations:
  - Bamlanivimab
  - unrelated [redacted]
  - [redacted]
- Pandemic supply update

You will find the slides for our meeting, minutes from last week, and MSSU reviews for unrelated [redacted] bamlanivimab, unrelated [redacted] attached.

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory

☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: Re: Bamlanivimab, unrelated
Date: Wednesday, March 10, 2021 at 10:34:50 AM Atlantic Standard Time
From: Ramsey, Tasha
To: Goodall, Barbara
Attachments: image001.png, image002.png

Thanks!

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Wednesday, March 10, 2021 at 9:13 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: FW: Bamlanivimab, unrelated

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Boulos, Leah M
Sent: Tuesday, March 9, 2021 9:10 AM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Subject: Bamlanivimab, unrelated

Hi Barb,

Here are this week's updates.

Cheers,
Leah

Leah Boulos, MLIS
Evidence Synthesis Coordinator
Maritime SPOR SUPPORT Unit
Email: LeahM.Boulos@nshealth.ca

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Subject: RE: Slides to distribute
Date: Monday, March 8, 2021 at 2:14:06 PM Atlantic Standard Time
From: Reid, Emma K
To: Ramsey, Tasha

Perfect thanks so much.
Emma

From: Ramsey, Tasha
Sent: Monday, March 8, 2021 1:19 PM
To: Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: Re: Slides to distribute

I have that bamlanivimab, unrelated are up for their 4 week review? So MSSU should be sending updated reviews tomorrow.

Tasha

From: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Date: Monday, March 8, 2021 at 12:33 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: Slides to distribute

Hello!

I have two slidesets for unrelated that can be distributed prior to the Advisory Group meeting on Thursday for everyone's info. Depending on the rest of the agenda can select a couple key slides to review in more detail.

unrelated

Can I confirm which other treatments are due for re-review this week?

Thanks,
Emma

third party [redacted]

third party

[redacted]

third party [redacted]

[redacted]

Subject: Re: Press release
Date: Thursday, February 25, 2021 at 3:27:25 PM Atlantic Standard Time
From: Ramsey, Tasha
To: Reid, Emma K

unrelated [redacted]

[redacted]

T

From: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Date: Thursday, February 25, 2021 at 3:14 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: Press release

unrelated [redacted]

unrelated [redacted]

From: Ramsey, Tasha
Sent: Thursday, February 25, 2021 2:51 PM
To: Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: Press release

unrelated [redacted]

[redacted]

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

third party [redacted]

[redacted]

third party [redacted]

[redacted]

[redacted]

[redacted]

third party [redacted]

Subject: unrelated [redacted]
Date: Wednesday, February 24, 2021 at 8:13:57 AM Atlantic Standard Time
From: Reid, Emma K
To: Ramsey, Tasha
Attachments: image001.png, image002.png

unrelated [redacted]

Emma

From: Ramsey, Tasha
Sent: Tuesday, February 23, 2021 9:09 PM
To: Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: Re: unrelated [redacted]

Hi Emma,

I ended up including your bam slides for their reference but we can certainly ask Lisa to lead the discussion.

Tasha

From: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Date: Tuesday, February 23, 2021 at 3:39 PM
To: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Subject: Re: unrelated

[redacted]

Perfect- I will forward the MSSU summaries and unrelated .

We can ask Lisa to comment on bam. unrelated [redacted]

Tasha

From: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Date: Tuesday, February 23, 2021 at 1:13 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: unrelated

Hey Tasha,

unrelated [redacted]

[redacted]

I still don't see any ground-breaking bamlanivimab updates, either. In retrospect I don't think the slides I forwarded last week add much so maybe Lisa can lead the discussion there?

unrelated [redacted]

[redacted]
Emma

From: Ramsey, Tasha
Sent: Tuesday, February 23, 2021 12:26 PM
To: Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: FW: unrelated

Hi Emma,

[redacted] am wondering if you can take a quick peek to see if there is anything in these MSSU documents you feel we should address in the meeting package that will be sent out today.

Tasha

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Tuesday, February 23, 2021 at 11:56 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: FW: [redacted]

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Boulos, Leah M
Sent: Tuesday, February 23, 2021 10:58 AM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Subject: [redacted]

Hi Barb,

[redacted]

Cheers,
Leah

Leah Boulos, MLIS
Evidence Synthesis Coordinator
Maritime SPOR SUPPORT Unit
Email: LeahM.Boulos@nshealth.ca

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Subject: COVID-19 therapeutics and prophylactics
Date: Tuesday, February 23, 2021 at 9:05:53 PM Atlantic Standard Time
From: Ramsey, Tasha
To: Richard, Gabrielle, Barrett, Lisa L, Grandy Allen, Lisa, Coleman, Kathleen, Neale, Siony, Cox, Glenn, Reid, Emma K, Goodall, Barbara, Rockwood, Kenneth, Amanda Porter
CC: McNeil, Shelly
Attachments: 1. Feb 25 Slides.pdf, 2. Feb 4 Minutes.pdf, 3. COI form.docx, unrelated [redacted]

Hi everyone,

Here is the agenda for our Feb 25th meeting:

- Minutes
- unrelated [redacted]
- Review recommendations:

- unrelated
- [redacted]
- Bamlanivimab

- Pandemic supply update

Please review the attached slides and updated MSSU summary sheets in advance of the meeting.

Feel free to let me know if you have questions,

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
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Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: Re: unrelated [redacted]
Date: Tuesday, February 23, 2021 at 3:39:23 PM Atlantic Standard Time
From: Ramsey, Tasha
To: Reid, Emma K
Attachments: image001.png, image002.png

unrelated

Perfect- I will forward the MSSU summaries unrelated .

We can ask Lisa to comment on bam. unrelated [redacted]

Tasha

From: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>

Date: Tuesday, February 23, 2021 at 1:13 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: unrelated

Hey Tasha,

unrelated

I still don't see any ground-breaking bamlanivimab updates, either. In retrospect I don't think the slides I forwarded last week add much so maybe Lisa can lead the discussion there?

unrelated

Emma

From: Ramsey, Tasha
Sent: Tuesday, February 23, 2021 12:26 PM
To: Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: FW: unrelated

Hi Emma,

unrelated am wondering if you can take a quick peek to see if there is anything in these MSSU documents you feel we should address in the meeting package that will be sent out today.

Tasha

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Tuesday, February 23, 2021 at 11:56 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: FW: unrelated

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Boulos, Leah M
Sent: Tuesday, February 23, 2021 10:58 AM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Subject: unrelated

Hi Barb,

unrelated

Cheers,
Leah

Leah Boulos, MLIS
Evidence Synthesis Coordinator
Maritime SPOR SUPPORT Unit
Email: LeahM.Boulos@nshealth.ca

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Subject: Re: Media Inquiry: bamlanivimab
Date: Monday, February 22, 2021 at 3:39:15 PM Atlantic Standard Time
From: Vanessa Chouinard
To: Ramsey, Tasha
CC: Barrett, Lisa L, McNeil, Shelly

Thank you.

On Feb 22, 2021, at 8:22 AM, Ramsey, Tasha <Tasha.Ramsey@nshealth.ca> wrote:

Hi,

Sorry for the delay. I agree with Lisa- we received 50 vials and have used none.

Our current recommendation for use is “in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units.”

Tasha

From: "Chouinard, Vanessa P" <Vanessa.Chouinard@novascotia.ca>
Date: Sunday, February 21, 2021 at 3:36 PM
To: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Cc: "McNeil, Shelly" <Shelly.McNeil@nshealth.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: Re: Media Inquiry: bamlanivimab

Thank you very much!

> On Feb 21, 2021, at 2:07 PM, Barrett, Lisa L <Lisa.Barrett@nshealth.ca> wrote:
>
> Thought we received 50 doses, used 0.
>
> For patients over 65, with early disease, in the context of research setting.

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: McNeil, Shelly
Sent: Sunday, February 21, 2021 1:13 PM
To: Ramsey, Tasha; Chouinard, Vanessa P
Cc: Barrett, Lisa L
Subject: FW: Media Inquiry: bamlanivimab

Hi Tasha
Can you please respond to Vanessa's questions below
Thanks
Shelly

From: Chouinard, Vanessa P [mailto:Vanessa.Chouinard@novascotia.ca]
Sent: Friday, February 19, 2021 5:42 PM
To: McNeil, Shelly <Shelly.McNeil@nshealth.ca>
Subject: FW: Media Inquiry: bamlanivimab

Hi Shelly,

Jenni suggested you might have an answer to a question comms received from media today on a drug. Are you able to assist? Here is the question that came in:

Questions: We asked Health Canada about how many doses of bamlanivimab, a monoclonal antibody treatment, the government has bought. It said that it has purchased 17K doses between Dec 2020 and February 2021.

I was wondering:
- how many doses your province has received
- how many doses your province has been used
- in what way are they being used (for which patients, in which settings, etc.)

Thanks in advance!

From: Cram, Jennifer <Jennifer.Cram@nshealth.ca>
Sent: February 19, 2021 5:34 PM
To: Chouinard, Vanessa P <Vanessa.Chouinard@novascotia.ca>; Deeks, Shelley <Shelley.Deeks@novascotia.ca>
Subject: Re: Media Inquiry: bamlanivimab

I would suggest asking Shelly McNeil.

Jenni

Dr. Jennifer Cram MD MPH FRCPC
Medical Officer of Health
Western Zone
821 St. George Street
Annapolis Royal, NS B0S 1A0

Email: Jennifer.cram@nshealth.ca

From: Chouinard, Vanessa P <Vanessa Chouinard@novascotia ca>
Sent: Friday, February 19, 2021 5:29:51 PM
To: Deeks, Shelley; Cram, Jennifer
Subject: FW: Media Inquiry: bamlanivimab

Help! Are either of you familiar?

From: Barbrick, Tracey L <Tracey.Barbrick@novascotia.ca>
Sent: February 19, 2021 2:11 PM
To: MacInnis, Marla J <Marla.MacInnis@novascotia.ca>; Benoit, David James <David.Benoit@novascotia.ca>
Cc: Kiritsis, Tony <Tony.Kiritsis@novascotia.ca>; Chouinard, Vanessa P <Vanessa.Chouinard@novascotia.ca>
Subject: RE: Media Inquiry: bamlanivimab

I haven't a clue!! Vanessa? I think it's a covid treatment drug – not a vaccine.

From: MacInnis, Marla J <Marla.MacInnis@novascotia.ca>
Sent: February 19, 2021 2:03 PM
To: Barbrick, Tracey L <Tracey.Barbrick@novascotia.ca>; Benoit, David James <David.Benoit@novascotia.ca>
Cc: Kiritsis, Tony <Tony.Kiritsis@novascotia.ca>
Subject: Media Inquiry: bamlanivimab

Hi Tracey and David – please see the media inquiry below from Power and Politics. Do we have any bamlanivimab in Nova Scotia?

Questions: We asked Health Canada about how many doses of

bamlanivimab, a monoclonal antibody treatment, the government has bought. It said that it has purchased 17K doses between Dec 2020 and February 2021.

I was wondering:
- how many doses your province has received
- how many doses your province has been used
- in what way are they being used (for which patients, in which settings, etc.)

Marla MacInnis
Media Relations Advisor, Province of Nova Scotia
Department of Health and Wellness
t: 902-499-6428 | **e:** marla.macinnis@novascotia.ca

Subject: Re: Media Inquiry: bamlanivimab
Date: Monday, February 22, 2021 at 8:20:53 AM Atlantic Standard Time
From: Ramsey, Tasha

To: Chouinard, Vanessa P, Barrett, Lisa L
CC: McNeil, Shelly

Hi,

Sorry for the delay. I agree with Lisa- we received 50 vials and have used none.

Our current recommendation for use is “in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units.”

Tasha

From: "Chouinard, Vanessa P" <Vanessa.Chouinard@novascotia.ca>
Date: Sunday, February 21, 2021 at 3:36 PM
To: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Cc: "McNeil, Shelly" <Shelly.McNeil@nshealth.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: Re: Media Inquiry: bamlanivimab

Thank you very much!

> On Feb 21, 2021, at 2:07 PM, Barrett, Lisa L <Lisa.Barrett@nshealth.ca> wrote:
>
> Thought we received 50 doses, used 0.
>
> For patients over 65, with early disease, in the context of research setting.

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: McNeil, Shelly
Sent: Sunday, February 21, 2021 1:13 PM
To: Ramsey, Tasha; Chouinard, Vanessa P
Cc: Barrett, Lisa L
Subject: FW: Media Inquiry: bamlanivimab

Hi Tasha
Can you please respond to Vanessa’s questions below
Thanks
Shelly

From: Chouinard, Vanessa P [mailto:Vanessa.Chouinard@novascotia.ca]
Sent: Friday, February 19, 2021 5:42 PM
To: McNeil, Shelly <Shelly.McNeil@nshealth.ca>
Subject: FW: Media Inquiry: bamlanivimab

Hi Shelly,

Jenni suggested you might have an answer to a question comms received from media today on a drug. Are you able to assist? Here is the question that came in:

Questions: We asked Health Canada about how many doses of bamlanivimab, a monoclonal antibody treatment, the government has bought. It said that it has purchased 17K doses between Dec 2020 and February 2021.

I was wondering:
- how many doses your province has received
- how many doses your province has been used
- in what way are they being used (for which patients, in which settings, etc.)

Thanks in advance!

From: Cram, Jennifer <Jennifer.Cram@nshealth.ca>
Sent: February 19, 2021 5:34 PM
To: Chouinard, Vanessa P <Vanessa.Chouinard@novascotia.ca>; Deeks, Shelley <Shelley.Deeks@novascotia.ca>
Subject: Re: Media Inquiry: bamlanivimab

I would suggest asking Shelly McNeil.

Jenni

Dr. Jennifer Cram MD MPH FRCPC
Medical Officer of Health
Western Zone
821 St. George Street
Annapolis Royal, NS B0S 1A0

Email: Jennifer.cram@nshealth.ca

From: Chouinard, Vanessa P <Vanessa.Chouinard@novascotia.ca>
Sent: Friday, February 19, 2021 5:29:51 PM
To: Deeks, Shelley; Cram, Jennifer
Subject: FW: Media Inquiry: bamlanivimab

Help! Are either of you familiar?

From: Barbrick, Tracey L <Tracey.Barbrick@novascotia.ca>
Sent: February 19, 2021 2:11 PM
To: MacInnis, Marla J <Marla.MacInnis@novascotia.ca>; Benoit, David James <David.Benoit@novascotia.ca>
Cc: Kiritsis, Tony <Tony.Kiritsis@novascotia.ca>; Chouinard, Vanessa P <Vanessa.Chouinard@novascotia.ca>
Subject: RE: Media Inquiry: bamlanivimab

I haven't a clue!! Vanessa? I think it's a covid treatment drug – not a vaccine.

From: MacInnis, Marla J <Marla.MacInnis@novascotia.ca>
Sent: February 19, 2021 2:03 PM
To: Barbrick, Tracey L <Tracey.Barbrick@novascotia.ca>; Benoit, David James <David.Benoit@novascotia.ca>
Cc: Kiritsis, Tony <Tony.Kiritsis@novascotia.ca>
Subject: Media Inquiry: bamlanivimab

Hi Tracey and David – please see the media inquiry below from Power and Politics. Do we have any bamlanivimab in Nova Scotia?

Questions: We asked Health Canada about how many doses of bamlanivimab, a monoclonal antibody treatment, the government has bought. It said that it has purchased 17K doses between Dec 2020 and February 2021.

I was wondering:
- how many doses your province has received
- how many doses your province has been used
- in what way are they being used (for which patients, in which settings, etc.)

Marla MacInnis
Media Relations Advisor, Province of Nova Scotia
Department of Health and Wellness
t: 902-499-6428 | **e:** marla.macinnis@novascotia.ca

Subject: RE: Slides for next week's Therapeutics and Prophylactics

Date: Friday, February 19, 2021 at 11:32:01 AM Atlantic Standard Time

From: Reid, Emma K

To: Ramsey, Tasha

unrelated [redacted]

From: Ramsey, Tasha
Sent: Friday, February 19, 2021 11:29 AM
To: Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: Re: Slides for next week's Therapeutics and Prophylactics

unrelated [redacted]

Tasha

From: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Date: Friday, February 19, 2021 at 11:22 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: Slides for next week's Therapeutics and Prophylactics

Hi Tasha,

unrelated [redacted]

I did have another close look at bamlanivimab and there isn't much to add to what we have previously discussed. I did throw the info on slides but not sure it's necessary (attached). Maybe things will change by next week, so I'll keep an eye out!

Emma

Subject: Re: T and P Advisory Group Meeting
Date: Tuesday, February 16, 2021 at 1:19:59 PM Atlantic Standard Time
From: Ramsey, Tasha
To: Barrett, Lisa L, Reid, Emma K

Sounds like we have a plan:

Feb 25: unrelated bam
Mar 4: unrelated

[redacted]

Tasha

From: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Date: Tuesday, February 16, 2021 at 11:46 AM
To: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: Re: T and P Advisory Group Meeting

unrelated [redacted] With variants, think [redacted] will supplant bam pretty fast

---

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Reid, Emma K
Sent: Tuesday, February 16, 2021 11:12 AM
To: Barrett, Lisa L; Ramsey, Tasha
Subject: RE: T and P Advisory Group Meeting

unrelated [redacted]

[redacted]

[redacted] Bamlanivimab would be on the agenda for the week after so can dig into prophylaxis again then if it isn't pushing it too late.

unrelated [redacted]
Thanks!
Emma

From: Barrett, Lisa L
Sent: Tuesday, February 16, 2021 10:55 AM
To: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>

Subject: Re: T and P Advisory Group Meeting

Sounds good. We will want to unrelated [redacted] and also re-discuss bam as prophylaxis in the context of little vaccination and variants (guess where I'm using as an example!!!)

L.

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Ramsey, Tasha
Sent: Tuesday, February 16, 2021 10:41 AM
To: Barrett, Lisa L; Reid, Emma K
Subject: T and P Advisory Group Meeting

Hi Lisa and Emma,

unrelated [redacted]

[redacted]

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: Re: unrelated
Date: Friday, February 5, 2021 at 10:17:47 AM Atlantic Standard Time
From: Ramsey, Tasha
To: Coleman, Kathleen

unrelated [redacted]

[redacted]

Have a great weekend,
Tasha

From: "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>
Date: Thursday, February 4, 2021 at 5:44 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: COI form

Hi Tasha,
unrelated [redacted]

[redacted]

Cheers
K

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: February 2, 2021 7:14 PM
To: Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Rockwood, Kenneth <Kenneth.Rockwood@nshealth.ca>; Amanda Porter <Amanda.Porter@dal.ca>
Cc: McNeil, Shelly <Shelly.McNeil@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics

Hi everyone,

Here is the agenda for our Feb 4th meeting:
- Minutes
-unrelated [redacted]

[redacted] bamlanivimab: Review previous recommendations

Please review the attached items in advance of the meeting and feel free to let me know if you have questions,
Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine

Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: COVID-19 therapeutics and prophylactics
Date: Tuesday, February 2, 2021 at 7:14:15 PM Atlantic Standard Time
From: Ramsey, Tasha
To: Richard, Gabrielle, Barrett, Lisa L, Grandy Allen, Lisa, Coleman, Kathleen, Neale, Siony, Cox,

Glenn, Reid, Emma K, Goodall, Barbara, Rockwood, Kenneth, Amanda Porter

CC: McNeil, Shelly

Attachments: 1. Feb 4 Slides.pdf, 1. Jan 28 NS COVID-19 Therapeutics and Prophylactics Minutes.docx, 2. COI form.docx, 3. Memo 2 DRAFT Feb 2021.doc, unrelated [redacted] 5. Barrett Ramsey_C-19 Therapeutics AG_Summary_Bamlanivimab_2021-02-02.pdf, unrelated [redacted] 5. CADTH Implementation Panel Jan 14 2021.pdf

Hi everyone,

Here is the agenda for our Feb 4th meeting:
- Minutes
- unrelated [redacted] bamlanivimab: Review previous recommendations

Please review the attached items in advance of the meeting and feel free to let me know if you have questions,
Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: Re: Bamlanivimab, unrelated [redacted]
Date: Tuesday, February 2, 2021 at 4:21:34 PM Atlantic Standard Time
From: Ramsey, Tasha
To: Goodall, Barbara

Attachments: image001.png, image002.png

Great! Thank you!!

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Tuesday, February 2, 2021 at 12:08 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: FW: Bamlanivimab, unrelated [redacted]

See attached ☺

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Boulos, Leah M
Sent: Tuesday, February 2, 2021 12:01 PM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Subject: Bamlanivimab, unrelated [redacted]

Hi Barb,

Here are the summaries for bamlanivimab, unrelated [redacted]

Cheers,
Leah

Leah Boulos, MLIS
Evidence Synthesis Coordinator
Maritime SPOR SUPPORT Unit
Email: LeahM.Boulos@nshealth.ca

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Subject: Re: Bamlanivimab, unrelated [redacted]

Date: Tuesday, February 2, 2021 at 4:19:25 PM Atlantic Standard Time

From: Ramsey, Tasha
To: Reid, Emma K
Attachments: image001.png, image002.png

Hi,

unrelated [redacted]

It doesn't hurt to review the press release info. I will include your slides with our meeting materials!

Tasha

From: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Date: Tuesday, February 2, 2021 at 3:20 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: Bamlanivimab, unrelated [redacted]

Partly for my own understanding I made these – take/leave/adapt as you see fit for upcoming agenda!

From: Reid, Emma K
Sent: Tuesday, February 2, 2021 2:03 PM
To: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Subject: RE: Bamlanivimab, unrelated [redacted]

I love these!

Wrapping my head around my interpretation. From my perspective the 4-week revisit suggests:

- unrelated [redacted]
- For bamlanivimab:
  - The Phase 3 press release for Blaze-1 continues to support a benefit for bamlanivimab in non-severe population, but they only talk about outcomes in combo with etesevimab. I still want to know how bamlanivimab fared on its own in this Phase 3 setting, but the info isn't publicly available yet. So not enough info to suggest we should change our recommendation.
  - The BLAZE-2 press release is exciting in terms of its role in prophylaxis, but it strikes me as something hugely resource intensive and not aligned with the federal pandemic supply we received. I think it is logical to continue to use in the population we outlined knowing they will be in RCUs and no longer in their LTC settings... and there may still be a side benefit of less transmission to others. Again, no publicly available study so hard to draw a firm conclusion. So I still don't see a need to change our original recommendation.

Do you think it is worth it to create a couple slides for both the Phase 3 BLAZE-1 and BLAZE 2 studies for what we know from press releases? Will this just confuse things??

Feel free to give me a call to discuss when you have a sec.

Thanks,
Emma

From: Ramsey, Tasha
Sent: Tuesday, February 2, 2021 12:53 PM
To: Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: Fw: Bamlanivimab, unrelated [redacted]

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
•902-473-6829
• Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
• Tramsey@dal.ca

From: Goodall, Barbara
Sent: February 2, 2021 12:08:45 PM
To: Ramsey, Tasha
Subject: FW: Bamlanivimab, unrelated [redacted]

See attached ☺

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Boulos, Leah M
Sent: Tuesday, February 2, 2021 12:01 PM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Subject: Bamlanivimab, unrelated [redacted]

Hi Barb,

Here are the summaries for bamlanivimab, unrelated [redacted]

Cheers,
Leah

Leah Boulos, MLIS
Evidence Synthesis Coordinator
Maritime SPOR SUPPORT Unit
Email: LeahM.Boulos@nshealth.ca

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Subject: FW: Bamlanivimab, unrelated [redacted]

Date: Tuesday, February 2, 2021 at 12:08:45 PM Atlantic Standard Time
From: Goodall, Barbara
To: Ramsey, Tasha
Attachments: Barrett Ramsey_C-19 Therapeutics AG_Summary_Bamlanivimab_2021-02-02.pdf, [redacted] image001.png, image003.png

See attached ☺

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Boulos, Leah M
Sent: Tuesday, February 2, 2021 12:01 PM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Subject: Bamlanivimab, unrelated

Hi Barb,

Here are the summaries for bamlanivimab, unrelated

Cheers,
Leah

Leah Boulos, MLIS
Evidence Synthesis Coordinator
Maritime SPOR SUPPORT Unit
Email: LeahM.Boulos@nshealth.ca

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Subject: RE: COVID-19 therapeutics and prophylactics

Date: Monday, February 1, 2021 at 4:20:55 PM Atlantic Standard Time
From: Reid, Emma K
To: Ramsey, Tasha

Great! I'll keep an eye on the feeds. Otherwise probably being up to speed on the latest BLAZE bamlan prophylaxis information will be handy. We'll see what MSSU sends and if we think there should any additional slides made.

E

From: Ramsey, Tasha
Sent: Monday, February 1, 2021 12:39 PM
To: Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: Re: COVID-19 therapeutics and prophylactics

Thank you!

unrelated [redacted]. We are going to look at the MSSU documents for bam, unrelated [redacted]. I will send them to you when I receive them. If you see anything that is worth having a slide or two on, we can look at creating them tomorrow.

T

From: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Date: Monday, February 1, 2021 at 10:53 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics

Hi Tasha,

See attached for minutes. Let me know if any feedback with regards to content/incorporation of recommendations. I realize that the minutes will be particularly important if the rationale piece is no longer provided.

Any particular agent I should do some slides up for this week?

Thanks,
Emma

From: Ramsey, Tasha
Sent: Tuesday, January 26, 2021 9:50 PM
To: Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Rockwood, Kenneth <Kenneth.Rockwood@nshealth.ca>; Amanda Porter <Amanda.Porter@dal.ca>
Cc: McNeil, Shelly <Shelly.McNeil@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics

Hi everyone,

Here is the agenda for our Jan 28th meeting:

- Minutes
- unrelated
- unrelated
- unrelated
- [redacted] Bamlanivimab: Review previous recommendation

Please review the attached items in advance of the meeting and feel free to let me know if you have any questions,
Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: Re: COVID-19 therapeutics and prophylactics

Date: Thursday, January 28, 2021 at 11:22:21 PM Atlantic Standard Time

From: McNeil, Shelly

To: Ramsey, Tasha

CC: Richard, Gabrielle, Barrett, Lisa L, Grandy Allen, Lisa, Coleman, Kathleen, Neale, Siony, Cox, Glenn, Reid, Emma K, Goodall, Barbara, Rockwood, Kenneth, Amanda Porter, Milligan, Samantha

Attachments: 1. Jan 28 Slides.pdf, 2. Jan 21 NS COVID-19 Therapeutics and Prophylactics Minutes.docx, 3. NS COVID-19 Therapeutics and Prophylactics Advisory Group TOR DRAFT.docx, 4. COI form.docx, unrelated [redacted] 9. CADTH Implementation Panel Jan 14 2021.pdf

unrelated [redacted]

5

Sent from my iPhone

On Jan 26, 2021, at 9:49 PM, Ramsey, Tasha <Tasha.Ramsey@nshealth.ca> wrote:

Hi everyone,

Here is the agenda for our Jan 28th meeting:

- Minutes
- unrelated [redacted]
- unrelated [redacted]
- unrelated [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted] Bamlanivimab: Review previous recommendation

Please review the attached items in advance of the meeting and feel free to let me know if you have any questions,
Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy

Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: FW: Bamlanivimab - Lilly BLAZE-1 press release
Date: Wednesday, January 27, 2021 at 5:35:49 PM Atlantic Standard Time
From: Gray, Thomas
To: Ramsey, Tasha
CC: Grandy Allen, Lisa
Attachments: BLAZE-1_Topline Canada final 21.01.26.pdf

New info from Lilly on BamBam. ☺

Tom

third party

[redacted]

third party [redacted]

[redacted]

Subject: COVID-19 therapeutics and prophylactics
Date: Tuesday, January 26, 2021 at 9:49:51 PM Atlantic Standard Time
From: Ramsey, Tasha
To: Richard, Gabrielle, Barrett, Lisa L, Grandy Allen, Lisa, Coleman, Kathleen, Neale, Siony, Cox, Glenn, Reid, Emma K, Goodall, Barbara, Rockwood, Kenneth, Amanda Porter
CC: McNeil, Shelly
Attachments: 1. Jan 28 Slides.pdf, 2. Jan 21 NS COVID-19 Therapeutics and Prophylactics Minutes.docx, 3. NS COVID-19 Therapeutics and Prophylactics Advisory Group TOR DRAFT.docx, 4. COI form.docx, unrelated [redacted] 9. CADTH Implementation Panel Jan 14 2021.pdf

Hi everyone,

Here is the agenda for our Jan 28th meeting:

- Minutes
- unrelated [redacted]
- [redacted]
- unrelated [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted], Bamlanivimab: Review previous recommendation

Please review the attached items in advance of the meeting and feel free to let me know if you have any questions,
Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: RE: MSSU Rapid Review
Date: Tuesday, January 26, 2021 at 12:22:59 PM Atlantic Standard Time
From: Goodall, Barbara
To: Ramsey, Tasha
Attachments: image001.png, image002.png

Thank you!!!

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Ramsey, Tasha
Sent: Tuesday, January 26, 2021 12:22 PM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Subject: Re: MSSU Rapid Review

Ideally she would have summaries ready the Tuesday before each meeting. So it would be great if she could send us a summary page by the date indicated and then update it for us every 4 weeks

- unrelated
- Bamlanivimab: ideally feb 2 then every 4 weeks afterwards (march 2, etc).
- unrelated

Tasha

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Tuesday, January 26, 2021 at 11:50 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: MSSU Rapid Review

I am trying to align dates to these to provide to Leah – do you have a record of what "date" would be the 4 week mark for those we have put forth recommendations and what "Date" the upcoming will be reviewed?

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Ramsey, Tasha
Sent: Monday, January 25, 2021 4:51 PM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>
Subject: Re: MSSU Rapid Review

Perfect- thank you for asking for a colchicine review! I appreciate it may take a bit to catch up with the advisory group, but I would also appreciate if she can complete an initial document and rolling review (every 4 weeks) for the agents we have made recommendations on:

- unrelated
- Bamlanivimab
- unrelated

Tasha

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Monday, January 25, 2021 at 1:32 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Subject: MSSU Rapid Review

Hello,

Had a meeting with Leah Boulos today, she did the rapid reviews for COVIC … she will do them for the COVID therapeutics advisory group starting this week. unrelated

Thanks!
Barb

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

Subject: Re: Eli Lilly: positive BLAZE-1 results of 2800mg bamlanivimab and 2800mg etesevimab combo
Date: Tuesday, January 26, 2021 at 11:42:23 AM Atlantic Standard Time
From: Ramsey, Tasha
To: Barrett, Lisa L

Thanks for sharing

From: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Date: Tuesday, January 26, 2021 at 11:41 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: Fw: Eli Lilly: positive BLAZE-1 results of 2800mg bamlanivimab and 2800mg etesevimab combo

FYI....thankfully some of the confidential combo data coming out! Was getting tired of the angst

---

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: s.20(1) @teralyscapital.com>
Sent: Tuesday, January 26, 2021 11:33 AM
To: s.20(1) ; Barrett, Lisa L; s.20(1)
Subject: Eli Lilly: positive BLAZE-1 results of 2800mg bamlanivimab and 2800mg etesevimab combo

Dear CTTF colleagues,

These are breaking news – out this morning – more details from Lilly expected today at noon.

This is obviously very important. s.20(1) and I are speaking with our federal colleagues today, and we

will need to discuss this together very soon.

Best regards,

s.20(1)

_____

Source: BMO, January 26, 2021

B-mab Combo Positive Outcomes Support Greater Adoption

Load full report

Bottom Line:

Eli Lilly announced positive BLAZE-1 results of 2800mg bamlanivimab and 2800mg etesevimab combo, showing a 70% reduction (p=0.0004) in hospitalizations and deaths in 1,035 high-risk COVID-19 outpatients. We believe data are consistent with interim results (pooled monotherapy 72% reduction), reinforcing b-mab clinical benefit and should accelerate global approvals and greater adoption. In addition, ongoing evaluation of a 16-minute monotherapy infusion and low-dose SC combo can overcome delivery challenges and drive additional purchase agreements.

Key Points

Positive BLAZE-1 combo shows 70% reduction in hospitalizations. Eli Lilly announced positive Phase 3 BLAZE-1 results for 2800mg bamlanivimab and 2800mg etesevimab (LY-CoV016) combination, showing a 70% reduction (p=0.0004) in hospitalizations and deaths in 1,035 mild-moderate, high-risk COVID-19 patients in the outpatient setting. There were 11 events (2%) in the treatment group versus 36 in placebo (7%), with all 10 deaths occurring in the placebo group. The combination statistically met key secondary endpoints, including viral load reductions and symptom improvement. The safety profile was clean and consistent with no significant differences versus placebo group.

Initial BLAZE-4 supports potential low-dose SC combo. Lilly also noted that initial BLAZE-4 data evaluating a low dose IV combo, with the 700mg b-mab and 1400mg etesevimab combo showing consistent viral load reductions and PK/PD to the 2800mg combo, supporting the potential to show similar clinical benefit. Lilly is currently evaluating even lower doses in order to maximize the potential supply, in addition to enabling a potential subcutaneous option. With more than 250K doses of the combination therapy available in 1Q21, Lilly is ramping manufacturing to provide up to 1mm doses by mid-2021. We expect initial BLAZE-4 data to support a potential low-dose EUA approval in as early as 2Q21.

Overcoming initial challenges should see increased demand. In addition to a potential SC option, Lilly is working with the

FDA to reduce b-mab infusion times from 1 hour to potentially 16 minutes, significantly reducing the burden on the healthcare system. With Germany as the first country in the EU to authorize use of COVID-19 antibodies, purchasing up to 200K doses (€400M) of b-mab and REGN-CoV2, we expect additional EU countries to follow suit. We expect Lilly to provide additional details on the b-mab program in an investor webcast Today (January 26) at 12 noon ET.

Subject: Fw: Eli Lilly: positive BLAZE-1 results of 2800mg bamlanivimab and 2800mg etesevimab combo
Date: Tuesday, January 26, 2021 at 11:41:29 AM Atlantic Standard Time
From: Barrett, Lisa L
To: Ramsey, Tasha
Priority: High

FYI....thankfully some of the confidential combo data coming out! Was getting tired of the angst

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

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Sent: Tuesday, January 26, 2021 11:33 AM
To: s.20(1) ; Barrett, Lisa L s.20(1)
Subject: Eli Lilly: positive BLAZE-1 results of 2800mg bamlanivimab and 2800mg etesevimab combo

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This is obviously very important. s.20(1) and I are speaking with our federal colleagues today, and we will need to discuss this together very soon.

Best regards,

s.20(1)

Source: BMO, January 26, 2021

B-mab Combo Positive Outcomes Support Greater Adoption

Load full report

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Subject: Conversation with Richard, Gabrielle

Date: Monday, January 25, 2021 at 2:12:32 PM Atlantic Standard Time

From: Richard, Gabrielle

To: Richard, Gabrielle, Ramsey, Tasha

Richard, Gabrielle 2:10 PM:

they did not
government tends to not do that necessarily I'm learning

Ramsey, Tasha 2:12 PM:

Gotcha- I have only been to the one meeting with this group on bamlanivimab and they shared slides for it

Subject: RE: COVID-19 therapeutics and prophylactics
Date: Wednesday, January 20, 2021 at 1:55:13 PM Atlantic Standard Time
From: Barrett, Lisa L
To: Richard, Gabrielle, Ramsey, Tasha, Grandy Allen, Lisa, Coleman, Kathleen, Neale, Siony, Cox, Glenn, Reid, Emma K, Goodall, Barbara, Rockwood, Kenneth, Amanda Porter
CC: McNeil, Shelly
Attachments: image001.gif

unrelated [redacted].

Lisa

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Richard, Gabrielle [Gabrielle.Richard@novascotia.ca]
Sent: Wednesday, January 20, 2021 1:16 PM
To: Ramsey, Tasha; Barrett, Lisa L; Grandy Allen, Lisa; Coleman, Kathleen; Neale, Siony; Cox, Glenn; Reid, Emma K; Goodall, Barbara; Rockwood, Kenneth; Amanda Porter
Cc: McNeil, Shelly
Subject: RE: COVID-19 therapeutics and prophylactics

Hi

unrelated [redacted]

[redacted]

Thanks
Gabrielle

[redacted]
Health and Wellness

Dr. Gabrielle Richard BSc (Pharm), Pharm D
Pharmacist Consultant
Pharmaceutical Services and Extended Health Benefits
gabrielle.richard@novascotia.ca

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: January 19, 2021 1:24 PM
To: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Rockwood, Kenneth <Kenneth.Rockwood@nshealth.ca>; Amanda Porter <Amanda.Porter@dal.ca>
Cc: McNeil, Shelly <Shelly.McNeil@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics

Hi everyone,

Here is the agenda for our Jan 21st advisory group meeting:
- Introductions
[redacted]
- Minutes (attached)
- [redacted] Bamlanivimab (see slides and CADTH bamlanivimab implementation panel advice)

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: RE: For Thursday's agenda
Date: Wednesday, January 20, 2021 at 1:36:44 PM Atlantic Standard Time
From: Barrett, Lisa L
To: Ramsey, Tasha, Coleman, Kathleen
Attachments: image001.gif

unrelated [redacted]

[redacted]

[redacted]

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Ramsey, Tasha
Sent: Wednesday, January 20, 2021 1:13 PM
To: Coleman, Kathleen; Barrett, Lisa L
Subject: Re: For Thursday's agenda

unrelated [redacted]

[redacted]

[redacted].

Tasha

From: "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>
Date: Wednesday, January 20, 2021 at 1:07 PM
To: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: For Thursday's agenda

unrelated [redacted]

unrelated [redacted]

K

From: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>
Sent: January 15, 2021 9:27 AM
To: Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Subject: RE: For Thursday's agenda

third party [redacted]

unrelated [redacted]

Lisa

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Coleman, Kathleen [Kathleen.Coleman@novascotia.ca]
Sent: Wednesday, January 13, 2021 9:49 AM
To: Ramsey, Tasha; Barrett, Lisa L; Richard, Gabrielle; Neale, Siony; Cox, Glenn; Goodall, Barbara; Grandy Allen, Lisa
Subject: RE: For Thursday's agenda

unrelated [redacted]

[redacted]

[redacted]

Kathleen

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: January 12, 2021 9:09 PM
To: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Coleman, Katie <Katie.Coleman@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Subject: Re: For Thursday's agenda

unrelated [redacted]

[redacted]

Tasha

From: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Date: Tuesday, January 12, 2021 at 6:04 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Coleman, Katie" <Katie.Coleman@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
Subject: RE: For Thursday's agenda

Hello
unrelated [redacted]

Lisa

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Ramsey, Tasha
Sent: Tuesday, January 12, 2021 5:51 PM
To: Richard, Gabrielle; Neale, Siony; Barrett, Lisa L; Coleman, Kathleen; Coleman, Katie; Cox, Glenn; Goodall, Barbara; Grandy Allen, Lisa
Subject: Re: For Thursday's agenda

Hi Gabrielle,

Thanks for this update.

elated

third party

unrelated

Tasha

From: "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>
Date: Tuesday, January 12, 2021 at 4:49 PM
To: "Neale, Siony" <Siony.Neale@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Coleman, Katie" <Katie.Coleman@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: For Thursday's agenda

Hi everyone

unrelated

Thanks! See everyone on Thursday!
Gabrielle

[redacted]

Health and Wellness

Dr. Gabrielle Richard BSc (Pharm), Pharm D
Pharmacist Consultant
Pharmaceutical Services and Extended Health Benefits
T: 902.424.0059
gabrielle.richard@novascotia.ca

Subject: Re: For Thursday's agenda
Date: Tuesday, January 12, 2021 at 9:06:05 PM Atlantic Standard Time
From: Ramsey, Tasha
To: Richard, Gabrielle
Attachments: image001.gif, image002.gif

unrelated

[redacted]

Tasha

From: "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>
Date: Tuesday, January 12, 2021 at 6:43 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: For Thursday's agenda

Hi Tasha

unrelated

Gabrielle

[redacted]
Health and Wellness

Dr. Gabrielle Richard BSc (Pharm), Pharm D
Pharmacist Consultant
Pharmaceutical Services and Extended Health Benefits
T: 902.424.0059
gabrielle.richard@novascotia.ca

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: January 12, 2021 5:52 PM
To: Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Coleman, Katie <Katie.Coleman@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Subject: Re: For Thursday's agenda

Hi Gabrielle,

Thanks for this update.

unrelated [redacted]

third party [redacted]

unrelated [redacted]

[redacted]

Tasha

From: "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>
Date: Tuesday, January 12, 2021 at 4:49 PM
To: "Neale, Siony" <Siony.Neale@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Coleman, Katie" <Katie.Coleman@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: For Thursday's agenda

Hi everyone

unrelated [redacted]

unrelated [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

Thanks! See everyone on Thursday!
Gabrielle

[redacted]

Health and Wellness

Dr. Gabrielle Richard BSc (Pharm), Pharm D
Pharmacist Consultant
Pharmaceutical Services and Extended Health Benefits
T: 902.424.0059
gabrielle.richard@novascotia.ca

Subject: FW: Bamlanivimab Supporting Materials
Date: Wednesday, January 6, 2021 at 3:24:15 PM Atlantic Standard Time
From: Ramsey, Tasha
To: Reid, Emma K
Attachments: image001.jpg

FYI- looks like the Canadian playbook is out

[redacted]

** EXTERNAL EMAIL / COURRIEL EXTERNE **
Exercise caution when opening attachments or clicking on links / Faites preuve de prudence si vous ouvrez une pièce jointe ou cliquez sur un lien

third party

[redacted]


third party

Subject: Re: COVID-19 therapeutics and prophylactics
Date: Wednesday, January 6, 2021 at 11:03:47 AM Atlantic Standard Time
From: Ramsey, Tasha
To: Coleman, Kathleen, Barrett, Lisa L, Grandy Allen, Lisa, Neale, Siony, Cox, Glenn, Richard, Gabrielle, Reid, Emma K, Goodall, Barbara
Attachments: unrelated

[redacted]

Tasha

From: "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>
Date: Wednesday, January 6, 2021 at 8:55 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Reid, Emma K" <EmmaK.Reid@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics

Hi Tasha
unrelated [redacted]

[redacted]

unrelated [redacted]

[redacted]

Thanks,
Kathleen

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: January 5, 2021 2:03 PM
To: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics

Hi everyone,

Here is the agenda for our Jan 7th meeting:

- Review minutes from Dec 17 and 18th (all)
- Bamlanivimab, unrelated [redacted]: discuss outcome of COVID Network recommendations (T. Ramsey)
- unrelated [redacted]

[redacted]

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: RE: Bamlanivimab Supporting Materials
Date: Tuesday, January 5, 2021 at 3:32:23 PM Atlantic Standard Time
From: Gray, Thomas
To: s.20(1)
CC: Ramsey, Tasha, Grandy Allen, Lisa
Attachments: image003.jpg

Good afternoon,
Thanks for the info. I'm looping in some colleagues on your offer/assistance.

Best Regards,
Tom

[redacted]

Thomas Gray, BSc
Manager, Provincial Drug Distribution Program
Victoria Bldg West, Rm 5W250
1276 South Park Street Halifax NS B3H2Y9
Office: 902-473-8490 Cell: 902-471-7541
thomas.gray@nshealth.ca

third party [redacted]

[redacted]


third party

Subject: RE: COVID-19 therapeutics and prophylactics
Date: Tuesday, January 5, 2021 at 3:19:37 PM Atlantic Standard Time
From: Goodall, Barbara
To: Ramsey, Tasha
Attachments: image002.png

Thank you Tasha!

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Ramsey, Tasha
Sent: Tuesday, January 5, 2021 2:03 PM
To: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Reid, Emma K

<EmmaK.Reid@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics

Hi everyone,

Here is the agenda for our Jan 7th meeting:

- Review minutes from Dec 17 and 18th (all)
- Bamlanivimab,unrelated discuss outcome of COVID Network recommendations (T. Ramsey)
- unrelated

[redacted]

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: COVID-19 therapeutics and prophylactics

Date: Tuesday, January 5, 2021 at 2:02:55 PM Atlantic Standard Time

From: Ramsey, Tasha

To: Barrett, Lisa L, Grandy Allen, Lisa, Coleman, Kathleen, Neale, Siony, Cox, Glenn, Richard, Gabrielle, Reid, Emma K, Goodall, Barbara

Attachments: 3. Dec 17 NS COVID-19 Therapeutics and Prophylactics Minutes.docx, 4. Dec 18 NS COVID-19 Therapeutics and Prophylactics Minutes.docx, unrelated [redacted]

Hi everyone,

Here is the agenda for our Jan 7th meeting:

- Review minutes from Dec 17 and 18th (all)
- Bamlanivimab, unrelated [redacted]: discuss outcome of COVID Network recommendations (T. Ramsey)
- unrelated [redacted]

[redacted]

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: Re: Subgroup re COVID therapies
Date: Wednesday, December 30, 2020 at 8:47:56 AM Atlantic Standard Time
From: Ramsey, Tasha
To: Gray, Thomas, Grandy Allen, Lisa
CC: MacFadyen, Suzanne M
Attachments: image001.jpg

Hi,

On December 22nd the COVID Network approved the following recommendation for use in NS:

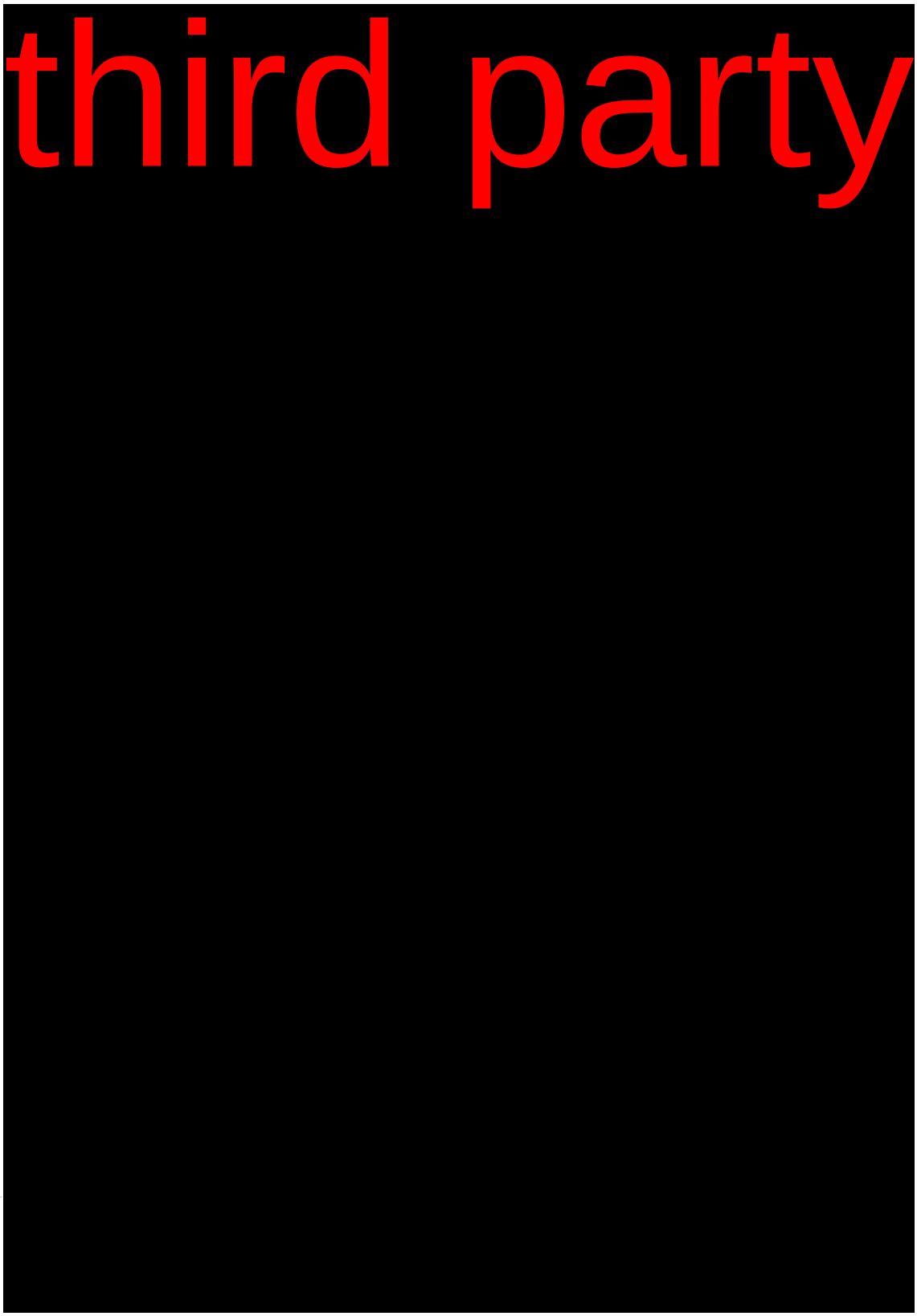
Bamlanivimab Recommendation: use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with non-severe COVID-19 65 years of age and older in NS Health affiliated Regional Care Units.

So we are waiting for the CO-VIC study to update its protocol and then we will have to distribute it to the designated RCUs listed in the protocol.

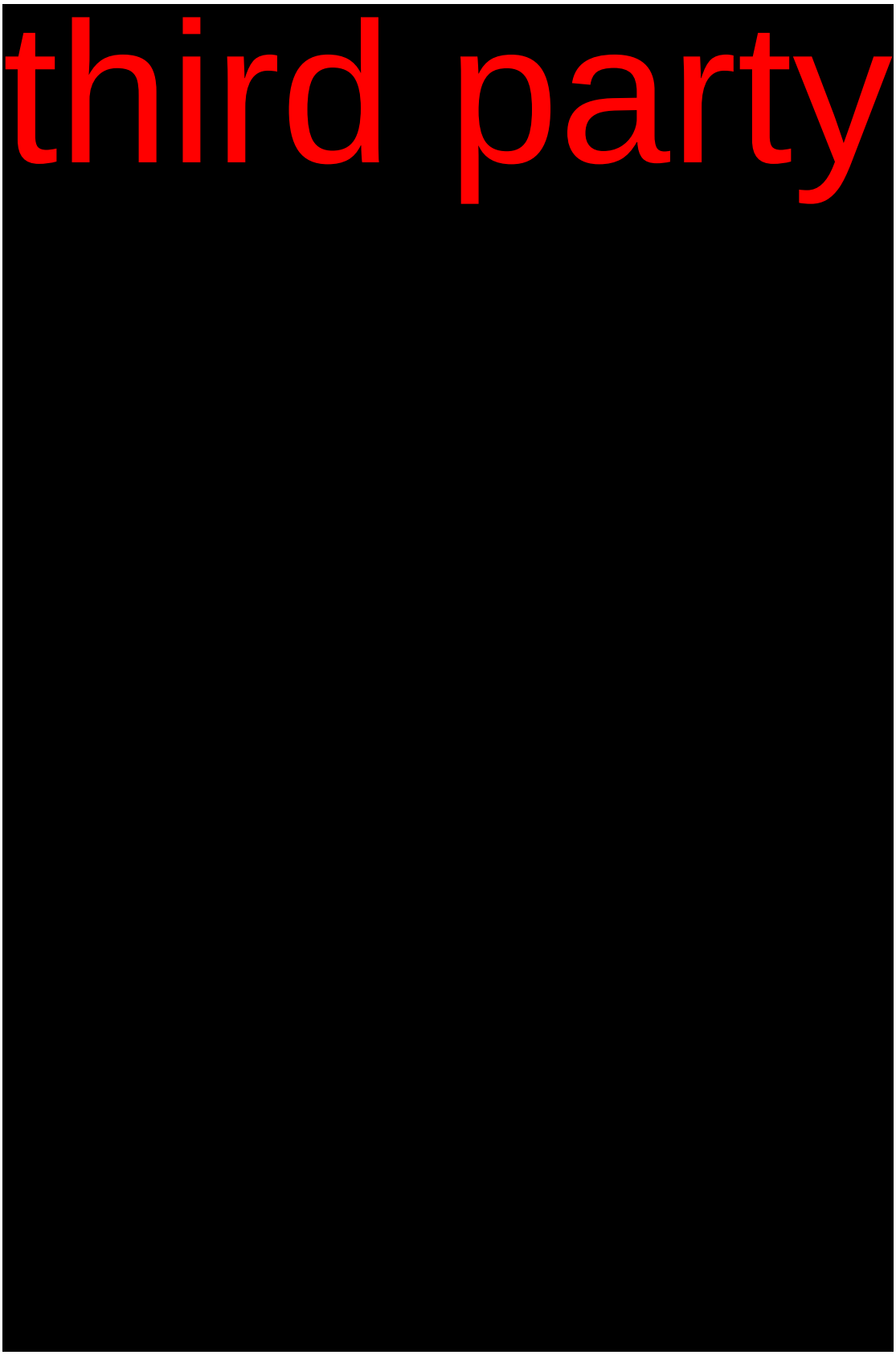
Tasha

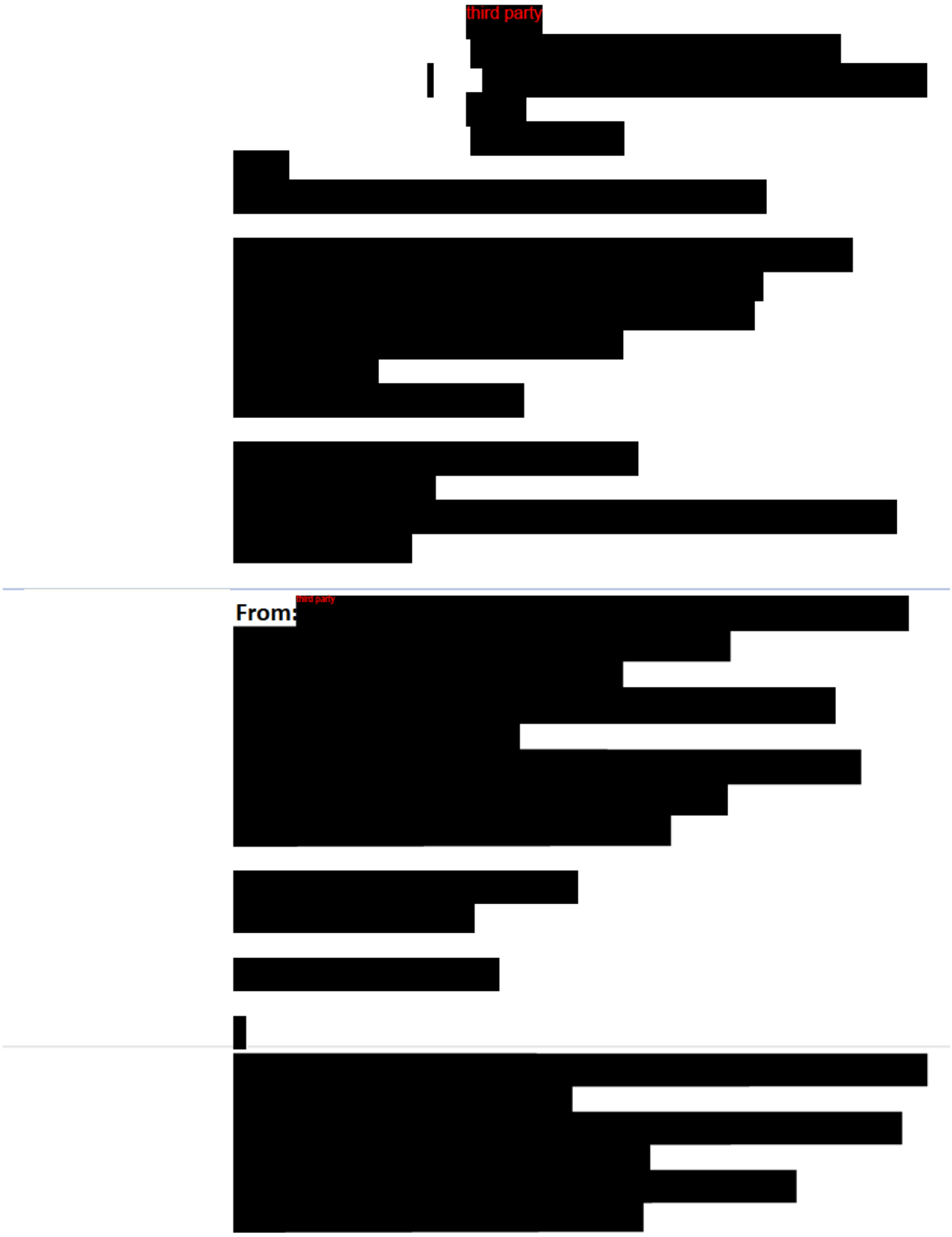
third party [redacted]

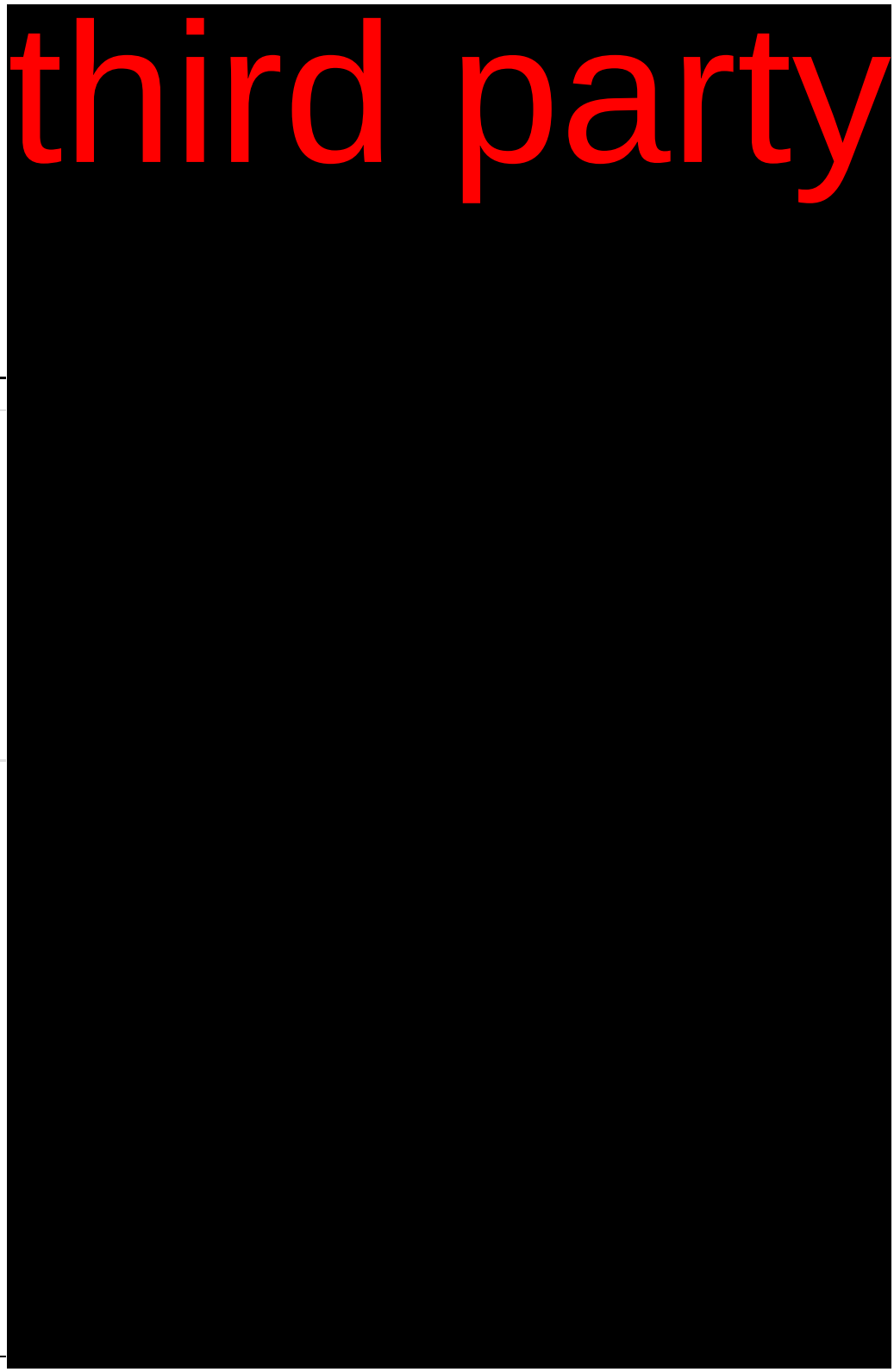

third party
third party

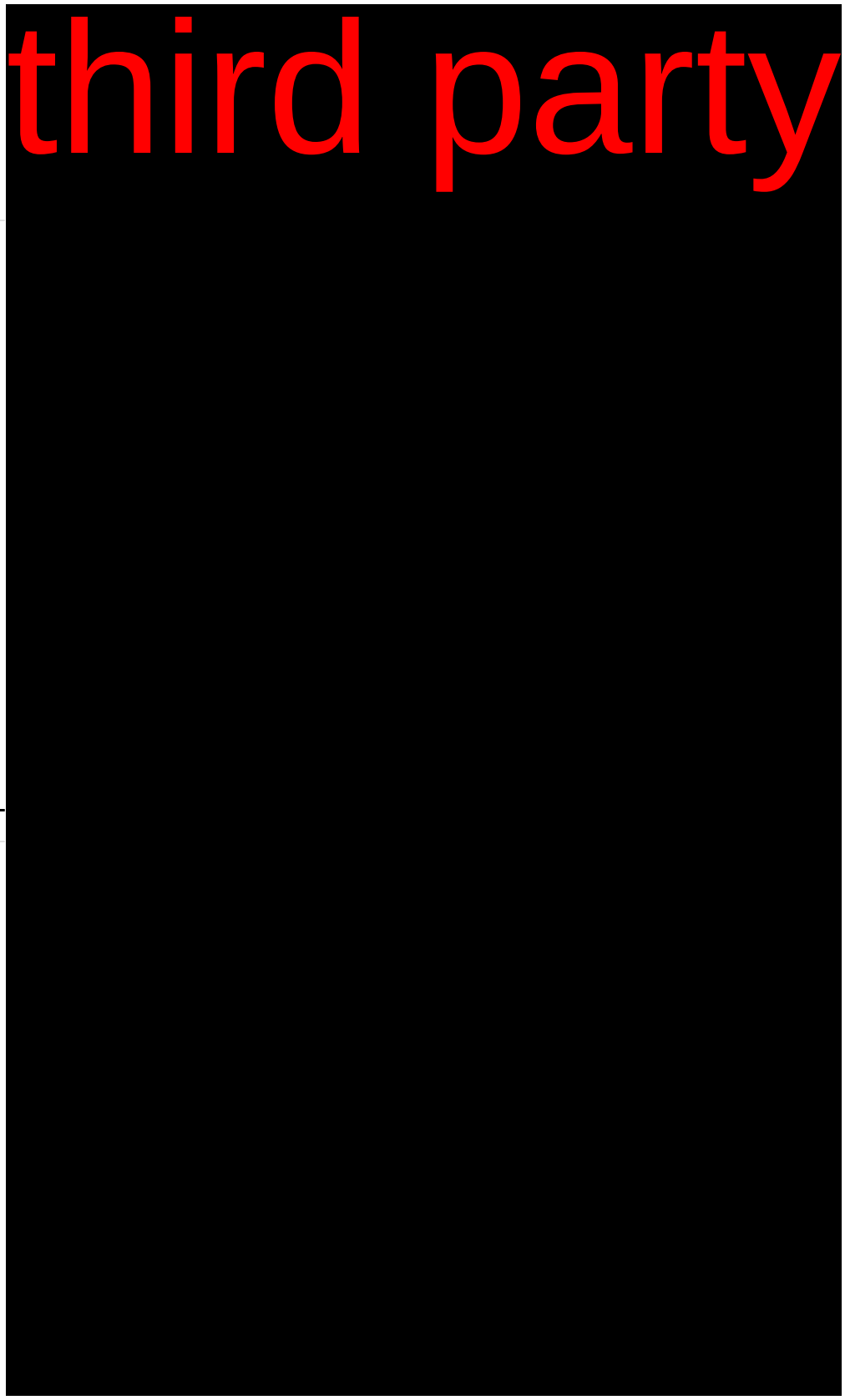

third party


third party


third party


third party
From:
third party


third party


third party

Subject: COVID Network - Document for discussion - Therapeutics Update
Date: Tuesday, December 22, 2020 at 4:48:48 PM Atlantic Standard Time
From: Tracey, Angela

To: Hatchette, Todd, Sommers, Ryan, O'Toole, Gary, MacDonald, Tammy, Davis, Ian, Mercer, Kate, Barrett, Lisa L, Leblanc, Jason, Keenan, Angela, Comeau, Jeannette, Sampalli, Tara, Anderson, Kimberley, MacLeod, Katie E, Purvis, Deborah, Doyle, Nicki, Ramsey, Tasha, Wolfe, Heather, Stockman, Cynthia, Heighton, Andrew, Davis, Darlene, McCormick, Bethany, Johnston, Lynn, Patriquin, Glenn, DiQuinzio, Melanie, Lata, Chris, Gibson, Rick, Edwards, Lynn, Chisholm, Janice, Magee, Kirk, Hernandez, Paul, Penney, Tanya, Sullivan, Dr Tania, O'Leary, Tony, Henderson, David, Loring, Sally, Srivatsa, Kris, Howlett, Todd, Pugh, Cheryl, Smith, Aaron, Hirsch, Greg, Munroe, Tanya, Bowden, Lois, Elliott Rose, Annette, Connolly, Cindy, Short, Christine, Bernard, Andre, DePodesta, Michelle, Bussey, Christy, Harris, Andrew S., Grant, Doris, Sullivan, Vickie, Burris, Debbie, Matthews, Wanda, McNeil, Shelly, Lamb, Alyson, MacQuarrie, Cindy, Alexiadis, Maria, 'Kirk Magee', Hodder, Samantha, Stevens, Susan, Tschupruk, Cheryl, s.20(1) , Thompson, Shauna, s.20(1) @Dal.Ca', s.20(1) @eastlink.ca', MacDougall, Brett

CC: Milligan, Samantha, Tate, Natalie, Harris, Pamela, Whiteman, Alison, Fraser, Denise, MacLean, Marisa, Doucette, Alexandra, Whelan, Noella, MacConnell-Maxner, Nancy, MacDougall, Jennifer, Arsenault, Dylana, Casault, Cathy Ann, MacDonald, Carla, MacLean, Lorianne, Trethewey, Dawn, MacDougall, Melissa, Turpin, Carmel, Mawdsley, Scott, Harding, Ruth, s.20(1) @gmail.com'

Attachments: Bamlanivimab unrelated memo (002).pdf, image001.jpg

Hello, please see the attached document that Tasha Ramsey will be discussing later in the meeting.

Regards,
Angela

Angela Tracey
Administrative Assistant to Cindy MacQuarrie
Senior Director for Interprofessional Practice and Learning
Nova Scotia Health
716 King Street
New Waterford, NS B1H 3Z5
Office: 902-592-3421
Fax: 902-592-3344
Email: Angela.Tracey@nshealth.ca

Subject: RE: Therapeutics Update to COVID Network---agenda for tomorrow's meeting
Date: Tuesday, December 22, 2020 at 4:46:08 PM Atlantic Standard Time
From: Tracey, Angela

To: Ramsey, Tasha
Attachments: image001.jpg, image002.jpg, image003.jpg

Yes, Shelly will make you cohost

From: Ramsey, Tasha
Sent: Tuesday, December 22, 2020 4:45 PM
To: Tracey, Angela <Angela.Tracey@nshealth.ca>
Subject: Re: Therapeutics Update to COVID Network---agenda for tomorrow's meeting

Can you allow me to share my screen? I have slides.

T

From: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Date: Tuesday, December 22, 2020 at 4:43 PM
To: "Tracey, Angela" <Angela.Tracey@nshealth.ca>
Subject: Re: Therapeutics Update to COVID Network---agenda for tomorrow's meeting

Sure- it may be helpful

From: "Tracey, Angela" <Angela.Tracey@nshealth.ca>
Date: Tuesday, December 22, 2020 at 4:42 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: Therapeutics Update to COVID Network---agenda for tomorrow's meeting

Thanks Tasha. Should I share with group now?

From: Ramsey, Tasha
Sent: Tuesday, December 22, 2020 4:41 PM
To: Tracey, Angela <Angela.Tracey@nshealth.ca>
Subject: Re: Therapeutics Update to COVID Network---agenda for tomorrow's meeting

Hi,

Here are the recommendations from the advisory group I will discuss.

Tasha

From: "Tracey, Angela" <Angela.Tracey@nshealth.ca>
Date: Monday, December 21, 2020 at 12:56 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: Therapeutics Update to COVID Network---agenda for tomorrow's meeting

Perfect. Thank you for confirming.

Angela

From: Ramsey, Tasha
Sent: Monday, December 21, 2020 12:56 PM
To: Tracey, Angela <Angela.Tracey@nshealth.ca>
Subject: Re: Therapeutics Update to COVID Network---agenda for tomorrow's meeting

Hi,

I believe about 15 min will be required. I do not have anything to share in advance of the meeting, but will have slides to present during the meeting.

Tasha

From: "Tracey, Angela" <Angela.Tracey@nshealth.ca>
Date: Monday, December 21, 2020 at 11:10 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: Therapeutics Update to COVID Network---agenda for tomorrow's meeting

Good Morning Tasha, just wanting to follow up on the email below.
Are you ready to move forward with tomorrow's discussion and do you have any documents that need to be shared?
How much time will be required?

Regards,
Angela

Angela Tracey
Administrative Assistant to Cindy MacQuarrie
Senior Director for Interprofessional Practice and Learning
Nova Scotia Health
716 King Street
New Waterford, NS B1H 3Z5
Office: 902-592-3421
Fax: 902-592-3344
Email: Angela.Tracey@nshealth.ca

From: Ramsey, Tasha
Sent: Monday, December 14, 2020 8:14 AM
To: Tracey, Angela <Angela.Tracey@nshealth.ca>
Subject: Re: Therapeutics Update to COVID Network---few points of clarification

Hi Angela,

I have modified your minutes below. Lisa Barrett and I are also hoping to postpone the follow up discussion

until the next COVID Network Meeting on Dec 22nd. The COVID-19 Therapeutics and Prophylactics Advisory Group we co-chair does not meet again until this Thursday (Dec 17th) and we would like to ensure all advice is created by and endorsed by this group.

Minutes:

- There are [redacted] medications the COVID-19 Therapeutics and Prophylactics Advisory Group have discussed for use in Nova Scotia. unrelated [redacted] Bamlanivimab, unrelated [redacted] may be used in the context of pragmatic research.
- Several monoclonal antibodies have just come out (or are about to come out) that require infusion. Monoclonal antibodies require infusion and monitoring for infusion reactions. This is typically done in infusion centers. However, infusion clinics in Nova Scotia are usually booked well in advance and often to capacity with patients that are immunocompromised. Use of these agents will depend on the level of disease (non-severe vs. severe) and those with non-severe disease will require infusion on an outpatient basis. Administration logistics for the wave of monoclonal antibodies that are about to come out will require careful consideration.
- unrelated [redacted]
- Tasha will provide the network with information on each agent and suggestions of how bamlanivimab could potentially be implemented. **Further discussion will occur at next week's meeting.**

Tasha

From: "Tracey, Angela" <Angela.Tracey@nshealth.ca>
Date: Friday, December 11, 2020 at 11:06 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: Therapeutics Update to COVID Network---few points of clarification

Good Morning Tasha, I am working on the network meeting notes and wondering if you could fill in a few blanks for me (and add additional points if necessary)?

- There are currently [redacted] medications available. unrelated [redacted] will be used in the context of pragmatic research. Can you to confirm the names of these agents?
- Several that have just come out (or are about to come out) require infusion. Some will require infusion on an outpatient basis (in non-severe patients). Most infusion clinics are already filled with immune compromised patients; not necessarily an area where you should bring COVID-19 patients. How do we get these agents to patients?
- Use of agents will depend on the level of disease (mild, moderate, severe).

- unrelated [redacted].
- Tasha will provide the network with information on each agent and recommendations of how they could potentially be implemented. **Further discussion will occur at next week's meeting.**

Greatly appreciated.

Angela

Angela Tracey
Administrative Assistant to Cindy MacQuarrie
Senior Director for Interprofessional Practice and Learning
Nova Scotia Health
716 King Street
New Waterford, NS B1H 3Z5
Office: 902-592-3421
Fax: 902-592-3344
Email: Angela.Tracey@nshealth.ca

From: Ramsey, Tasha
Sent: Thursday, December 03, 2020 12:11 PM
To: Tracey, Angela <Angela.Tracey@nshealth.ca>
Subject: Re: Therapeutics Update to COVID Network

Yes- I am happy to. I can go over the unrelated [redacted] we plan to use in the context of pragmatic research.

I would also like to ask the network for their thoughts on the implementation of these agents. Several that have just come out (or are about to come out) require infusion. Some will require infusion on an outpatient basis (in non-severe patients).

We may have to put some thought into the creation of something along the lines of a NS Health affiliated infusion clinic specifically for COVID patients.

unrelated [redacted] it looks like NS Health is going to be provided with bamlanivimab for free from the federal government. We have to determine how to get it to non-severe patients.

It would be helpful to at least introduce the problem to the COVID network and initiate the process of determining who the key people will be to create a solution.

Tasha

From: "Tracey, Angela"
Date: Thursday, December 3, 2020 at 10:10 AM
To: "Ramsey, Tasha"
Subject: Therapeutics Update to COVID Network

Good Morning Tasha,

Cindy has asked me to reach out to see if you would be able to provide a quick (15 minute) Therapeutics update at our next network meeting (Tuesday, December 8th).

If you could please confirm, it would be greatly appreciated.

Regards,
Angela

Angela Tracey
Administrative Assistant to Cindy MacQuarrie
Senior Director for Interprofessional Practice and Learning
Nova Scotia Health
716 King Street
New Waterford, NS B1H 3Z5
Office: 902-592-3421
Fax: 902-592-3344
Email: Angela.Tracey@nshealth.ca

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Subject: Re: COVID-19 therapeutics and prophylactics

Date: Tuesday, December 22, 2020 at 10:43:45 AM Atlantic Standard Time

From: Ramsey, Tasha

To: Coleman, Kathleen, Grandy Allen, Lisa, Neale, Siony, Cox, Glenn, Barrett, Lisa L, Richard, Gabrielle, Reid, Emma K, Goodall, Barbara

Attachments: Bamlanivimab, [redacted] memo.doc

Hi everyone,

I have attached our updated recommendations for the COVID network.

Tasha

From: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Date: Tuesday, December 22, 2020 at 10:09 AM
To: "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Reid, Emma K" <EmmaK.Reid@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Subject: Re: COVID-19 therapeutics and prophylactics

Thank you Kathleen!
Tasha

From: "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>
Date: Monday, December 21, 2020 at 11:51 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Reid, Emma K" <EmmaK.Reid@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics

Hi all,

Great job Tasha. Attached are my comments for consideration.

Kathleen

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: December 21, 2020 10:25 AM
To: Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics

Hi everyone,

As promised Thursday, the draft recommendations for the COVID Network are attached for your review.

If you have any additions or comments- feel free to forward them to me by tomorrow AM (the COVID Network meeting is tomorrow).

Thanks!
Tasha

Subject: RE: covid NETWORK

Date: Monday, December 21, 2020 at 6:08:52 PM Atlantic Standard Time

From: McNeil, Shelly
To: Ramsey, Tasha, Barrett, Lisa L

Great- sounds good
S

From: Ramsey, Tasha
Sent: Monday, December 21, 2020 6:00 PM
To: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; McNeil, Shelly <Shelly.McNeil@nshealth.ca>
Subject: Re: covid NETWORK

I think we can do it tomorrow. We were asked to "provide the network with information on each agent (referring to unrelated , bamlanivimab, unrelated) and suggestions of how bamlanivimab could potentially be implemented".

I have a few slides to provide background information on each agent, the advisory group recommendations for unrelated , and bamlanivimab, and a few thoughts on bamlanivimab implementation.

Tasha

From: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Date: Monday, December 21, 2020 at 4:31 PM
To: "McNeil, Shelly" <Shelly.McNeil@nshealth.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: covid NETWORK

Up to Tasha and yourself!
I can do either!!

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: McNeil, Shelly
Sent: Monday, December 21, 2020 4:26 PM
To: Ramsey, Tasha; Barrett, Lisa L
Subject: covid NETWORK

Hi ladies
Do you still want to present at the Network meeting tomorrow or hold off til Jan 5?
S

Shelly McNeil, MD, FRCPC
Chief, Division of Infectious Diseases
Nova Scotia Health Authority
Professor of Medicine, Dalhousie University
Phone: 902-473-5553

Administrative Assistant: Samantha.milligan@nshealth.ca

Subject: RE: Therapeutics Update to COVID Network---agenda for tomorrow's meeting
Date: Monday, December 21, 2020 at 12:56:50 PM Atlantic Standard Time

From: Tracey, Angela
To: Ramsey, Tasha
Attachments: image001.jpg, image002.jpg, image003.jpg

Perfect. Thank you for confirming.

Angela

From: Ramsey, Tasha
Sent: Monday, December 21, 2020 12:56 PM
To: Tracey, Angela <Angela.Tracey@nshealth.ca>
Subject: Re: Therapeutics Update to COVID Network---agenda for tomorrow's meeting

Hi,

I believe about 15 min will be required. I do not have anything to share in advance of the meeting, but will have slides to present during the meeting.

Tasha

From: "Tracey, Angela" <Angela.Tracey@nshealth.ca>
Date: Monday, December 21, 2020 at 11:10 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: Therapeutics Update to COVID Network---agenda for tomorrow's meeting

Good Morning Tasha, just wanting to follow up on the email below.
Are you ready to move forward with tomorrow's discussion and do you have any documents that need to be shared?
How much time will be required?

Regards,
Angela

Angela Tracey
Administrative Assistant to Cindy MacQuarrie
Senior Director for Interprofessional Practice and Learning
Nova Scotia Health
716 King Street
New Waterford, NS B1H 3Z5
Office: 902-592-3421
Fax: 902-592-3344
Email: Angela.Tracey@nshealth.ca

From: Ramsey, Tasha
Sent: Monday, December 14, 2020 8:14 AM
To: Tracey, Angela <Angela.Tracey@nshealth.ca>
Subject: Re: Therapeutics Update to COVID Network---few points of clarification

Hi Angela,

I have modified your minutes below. Lisa Barrett and I are also hoping to postpone the follow up discussion until the next COVID Network Meeting on Dec 22nd. The COVID-19 Therapeutics and Prophylactics Advisory Group we co-chair does not meet again until this Thursday (Dec 17th) and we would like to ensure all advice is created by and endorsed by this group.

Minutes:

- There are 4 medications the COVID-19 Therapeutics and Prophylactics Advisory Group have discussed for use in Nova Scotia. unrelated [redacted]. Bamlanivimab, unrelated [redacted] may be used in the context of pragmatic research.
- Several monoclonal antibodies have just come out (or are about to come out) that require infusion. Monoclonal antibodies require infusion and monitoring for infusion reactions. This is typically done in infusion centers. However, infusion clinics in Nova Scotia are usually booked well in advance and often to capacity with patients that are immunocompromised. Use of these agents will depend on the level of disease (non-severe vs. severe) and those with non-severe disease will require infusion on an outpatient basis. Administration logistics for the wave of monoclonal antibodies that are about to come out will require careful consideration.
- unrelated [redacted]
- Tasha will provide the network with information on each agent and suggestions of how bamlanivimab could potentially be implemented. **Further discussion will occur at next week's meeting.**

Tasha

From: "Tracey, Angela" <Angela.Tracey@nshealth.ca>
Date: Friday, December 11, 2020 at 11:06 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: Therapeutics Update to COVID Network---few points of clarification

Good Morning Tasha, I am working on the network meeting notes and wondering if you could fill in a few blanks for me (and add additional points if necessary)?

- There are currently [redacted] medications available. unrelated [redacted] will be used in the context of pragmatic research. Can you to confirm the names of these agents?
- Several that have just come out (or are about to come out) require infusion. Some will require infusion on an outpatient basis (in non-severe patients). Most infusion clinics are already filled with immune compromised patients; not necessarily an area where you should bring COVID-19 patients. How do we get these agents to patients?
- Use of agents will depend on the level of disease (mild, moderate, severe).
- unrelated [redacted].
- Tasha will provide the network with information on each agent and recommendations of how they could potentially be implemented. **Further discussion will occur at next week's meeting.**

Greatly appreciated.

Angela

Angela Tracey
Administrative Assistant to Cindy MacQuarrie
Senior Director for Interprofessional Practice and Learning
Nova Scotia Health
716 King Street
New Waterford, NS B1H 3Z5
Office: 902-592-3421
Fax: 902-592-3344
Email: Angela.Tracey@nshealth.ca

From: Ramsey, Tasha
Sent: Thursday, December 03, 2020 12:11 PM
To: Tracey, Angela <Angela.Tracey@nshealth.ca>
Subject: Re: Therapeutics Update to COVID Network

Yes- I am happy to. I can go over the unrelated [redacted] we plan to use in the context of pragmatic research.

I would also like to ask the network for their thoughts on the implementation of these agents. Several that have just come out (or are about to come out) require infusion. Some will require infusion on an outpatient basis (in non-severe patients).

We may have to put some thought into the creation of something along the lines of a NS Health affiliated infusion clinic specifically for COVID patients.

unrelated [redacted] it looks like NS Health is going to be provided with bamlanivimab for free from the federal government. We have to determine how to get it to non-severe patients.

It would be helpful to at least introduce the problem to the COVID network and initiate the process of determining who the key people will be to create a solution.

Tasha

From: "Tracey, Angela"
Date: Thursday, December 3, 2020 at 10:10 AM
To: "Ramsey, Tasha"
Subject: Therapeutics Update to COVID Network

Good Morning Tasha,

Cindy has asked me to reach out to see if you would be able to provide a quick (15 minute) Therapeutics update at our next network meeting (Tuesday, December 8th).

If you could please confirm, it would be greatly appreciated.

Regards,
Angela

Angela Tracey
Administrative Assistant to Cindy MacQuarrie
Senior Director for Interprofessional Practice and Learning
Nova Scotia Health
716 King Street
New Waterford, NS B1H 3Z5
Office: 902-592-3421
Fax: 902-592-3344
Email: Angela.Tracey@nshealth.ca

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Subject: Bamlanivimab recommendations
Date: Friday, December 18, 2020 at 4:31:15 PM Atlantic Standard Time
From: Ramsey, Tasha
To: Barrett, Lisa L
Attachments: 3. Dec 17 NS COVID-19 Therapeutics and Prophylactics Minutes.docx, 4. Dec 18 NS COVID-19 Therapeutics and Prophylactics Minutes.docx, COVID Network Reocmmendations.docx

Hi Lisa,

unrelated [redacted] I have attached our draft minutes from the last 2 advisory group meetings that occurred yesterday and today.

I also started to draft the rationale for our bamlanivimab recommendation for the COVID network meeting (see the third attachment).

Can you provide feedback on the rough draft of the recommendation document? The group had asked to look over it this weekend, but I want to ensure you are happy with it first.

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: Slides for education Monday
Date: Friday, December 18, 2020 at 4:02:16 PM Atlantic Standard Time
From: Reid, Emma K
To: Ramsey, Tasha
Attachments: Bamlanivimab Dec 17 for frontline staff meeting.pptx, Donning and Doffing slide.pptx

Hi,

Attached are some slightly modified slides for BLAZE-1 and a donning/doffing slide.

Have a nice weekend!
Emma

Subject: Minutes from today
Date: Thursday, December 17, 2020 at 2:16:13 PM Atlantic Standard Time
From: Reid, Emma K
To: Ramsey, Tasha
Attachments: NS COVID-19 Therapeutics and Prophylactics Minutes Dec 17.docx

HI Tasha,

Don’t know if the expectation is that we distribute these before tomorrow or not… but they should be in decent shape. Tried to be extra detailed around Bamlanivimab in case it helps with preparation for tomorrow.

Emma

Subject: COVID-19 therapeutics and prophylactics

Date: Tuesday, December 15, 2020 at 8:23:02 AM Atlantic Standard Time

From: Ramsey, Tasha

To: Barrett, Lisa L, Grandy Allen, Lisa, Coleman, Kathleen, Neale, Siony, Cox, Glenn, Richard, Gabrielle, Reid, Emma K, Goodall, Barbara

Attachments: 2. Dec 10 2020 NS COVID-19 Therapeutics and Prophylactics Minutes.docx, Bamlanivimab Advisory Group Review.pdf, 3. Bamlanivimab summary sheet.docx, BLAZE 1 NEJM 2020.pdf, unrelated [redacted]

Hi everyone,

Here is the agenda for our December 17th Meeting:

- Review minutes (all)
- Bamlanivimab: discuss role in therapy and create bamlanivimab implementation suggestions (E. Reid to present slides, L. Barrett to discuss virology)
- CO-VIC and unrelated [redacted] (B. Goodall)
- unrelated [redacted]

I have attached the bamlanivimab slides Emma will present, the bamlanivimab summary sheet, and BLAZE-1 for you to review prior to our discussion.

unrelated [redacted]

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: RE: Slides for next week
Date: Monday, December 14, 2020 at 3:15:34 PM Atlantic Standard Time
From: Reid, Emma K
To: Ramsey, Tasha
Attachments: Bamlanivimab Dec 14 final slides.pptx

Fantastic, thanks! Yes, more than happy to run through BLAZE-1 on Wednesday.

These slides should be done and ready to share with the Advisory Group.

Emma

From: Ramsey, Tasha
Sent: Monday, December 14, 2020 9:42 AM
To: Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: Re: Slides for next week

Hi Emma,

This looks great! I have added 2 slides at the beginning explaining how MABs work in general and the few in phase 3 trials that I plan to use on Wednesday. Do you want to run through your Blaze 1 slides quickly during the general staff overview session on Wednesday?

I also added (on the second last slide) a comment about clinic options.

Tasha

From: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Date: Sunday, December 13, 2020 at 9:44 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: Slides for next week

Hey Tasha,

Here are some slides for next week! Or a start, anyway. Don't mind the speaker notes – that's just scrap notes. I'm still in the process of updating the clinic needs document (will throw that up at the end) unrelated [redacted]. Can either add your part about the other mAbs where the blank slide is now or after!

Talk soon,

Emma

Subject: RE: Therapeutics Update to COVID Network---few points of clarification
Date: Monday, December 14, 2020 at 9:32:38 AM Atlantic Standard Time
From: Tracey, Angela
To: Ramsey, Tasha
Attachments: image003.jpg, image004.jpg, image005.jpg

Thank you Tasha.
I will let Shelly, Cindy and Alyson know and we can then schedule you in for the following week.

Regards,
Angela

Angela Tracey
Administrative Assistant to Cindy MacQuarrie
Senior Director for Interprofessional Practice and Learning
Nova Scotia Health
716 King Street
New Waterford, NS B1H 3Z5
Office: 902-592-3421
Fax: 902-592-3344
Email: Angela.Tracey@nshealth.ca

From: Ramsey, Tasha
Sent: Monday, December 14, 2020 8:14 AM
To: Tracey, Angela <Angela.Tracey@nshealth.ca>
Subject: Re: Therapeutics Update to COVID Network---few points of clarification

Hi Angela,

I have modified your minutes below. Lisa Barrett and I are also hoping to postpone the follow up discussion until the next COVID Network Meeting on Dec 22nd. The COVID-19 Therapeutics and Prophylactics Advisory Group we co-chair does not meet again until this Thursday (Dec 17th) and we would like to ensure all advice is created by and endorsed by this group.

Minutes:

- There are [redacted] medications the COVID-19 Therapeutics and Prophylactics Advisory Group have discussed for use in Nova Scotia. unrelated [redacted]. Bamlanivimab, unrelated [redacted] may be used in the context of pragmatic research.
- Several monoclonal antibodies have just come out (or are about to come out) that require infusion. Monoclonal antibodies require infusion and monitoring for infusion reactions. This is typically done in infusion centers. However, infusion clinics in Nova Scotia are usually booked well in advance and often to capacity with patients that are immunocompromised. Use of these agents will depend on the level of disease (non-severe vs. severe) and those with non-severe disease will require infusion on an outpatient basis. Administration logistics for the wave of monoclonal antibodies that are about to come out will require careful consideration.
- unrelated [redacted]
- Tasha will provide the network with information on each agent and suggestions of how bamlanivimab could potentially be implemented. **Further discussion will occur at next week's meeting.**

Tasha

From: "Tracey, Angela" <Angela.Tracey@nshealth.ca>
Date: Friday, December 11, 2020 at 11:06 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: Therapeutics Update to COVID Network---few points of clarification

Good Morning Tasha, I am working on the network meeting notes and wondering if you could fill in a few blanks for me (and add additional points if necessary)?

- There are currently [redacted] medications available. related [redacted] will be used in the context of pragmatic research. Can you to confirm the names of these agents?
- Several that have just come out (or are about to come out) require infusion. Some will require infusion on an outpatient basis (in non-severe patients). Most infusion clinics are already filled with immune compromised patients; not necessarily an area where you should bring COVID-19 patients. How do we get these agents to patients?
- Use of agents will depend on the level of disease (mild, moderate, severe).
- unrelated [redacted]
- Tasha will provide the network with information on each agent and recommendations of how they could potentially be implemented. **Further discussion will occur at next week's meeting.**

Greatly appreciated.

Angela

Angela Tracey
Administrative Assistant to Cindy MacQuarrie
Senior Director for Interprofessional Practice and Learning
Nova Scotia Health
716 King Street
New Waterford, NS B1H 3Z5
Office: 902-592-3421
Fax: 902-592-3344
Email: Angela.Tracey@nshealth.ca

From: Ramsey, Tasha
Sent: Thursday, December 03, 2020 12:11 PM
To: Tracey, Angela <Angela.Tracey@nshealth.ca>
Subject: Re: Therapeutics Update to COVID Network

Yes- I am happy to. I can go over [redacted] we plan to use in the context of pragmatic research.

I would also like to ask the network for their thoughts on the implementation of these agents. Several that have just come out (or are about to come out) require infusion. Some will require infusion on an outpatient basis (in non-severe patients).

We may have to put some thought into the creation of something along the lines of a NS Health affiliated infusion clinic specifically for COVID patients.

[redacted] it looks like NS Health is going to be provided with bamlanivimab for free from the federal government. We have to determine how to get it to non-severe patients.

It would be helpful to at least introduce the problem to the COVID network and initiate the process of determining who the key people will be to create a solution.

Tasha

From: "Tracey, Angela"
Date: Thursday, December 3, 2020 at 10:10 AM
To: "Ramsey, Tasha"
Subject: Therapeutics Update to COVID Network

Good Morning Tasha,

Cindy has asked me to reach out to see if you would be able to provide a quick (15 minute) Therapeutics update at our next network meeting (Tuesday, December 8th).

If you could please confirm, it would be greatly appreciated.

Regards,
Angela

Angela Tracey
Administrative Assistant to Cindy MacQuarrie
Senior Director for Interprofessional Practice and Learning
Nova Scotia Health
716 King Street
New Waterford, NS B1H 3Z5
Office: 902-592-3421
Fax: 902-592-3344
Email: Angela.Tracey@nshealth.ca

Subject: Bamlanivimab review
Date: Thursday, December 10, 2020 at 10:15:25 AM Atlantic Standard Time
From: Ramsey, Tasha
To: Barrett, Lisa L
CC: Reid, Emma K

Hi Lisa,

Sorry for the confusion today. I think the disconnect for me is that I am wearing my ASC hat and know that I cannot recommend use in a specific population for standard of care unless there is compelling published efficacy and safety data. But we are not talking about agents with full Health Canada approval or the type of requests that usually go through ASC.

I had incorrectly assumed you would decide how all of the agents used in the context of pragmatic research will be used, including the population.

Where it sounds like our advisory group will be called on to make recommendations to inform where these medications will be used and who will use them, it will be great to sort out a process using bamlanivimab as an example.

To ensure Emma and I cover the appropriate background information to inform our next discussion, there will be slides on:

- How the monoclonal antibodies work (esp.: bamlanivimab)
- The other monoclonal antibodies in phase 3 trials and the patient population being studied
- Blaze 1 (with a close look at the risk factors)
- Health Canada indication
- A comparison of the risk factors in Blaze 1 and the Health Canada indication
- Practical considerations (IV monograph, order set, infusion clinic considerations)
- … then we can open a discussion on the population we recommend using it in (in the context of pragmatic research)

I will send the 1 page summary, Blaze 1, and the slides to the group on Tuesday with a request asking them to review the meeting materials and to be prepared to discuss and make recommendations on the use of bamlanivimab.

Just want to confirm we are going in the right direction. We welcome feedback!

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
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Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject:	COVID-19 therapeutics and prophylactics
Date:	Tuesday, December 8, 2020 at 4:18:35 PM Atlantic Standard Time
From:	Ramsey, Tasha
To:	Ramsey, Tasha, Barrett, Lisa L, Grandy Allen, Lisa, Coleman, Kathleen, Neale, Siony, Cox, Glenn, Richard, Gabrielle, Reid, Emma K, Goodall, Barbara
Attachments:	1. Dec 3 2020 NS COVID-19 Therapeutics and Prophylactics Minutes.docx, NS COVID-19 Therapeutics and Prophylactics Advisory Group TOR DRAFT.docx, 3. Bamlanivimab summary sheet.docx

Hi everyone,

I have attached the minutes from our last meeting and our updated draft terms of reference.

We will chat about the use of bamlanivimab on Thursday. To facilitate this conversation- the one-pager was updated to include short and snappy discussion points.

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: FW: Therapeutics Update to COVID Network
Date: Tuesday, December 8, 2020 at 3:06:04 PM Atlantic Standard Time
From: Ramsey, Tasha
To: Barrett, Lisa L
Attachments: image001.jpg, image002.jpg

Hi Lisa,

unrelated couldn't recall who asked me to talk about therapeutics today. It was Angela Tracey. Here is the email chain from last week.

Are you able to make it to the COVID Network Meeting today from 4-6?

I had said I would go over:

- unrelated we plan to use in the context of pragmatic research. AND
- ask the network for their thoughts on the implementation of the monoclonal antibodies in non-severe patients

I pictured just informally talking about these points. If you are able to make it, I do not mind if you prefer to present or if you would like to informally co-present.

Tasha

From: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Date: Thursday, December 3, 2020 at 3:37 PM
To: "Tracey, Angela" <Angela.Tracey@nshealth.ca>
Cc: Covid Network <CovidNetwork@nshealth.ca>
Subject: Re: Therapeutics Update to COVID Network

Hi,

Yes- 4:45 works for me

Tasha

From: "Tracey, Angela" <Angela.Tracey@nshealth.ca>
Date: Thursday, December 3, 2020 at 12:34 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Cc: Covid Network <CovidNetwork@nshealth.ca>
Subject: RE: Therapeutics Update to COVID Network

Thank you Tasha.
Copying Cindy, Shelly, and Alyson so that they are aware.
Can we confirm your start time for 4:45 p.m.?

Regards,
Angela

Angela Tracey
Administrative Assistant to Cindy MacQuarrie
Senior Director for Interprofessional Practice and Learning
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Office: 902-592-3421
Fax: 902-592-3344
Email: Angela.Tracey@nshealth.ca

From: Ramsey, Tasha
Sent: Thursday, December 03, 2020 12:11 PM
To: Tracey, Angela <Angela.Tracey@nshealth.ca>
Subject: Re: Therapeutics Update to COVID Network

Yes- I am happy to. I can go over the [redacted] we plan to use in the context of pragmatic research.

I would also like to ask the network for their thoughts on the implementation of these agents. Several that have just come out (or are about to come out) require infusion. Some will require infusion on an outpatient basis (in non-severe patients).

We may have to put some thought into the creation of something along the lines of a NS Health affiliated infusion clinic specifically for COVID patients.

[redacted] it looks like NS Health is going to be provided with bamlanivimab for free from the federal government. We have to determine how to get it to non-severe patients.

It would be helpful to at least introduce the problem to the COVID network and initiate the process of determining who the key people will be to create a solution.

Tasha

From: "Tracey, Angela" <Angela.Tracey@nshealth.ca>
Date: Thursday, December 3, 2020 at 10:10 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>

Subject: Therapeutics Update to COVID Network

Good Morning Tasha,

Cindy has asked me to reach out to see if you would be able to provide a quick (15 minute) Therapeutics update at our next network meeting (Tuesday, December 8th).

If you could please confirm, it would be greatly appreciated.

Regards,
Angela

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New Waterford, NS B1H 3Z5
Office: 902-592-3421
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third party

[redacted]

third party

[redacted]

third party [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Subject: RE: possible solution to bamlanivimab administration location issue
Date: Friday, December 4, 2020 at 3:12:58 PM Atlantic Standard Time
From: Cox, Glenn
To: Ramsey, Tasha, Richard, Gabrielle, Barrett, Lisa L, Grandy Allen, Lisa, Neale, Siony, Coleman, Kathleen
CC: Reid, Emma K

I think that in a lot of cases they were extensions of the SAC's, and not sure if they were set up to administer medications

---

From: Ramsey, Tasha
Sent: Friday, December 04, 2020 10:28 AM
To: Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>
Cc: Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: Re: possible solution to bamlanivimab administration location issue

Thanks for the info!

I had not heard of these in Central Zone…perhaps they are similar to the secondary assessment centers that were in the HRM? Glenn-were you aware of the ILIs and how they are similar or different to SACs? There is talk of not re-opening the SACs this wave in Central Zone.

Tasha

From: "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>
Date: Friday, December 4, 2020 at 10:21 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>
Cc: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Subject: RE: possible solution to bamlanivimab administration location issue

Hi
Yes they were in situ for the 1st wave and my understanding from my management colleagues involved in these, they are still in place and staffed.

Thanks
Gabrielle

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>

Sent: December 4, 2020 10:16 AM
To: Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>
Cc: Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: Re: possible solution to bamlanivimab administration location issue

Could be an option if NS Health decides to support the infusion clinics and staff them.

Just to clarify- for these influenza-like illness NS Health clinics, are they already in place and staffed?

Tasha

From: "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>
Date: Friday, December 4, 2020 at 8:20 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>
Cc: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Subject: possible solution to bamlanivimab administration location issue

Hi everyone

I wanted to reach out to my colleagues who were involved in this first before mentioning it in this group. NSHA did set up ILI clinics in locations that are INTENTIONALLY off-site from the hospitals. I checked with my local people to ensure this had been done in other sites in the province. So for example in Truro, it is located at the Seniors Clinic/PCU offices in the building across the road from CEHHC. And it is staffed with hospital staff waiting for patients with ILI sx to come. Because of a change in structure, the person I was talking to wasn't part of the initial set up but did confirm that there are multiple sites provincially that are not on hospital grounds. I was thinking this might be a good place for the administration of bamlanivimab around the province. I can't guarantee there is a site like this in Central but it might be a solution to our administration issue in other areas? Maybe someone else an speak to this a bit more than me?

Thanks
Gabrielle

Subject: Re: possible solution to bamlanivimab administration location issue
Date: Friday, December 4, 2020 at 10:13:17 AM Atlantic Standard Time
From: Ramsey, Tasha
To: Richard, Gabrielle

Thanks!

From: "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>
Date: Friday, December 4, 2020 at 10:10 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: possible solution to bamlanivimab administration location issue

Yep- no problem
Influenza-like Illness.
Gabrielle

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: December 4, 2020 10:07 AM
To: Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>
Subject: Re: possible solution to bamlanivimab administration location issue

Hi Gabrielle,

Forgive my ignorance- what is an ILI?

T

From: "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>
Date: Friday, December 4, 2020 at 8:20 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>
Cc: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
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Hi everyone

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Thanks
Gabrielle

Subject: FW: PAC Follow-up re: bamlanivimab
Date: Friday, December 4, 2020 at 10:00:22 AM Atlantic Standard Time
From: Coleman, Kathleen
To: Barrett, Lisa L, Ramsey, Tasha, Richard, Gabrielle, Cox, Glenn, Reid, Emma K, Grandy Allen, Lisa

Fyi
K

third party

[redacted]

third party [redacted]

Subject: Re: COVID-19 therapeutics and prophylactics advisory group TOR
Date: Friday, December 4, 2020 at 8:12:25 AM Atlantic Standard Time
From: Ramsey, Tasha
To: Reid, Emma K
Attachments: 1. Dec 3 2020 NS COVID-19 Therapeutics and Prophylactics Minutes.docx

This made my life so much easier- thank you! I made some minor updates, but it is now good to go.

I will send the minutes to our membership with our next meeting materials and to Lisa now so that she knows who to contact.

Tasha

From: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Date: Thursday, December 3, 2020 at 10:51 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics advisory group TOR

Draft minutes attached.

From: Ramsey, Tasha
Sent: Thursday, December 3, 2020 9:31 AM
To: Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics advisory group TOR

Hi,

Here is the updated TOR draft in case it helps with the minutes 😉 I also corrected spelling in a few spots on the one pager (attached).

Feel free to let me know if you need help with the minutes.

It sounds like the big task to be completed by Tuesday ish will be to digest the bamlanivimab one pager a bit more so it can be used when socializing the idea of using banlanivimab to representatives from government and the COVID network. Perhaps with color coding, bullet points, more lay language.

unrelated [redacted]

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
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1796 Summer Street, Halifax, NS | Canada | B3H 3A7
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5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: RE: Therapeutics Update to COVID Network
Date: Thursday, December 3, 2020 at 3:40:25 PM Atlantic Standard Time
From: Covid Network
To: Ramsey, Tasha, Tracey, Angela
Attachments: image001.jpg, image002.jpg

Thx

From: Ramsey, Tasha
Sent: Thursday, December 03, 2020 3:37 PM
To: Tracey, Angela <Angela.Tracey@nshealth.ca>
Cc: Covid Network <CovidNetwork@nshealth.ca>
Subject: Re: Therapeutics Update to COVID Network

Hi,

Yes- 4:45 works for me

Tasha

From: "Tracey, Angela" <Angela.Tracey@nshealth.ca>
Date: Thursday, December 3, 2020 at 12:34 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Cc: Covid Network <CovidNetwork@nshealth.ca>
Subject: RE: Therapeutics Update to COVID Network

Thank you Tasha.
Copying Cindy, Shelly, and Alyson so that they are aware.
Can we confirm your start time for 4:45 p.m.?

Regards,
Angela

Angela Tracey
Administrative Assistant to Cindy MacQuarrie
Senior Director for Interprofessional Practice and Learning
Nova Scotia Health

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Email: Angela.Tracey@nshealth.ca

From: Ramsey, Tasha
Sent: Thursday, December 03, 2020 12:11 PM
To: Tracey, Angela <Angela.Tracey@nshealth.ca>
Subject: Re: Therapeutics Update to COVID Network

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Tasha

From: "Tracey, Angela" <Angela.Tracey@nshealth.ca>
Date: Thursday, December 3, 2020 at 10:10 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: Therapeutics Update to COVID Network

Good Morning Tasha,

Cindy has asked me to reach out to see if you would be able to provide a quick (15 minute) Therapeutics update at our next network meeting (Tuesday, December 8th).

If you could please confirm, it would be greatly appreciated.

Regards,
Angela

Angela Tracey
Administrative Assistant to Cindy MacQuarrie
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Nova Scotia Health
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Office: 902-592-3421
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Email: Angela.Tracey@nshealth.ca

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Subject: COVID-19 therapeutics and prophylactics advisory group TOR
Date: Thursday, December 3, 2020 at 9:26:16 AM Atlantic Standard Time
From: Ramsey, Tasha
To: Coleman, Kathleen
Attachments: NS COVID-19 Therapeutics and Prophylactics Advisory Group TOR DRAFT.docx, COVID Network Membership.pdf, Bamlanivimab One-Pager.docx

Hi Kathleen,

I have attached the updated draft TOR, the COVID Network membership, and the draft bamlanivimab summary document.

I will work on making the summary document easier to use with simple bullet points, etc.

Thanks again for joining our meeting this morning,

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: COVID-19 therapeutics and prophylactics advisory group
Date: Wednesday, December 2, 2020 at 2:26:53 PM Atlantic Standard Time
From: Ramsey, Tasha
To: Barrett, Lisa L, Grandy Allen, Lisa, Coleman, Kathleen, Neale, Siony, Cox, Glenn, Richard, Gabrielle, Reid, Emma K
Attachments: NS COVID-19 Therapeutics and Prophylactics Advisory Group TOR DRAFT.docx, Bamlanivimab One-Pager.docx

Hi,

I have also attached a bamlanivimab info sheet Emma created that may help tomorrow.

Tasha

From: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Date: Wednesday, December 2, 2020 at 10:42 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics advisory group

Hi everyone,

I am hoping we can discuss the following during our meeting tomorrow:

1. unrelated [redacted]
2. Therapeutic agents being considered at NSH (including: bamlanivimab, unrelated [redacted])
3. Bamlanivimab administration logistics

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7

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Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: COVID-19 therapeutics and prophylactics advisory group
Date: Wednesday, December 2, 2020 at 10:42:35 AM Atlantic Standard Time
From: Ramsey, Tasha
To: Ramsey, Tasha, Barrett, Lisa L, Grandy Allen, Lisa, Coleman, Kathleen, Neale, Siony, Cox, Glenn, Richard, Gabrielle, Reid, Emma K
Attachments: NS COVID-19 Therapeutics and Prophylactics Advisory Group TOR DRAFT.docx

Hi everyone,

I am hoping we can discuss the following during our meeting tomorrow:

1. unrelated [redacted]
2. Therapeutic agents being considered at NSH (including: bamlanivimab, unrelated [redacted])
3. Bamlanivimab administration logistics

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

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5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject:	COVID-19 therapeutics and prophylactics advisory group
Date:	Wednesday, December 2, 2020 at 10:42:35 AM Atlantic Standard Time
From:	Ramsey, Tasha
To:	Ramsey, Tasha, Barrett, Lisa L, Grandy Allen, Lisa, Coleman, Kathleen, Neale, Siony, Cox, Glenn, Richard, Gabrielle, Reid, Emma K
Attachments:	NS COVID-19 Therapeutics and Prophylactics Advisory Group TOR DRAFT.docx

Hi everyone,

I am hoping we can discuss the following during our meeting tomorrow:

1. unrelated
2. Therapeutic agents being considered at NSH (including: bamlanivimab, unrelated
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Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

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5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Subject: FW: COVID-19 therapeutics and prophylactics- Bamlanivimab [redacted] request
Date: Tuesday, December 1, 2020 at 11:34:49 AM Atlantic Standard Time
From: Ramsey, Tasha
To: Reid, Emma K
Attachments: NS COVID-19 Therapeutics Committee TOR.docx, Blaze 1.pdf, Product Monograph Nov 2020.pdf

FYI from the last COVID-19 therapeutics and prophylactics meeting

---

From: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Date: Wednesday, November 25, 2020 at 10:50 AM
To: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
Cc: "Neale, Siony" <Siony.Neale@nshealth.ca>
Subject: Re: COVID-19 therapeutics and prophylactics- Bamlanivimab [redacted] request

Hi again,

I would like to suggest the following two items for discussion on our agenda for tomorrow:

1. unrelated [redacted]
2. Bamlanivimab

unrelated [redacted]

For our bamlanivimab conversation, please consider:

a. If you recommend use in NS and (if you recommend use)
b. Who you recommend using in
c. How you recommend using it

Background information: bamlanivimab is a monoclonal antibody recommended as a single 700 mg infusion. Its indication is for the "Treatment for adults and pediatric patients 12 years of age or older with mild to moderate COVID-19 who weigh at least 40 kg and are at high risk of progressing to severe COVID-19 illness/hospitalization". It is infused over 1 hour and requires at least 1 hour of observation post infusion.

High risk is defined as patients who meet at least one of the following criteria in the product monograph:

- Are ≥ 65 years of age
- Have a body mass index (BMI) ≥ 35 for patients ≥ 18 years of age
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥ 55 years of age **AND have**
    - o cardiovascular disease, OR
    - o hypertension, OR
    - o chronic obstructive pulmonary disease/other chronic respiratory disease
- Are 12-17 years of age **AND have**
    - o BMI ≥ 85th percentile for their age and gender, OR
    - o Sickle cell disease, OR
    - o Congenital or acquired heart disease, OR
    - o Neurodevelopmental disorders, for example, cerebral palsy, OR
    - o A medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
    - o Asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

Published evidence for bamlanivimab is limited to interim results of a phase 2 trial (attached). However, I am told the Health Canada interim order is based on unpublished evidence that looks more compelling and Lisa may be able to speak to this.

Tasha

From: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Date: Monday, November 23, 2020 at 8:01 PM
To: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
Cc: "Neale, Siony" <Siony.Neale@nshealth.ca>
Subject: Re: COVID-19 therapeutics and prophylactics- Bamlanivimab [redacted] request

Hi everyone,

As you likely already know, Health Canada granted market authorization for bamlanivimab (under interim orders) on Nov 20th. [redacted].

Prior to doing this, I feel we should discuss how/if it should be used clinically (ex: in long term care, outpatient infusion clinics, hospital, etc).

This request is going to be different than remdesivir in that non-severe patients in high-risk populations for

severe disease/hospitalization are being suggested as the target population. s.14(1)

[redacted]

third party

[redacted]

We had said 8 am works as a meeting time. **I am wondering if we can touch base Wednesday or Thursday at 8 am**? If not, feel free to suggest other dates/times.

Tasha

From: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Date: Wednesday, November 18, 2020 at 9:35 AM
To: "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
Cc: "Neale, Siony" <Siony.Neale@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics- [redacted] request

unrelated [redacted]

[redacted]

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Coleman, Kathleen [Kathleen.Coleman@novascotia.ca]
Sent: Wednesday, November 18, 2020 8:37 AM
To: Ramsey, Tasha; Cox, Glenn; Barrett, Lisa L; Grandy Allen, Lisa
Cc: Neale, Siony
Subject: RE: COVID-19 therapeutics and prophylactics-[redacted] request

Ok I will ask about any potential conflict. Lisa what is the name of the group you are on that vetted these agents? And thanks Tasha for your offer to step in as well.

Kathleen

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: November 18, 2020 7:28 AM
To: Cox, Glenn <Glenn.Cox@nshealth.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Cc: Neale, Siony <Siony.Neale@nshealth.ca>
Subject: Re: COVID-19 therapeutics and prophylactics-[redacted] request

[redacted]

Tasha

From: "Cox, Glenn" <Glenn.Cox@nshealth.ca>
Date: Tuesday, November 17, 2020 at 10:02 PM
To: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
Cc: "Neale, Siony" <Siony.Neale@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics-[redacted] request

[redacted]

From: Barrett, Lisa L
Sent: Tuesday, November 17, 2020 6:03 PM
To: Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Cc: Neale, Siony <Siony.Neale@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics-[redacted] request

[redacted]

From: Coleman, Kathleen [mailto:Kathleen.Coleman@novascotia.ca]
Sent: Tuesday, November 17, 2020 5:43 PM
To: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Cc: Neale, Siony <Siony.Neale@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics- [redacted] request

Hi all,

third party [redacted]

[redacted]

[redacted]
Kathleen

From: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>
Sent: November 12, 2020 8:42 AM
To: Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Cc: Neale, Siony <Siony.Neale@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics

Hello all.

unrelated [redacted]

[redacted]

Lisa

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

Subject: Re: [redacted]

Date: Monday, November 30, 2020 at 3:04:09 PM Atlantic Standard Time

From: Ramsey, Tasha

To: Coleman, Kathleen

Hi,

[redacted]

Tasha

From: "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>
Date: Monday, November 30, 2020 at 3:00 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: FW: [redacted]

HI Tasha
[redacted]

Many thanks!
K

From: Borden, Natalie <Natalie.Borden@novascotia.ca>
Sent: November 30, 2020 1:29 PM
To: Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>
Cc: Huynh, Tracy A <Tracy.Huynh@novascotia.ca>
Subject: FW: FPT ADM Drug Shortages Table Meeting / Réunion de la Table des SMA FPT pour les pénuries de

médicaments: Eli Lilly bamlanivimab

Kathleen,

At he ADM meeting they said they had the information for NS. On the attached there is a contact person (A), but no delivery information (B) and (C) may be new. Can you let me know if these have been submitted, and if not can you have them completed by the appropriate person and return them as indicated and copy me? Thanks. Natalie

third party

third party [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

- [redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

third party [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

third party

[redacted]

third party

[redacted]


third party


third party

third party [redacted]

Subject: Re: Action Required: Provision of Bamlonivimab (Eli Lilly) in Amb Care
Date: Thursday, November 26, 2020 at 10:13:41 AM Atlantic Standard Time
From: Ramsey, Tasha
To: McNeil, Shelly, Barrett, Lisa L, Cox, Glenn, McCormick, Bethany
CC: Stevenson, Colin
Attachments: image001.png, Blaze 1.pdf, Product Monograph Nov 2020.pdf

Hi Shelly,

Happy to discuss with the COVID Network.

I believe it will be used in the context of research (the CO-VIC trial) for non-severe patients at high risk of progressing to severe COVID-19 illness/hospitalization. Implementation will require careful consideration. We had talked about having a place to infuse and monitor it within the NSH public sphere…but details are yet to be determined.

Published evidence for bamlanivimab is limited to interim results of a phase 2 trial (attached). However, I am told the Health Canada interim order is based on unpublished evidence that looks more compelling and Lisa may be able to speak to this.

Tasha

From: "McNeil, Shelly" <Shelly.McNeil@nshealth.ca>
Date: Thursday, November 26, 2020 at 10:05 AM
To: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "McCormick, Bethany" <Bethany.McCormick@nshealth.ca>
Cc: "Stevenson, Colin" <Colin.Stevenson@nshealth.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: Action Required: Provision of Bamlonivimab (Eli Lilly) in Amb Care

HI All
I think it would make sense to have the Therapeutics group present to the COVID Network next week for discussion then go from there. I'm sure the issue of implementation will be thoroughly discussed. Lisa and Tasha. In advance of that, could you please share a summary of the evidence that lead to this recommendation? Is this outside of a trial and being recommended as routine care?

Thanks
Shelly

From: Barrett, Lisa L
Sent: Thursday, November 26, 2020 10:01 AM
To: Cox, Glenn <Glenn.Cox@nshealth.ca>; McCormick, Bethany <Bethany.McCormick@nshealth.ca>
Cc: Stevenson, Colin <Colin.Stevenson@nshealth.ca>; Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; McNeil, Shelly <Shelly.McNeil@nshealth.ca>
Subject: RE: Action Required: Provision of Bamlonivimab (Eli Lilly) in Amb Care

And Glenn, my understanding is we go through the covid network for approval on this...and that it would then move it's way up the chain.

L.

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Cox, Glenn
Sent: Thursday, November 26, 2020 9:20 AM
To: McCormick, Bethany
Cc: Stevenson, Colin; Barrett, Lisa L; Ramsey, Tasha
Subject: Action Required: Provision of Bamlonivimab (Eli Lilly) in Amb Care

Hi Bethany

On the COVID 19 Therapeutics/Prophylactics call this morning, discussion around the provision of bamlonivimab (monoclonal antibody) for the treatment of mild to moderate ill and use in an outpatient setting.

Would this be something that your group could give consideration to and plan for in the administration through our NSH facilities. Concerns were:

- Would need separate area within NSH facilities as these patients would be COVID +
- Staffing to provide the infusions
- The requirement for treatment could be in the range of 2-3 hrs (1 hr for infusion and 1hr for monitoring)
- Not sure about the number of treatments as of yet

I have copied Dr Tasha Ramsey (Pharmacy) and Dr Lisa Barrett as they are co-chairs of the advisory group.

Thanks
Glenn

nova scotia health authority

Glenn Cox RPh BSc Pharm MBA
Senior Director Pharmacy Services NSHA
Director Pharmacy Services
Cape Breton/Antigonish/Guysborough
Cape Breton Regional Hospital
1482 George St
Sydney, NS B1P 1P3
Office: 902-567-7713
Cell: 902-577-5784
www.nshealth.ca

Subject: RE: COVID-19 therapeutics and prophylactics

Date: Thursday, November 26, 2020 at 8:23:38 AM Atlantic Standard Time

From: Barrett, Lisa L

To: Ramsey, Tasha

CC: Top, Karina

Hi

Karina, Tasha is co-chairing this committee for therapeutics with me. We will send the TOR for your review and engagement on an as needed basis.

L

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Ramsey, Tasha
Sent: Wednesday, November 25, 2020 10:50 AM
To: Barrett, Lisa L; Coleman, Kathleen; Cox, Glenn; Grandy Allen, Lisa
Cc: Neale, Siony
Subject: Re: COVID-19 therapeutics and prophylactics- Bamlanivimab [redacted] request

Hi again,

I would like to suggest the following two items for discussion on our agenda for tomorrow:

1. unrelated
2. Bamlanivimab

unrelated

For our bamlanivimab conversation, please consider:

a. If you recommend use in NS and (if you recommend use)
b. Who you recommend using in
c. How you recommend using it

Background information: bamlanivimab is a monoclonal antibody recommended as a single 700 mg infusion. Its indication is for the "Treatment for adults and pediatric patients 12 years of age or older with mild to moderate COVID-19 who weigh at least 40 kg and are at high risk of progressing to severe COVID-19 illness/hospitalization". It is infused over 1 hour and requires at least 1 hour of observation post infusion.

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- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥ 55 years of age **AND have**
    - o cardiovascular disease, OR
    - o hypertension, OR
    - o chronic obstructive pulmonary disease/other chronic respiratory disease
- Are 12-17 years of age **AND have**
    - o BMI ≥ 85th percentile for their age and gender, OR
    - o Sickle cell disease, OR
    - o Congenital or acquired heart disease, OR
    - o Neurodevelopmental disorders, for example, cerebral palsy, OR
    - o A medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR

o Asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

Published evidence for bamlanivimab is limited to interim results of a phase 2 trial (attached). However, I am told the Health Canada interim order is based on unpublished evidence that looks more compelling and Lisa may be able to speak to this.

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To: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
Cc: "Neale, Siony" <Siony.Neale@nshealth.ca>
Subject: Re: COVID-19 therapeutics and prophylactics- Bamlanivimab PHAC request

Hi everyone,

As you likely already know, Health Canada granted market authorization for bamlanivimab (under interim orders) on Nov 20th. third party [redacted]

Prior to doing this, I feel we should discuss how/if it should be used clinically (ex: in long term care, outpatient infusion clinics, hospital, etc).

This request is going to be different than remdesivir in that non-severe patients in high-risk populations for severe disease/hospitalization are being suggested as the target population. This is tricky, because it would include consideration for long-term care, outpatient infusion clinics, hospital, etc. Logistically, it is especially challenging because infusion clinics are not going to be the ideal place for patients with COVID to receive therapy as the main population that uses infusion clinics are immunocompromised patients.

third party [redacted]

We had said 8 am works as a meeting time. **I am wondering if we can touch base Wednesday or Thursday at 8 am**? If not, feel free to suggest other dates/times.

Tasha

From: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Date: Wednesday, November 18, 2020 at 9:35 AM
To: "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
Cc: "Neale, Siony" <Siony.Neale@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics-[redacted] request

unrelated [redacted]

[redacted]

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
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Sent: Wednesday, November 18, 2020 8:37 AM
To: Ramsey, Tasha; Cox, Glenn; Barrett, Lisa L; Grandy Allen, Lisa
Cc: Neale, Siony
Subject: RE: COVID-19 therapeutics and prophylactics-[redacted] request

unrelated [redacted]

Kathleen

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: November 18, 2020 7:28 AM
To: Cox, Glenn <Glenn.Cox@nshealth.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Cc: Neale, Siony <Siony.Neale@nshealth.ca>
Subject: Re: COVID-19 therapeutics and prophylactics-[redacted] request

third party [redacted]

[redacted]

Tasha

From: "Cox, Glenn" <Glenn.Cox@nshealth.ca>
Date: Tuesday, November 17, 2020 at 10:02 PM
To: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
Cc: "Neale, Siony" <Siony.Neale@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics- [redacted] request

unrelated [redacted]

From: Barrett, Lisa L
Sent: Tuesday, November 17, 2020 6:03 PM
To: Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Cc: Neale, Siony <Siony.Neale@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics- [redacted] request

unrelated [redacted]

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Sent: Tuesday, November 17, 2020 5:43 PM
To: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Cc: Neale, Siony <Siony.Neale@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics- [redacted] request

Hi all,

third party [redacted]

[redacted]

[redacted]
Kathleen

From: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>
Sent: November 12, 2020 8:42 AM
To: Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Cc: Neale, Siony <Siony.Neale@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics

Hello all.

unrelated [redacted]

[redacted]

Lisa

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

Subject: RE: COVID-19 therapeutics and prophylactics- Bamlanivimab [redacted] request
Date: Thursday, November 26, 2020 at 7:58:20 AM Atlantic Standard Time
From: Richard, Gabrielle
To: Ramsey, Tasha

unrelated [redacted]

unrelated

Gabrielle

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: November 26, 2020 7:44 AM
To: Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>
Subject: Re: COVID-19 therapeutics and prophylactics- Bamlanivimab third party request

unrelated

.

T

From: "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>
Date: Wednesday, November 25, 2020 at 8:04 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: FW: COVID-19 therapeutics and prophylactics- Bamlanivimab third party request

Hi Tasha

unrelated

Thanks – chat with you tomorrow
Gabrielle

From: Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>
Sent: November 25, 2020 7:25 PM
To: Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>
Subject: FW: COVID-19 therapeutics and prophylactics- Bamlanivimab PHAC request

For meeting tomorrow.
I've attached some questions/comments I made mainly for myself re the TOR. Struggling to understand what "decisions" this group might make as I saw it more as an advisory group.

Sorry the meeting is so early tomorrow! That is going to be tough for me

K

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: November 25, 2020 10:50 AM
To: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Cc: Neale, Siony <Siony.Neale@nshealth.ca>
Subject: Re: COVID-19 therapeutics and prophylactics- Bamlanivimab third party request

Hi again,

I would like to suggest the following two items for discussion on our agenda for tomorrow:

1. unrelated [redacted]
2. Bamlanivimab

unrelated [redacted]

For our bamlanivimab conversation, please consider:

a. If you recommend use in NS and (if you recommend use)
b. Who you recommend using in
c. How you recommend using it

Background information: bamlanivimab is a monoclonal antibody recommended as a single 700 mg infusion. Its indication is for the "Treatment for adults and pediatric patients 12 years of age or older with mild to moderate COVID-19 who weigh at least 40 kg and are at high risk of progressing to severe COVID-19 illness/hospitalization". It is infused over 1 hour and requires at least 1 hour of observation post infusion.

High risk is defined as patients who meet at least one of the following criteria in the product monograph:

- Are ≥ 65 years of age
- Have a body mass index (BMI) ≥ 35 for patients ≥ 18 years of age
- Have chronic kidney disease
- Have diabetes
- Have immunosuppressive disease
- Are currently receiving immunosuppressive treatment
- Are ≥ 55 years of age **AND have**
  - o cardiovascular disease, OR
  - o hypertension, OR
  - o chronic obstructive pulmonary disease/other chronic respiratory disease
- Are 12-17 years of age **AND have**
  - o BMI ≥ 85th percentile for their age and gender, OR
  - o Sickle cell disease, OR
  - o Congenital or acquired heart disease, OR
  - o Neurodevelopmental disorders, for example, cerebral palsy, OR
  - o A medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR
  - o Asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

Published evidence for bamlanivimab is limited to interim results of a phase 2 trial (attached). However, I am told the Health Canada interim order is based on unpublished evidence that looks more compelling and Lisa may be able to speak to this.

Tasha

From: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Date: Monday, November 23, 2020 at 8:01 PM
To: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
Cc: "Neale, Siony" <Siony.Neale@nshealth.ca>
Subject: Re: COVID-19 therapeutics and prophylactics- Bamlanivimab [redacted] request

Hi everyone,

As you likely already know, Health Canada granted market authorization for bamlanivimab (under interim orders) on Nov 20th. third party [redacted]

Prior to doing this, I feel we should discuss how/if it should be used clinically (ex: in long term care, outpatient infusion clinics, hospital, etc).

This request is going to be different than remdesivir in that non-severe patients in high-risk populations for severe disease/hospitalization are being suggested as the target population. This is tricky, because it would include consideration for long-term care, outpatient infusion clinics, hospital, etc. Logistically, it is especially challenging because infusion clinics are not going to be the ideal place for patients with COVID to receive therapy as the main population that uses infusion clinics are immunocompromised patients.

We had said 8 am works as a meeting time. **I am wondering if we can touch base Wednesday or Thursday at 8 am**? If not, feel free to suggest other dates/times.

Tasha

From: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Date: Wednesday, November 18, 2020 at 9:35 AM
To: "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
Cc: "Neale, Siony" <Siony.Neale@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics- [redacted] request

unrelated [redacted]

[redacted]

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Coleman, Kathleen [Kathleen.Coleman@novascotia.ca]
Sent: Wednesday, November 18, 2020 8:37 AM
To: Ramsey, Tasha; Cox, Glenn; Barrett, Lisa L; Grandy Allen, Lisa
Cc: Neale, Siony
Subject: RE: COVID-19 therapeutics and prophylactics- [redacted] request

unrelated [redacted]

Kathleen

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: November 18, 2020 7:28 AM
To: Cox, Glenn <Glenn.Cox@nshealth.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Cc: Neale, Siony <Siony.Neale@nshealth.ca>
Subject: Re: COVID-19 therapeutics and prophylactics- [redacted] request

unrelated [redacted]

[redacted]

Tasha

From: "Cox, Glenn" <Glenn.Cox@nshealth.ca>
Date: Tuesday, November 17, 2020 at 10:02 PM
To: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
Cc: "Neale, Siony" <Siony.Neale@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics-[redacted] request

[redacted]

From: Barrett, Lisa L
Sent: Tuesday, November 17, 2020 6:03 PM
To: Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Cc: Neale, Siony <Siony.Neale@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics-[redacted] request

[redacted]

From: Coleman, Kathleen [mailto:Kathleen.Coleman@novascotia.ca]
Sent: Tuesday, November 17, 2020 5:43 PM
To: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Cc: Neale, Siony <Siony.Neale@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics-[redacted] request

Hi all,

[redacted]

[redacted]

[redacted]
Kathleen

From: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>
Sent: November 12, 2020 8:42 AM
To: Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Cc: Neale, Siony <Siony.Neale@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics

Hello all.

unrelated [redacted]

[redacted]

Lisa

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

Subject: RE: COVID-19 therapeutics and prophylactics- Bamlanivimab [third party] request
Date: Tuesday, November 24, 2020 at 7:28:26 AM Atlantic Standard Time
From: Ramsey, Tasha
To: Barrett, Lisa L, Cox, Glenn
CC: Grandy Allen, Lisa, Coleman, Kathleen, Neale, Siony

Perfect- I just sent a meeting invite using zoom for Thursday at 8

I agree- we can engage Thomas Gray for the delivery information once we determine if/how to use it.

Tasha

From: Barrett, Lisa L
Sent: November 23, 2020 11:04 PM
To: Cox, Glenn
Cc: Grandy Allen, Lisa; Coleman, Kathleen; Ramsey, Tasha; Neale, Siony
Subject: Re: COVID-19 therapeutics and prophylactics- Bamlanivimab [third party] request

Thursday good

Sent from my iPhone

> On Nov 23, 2020, at 10:09 PM, Cox, Glenn <Glenn.Cox@nshealth.ca> wrote:
>
> Either day for me as well
>
> ---
>
> **From:** Grandy Allen, Lisa
> **Sent:** Monday, November 23, 2020 9:56 PM
> **To:** Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>
> **Cc:** Neale, Siony <Siony.Neale@nshealth.ca>
> **Subject:** RE: COVID-19 therapeutics and prophylactics- Bamlanivimab [third party] request
>
> Either works for me.
> Aside from the therapeutic issues, [third party]
> Lisa
> Lisa R. Grandy Allen, B.Sc.(Pharm), ACPR
> Drug Information Pharmacist

Capital Health
(902) 473-6233, Fax (902)473-8612

From: Coleman, Kathleen [Kathleen.Coleman@novascotia.ca]
Sent: November 23, 2020 9:06 PM
To: Ramsey, Tasha; Barrett, Lisa L; Cox, Glenn; Grandy Allen, Lisa
Cc: Neale, Siony
Subject: RE: COVID-19 therapeutics and prophylactics- Bamlanivimab [redacted] request

Thanks Tasha. Thursday 8am would work for me.

Kathleen

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: November 23, 2020 8:02 PM
To: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Cc: Neale, Siony <Siony.Neale@nshealth.ca>
Subject: Re: COVID-19 therapeutics and prophylactics- Bamlanivimab [redacted] request

Hi everyone,

As you likely already know, Health Canada granted market authorization for bamlanivimab (under interim orders) on Nov 20th. third party [redacted]

Prior to doing this, I feel we should discuss how/if it should be used clinically (ex: in long term care, outpatient infusion clinics, hospital, etc).

This request is going to be different than remdesivir in that non-severe patients in high-risk populations for severe disease/hospitalization are being suggested as the target population. This is tricky, because it would include consideration for long-term care, outpatient infusion clinics, hospital, etc. Logistically, it is especially challenging because infusion clinics are not going to be the ideal place for patients with COVID to receive therapy as the main population that uses infusion clinics are immunocompromised patients.

third party [redacted]

third party [redacted]

We had said 8 am works as a meeting time. **I am wondering if we can touch base Wednesday or Thursday at 8 am**? If not, feel free to suggest other dates/times.

Tasha

From: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Date: Wednesday, November 18, 2020 at 9:35 AM
To: "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
Cc: "Neale, Siony" <Siony.Neale@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics- [redacted] request

unrelated [redacted]

[redacted]

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Coleman, Kathleen [Kathleen.Coleman@novascotia.ca]
Sent: Wednesday, November 18, 2020 8:37 AM
To: Ramsey, Tasha; Cox, Glenn; Barrett, Lisa L; Grandy Allen, Lisa
Cc: Neale, Siony
Subject: RE: COVID-19 therapeutics and prophylactics- [redacted] request

unrelated [redacted]

Kathleen

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: November 18, 2020 7:28 AM
To: Cox, Glenn <Glenn.Cox@nshealth.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Cc: Neale, Siony <Siony.Neale@nshealth.ca>
Subject: Re: COVID-19 therapeutics and prophylactics- [redacted] request

unrelated [redacted]

unrelated [redacted]

Tasha

From: "Cox, Glenn" <Glenn.Cox@nshealth.ca>
Date: Tuesday, November 17, 2020 at 10:02 PM
To: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>
Cc: "Neale, Siony" <Siony.Neale@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics- [redacted] request

unrelated [redacted]

From: Barrett, Lisa L
Sent: Tuesday, November 17, 2020 6:03 PM
To: Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Cc: Neale, Siony <Siony.Neale@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics- [redacted] request

unrelated [redacted]

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To: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Cc: Neale, Siony <Siony.Neale@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics- PHAC request

Hi all,

third party [redacted]

[redacted]

[redacted]
Kathleen

From: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>
Sent: November 12, 2020 8:42 AM

To: Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Cc: Neale, Siony <Siony.Neale@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics

Hello all.

unrelated [redacted]

[redacted]

Lisa

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

Subject: Re: Bamlanivimab information request
Date: Monday, November 23, 2020 at 8:00:07 PM Atlantic Standard Time
From: Ramsey, Tasha
To: Coleman, Kathleen
CC: Barrett, Lisa L

Yes- I would like to have the group chat and see if Lisa is planning to use it before we try to sort out logistics. I will send an email to the group asking if 8 am Wed or Thurs work.

If these do not work, feel free to suggest alternate dates/times,

Tasha

From: "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>
Date: Monday, November 23, 2020 at 6:34 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Cc: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Subject: Re: Bamlanivimab information request

Hi Tasha
Yes that sounds good.

I agree we should have a discussion of how we see/want this agent to be used in NS. All the information was new to me today- s.14(1) [redacted]

What is the best way to have that discussion? Should our provincial group have a call? I assume others will need to be involved from the logistical standpoint, nursing, NSHA leadership etc?

K

Sent from my iPhone

On Nov 23, 2020, at 2:50 PM, Ramsey, Tasha <Tasha.Ramsey@nshealth.ca> wrote:

Hi Kathleen,

Can I forward the request for bamlanivimab information to our NS COVID-19 therapeutics and prophylactics group and Thomas Gray?

We should discuss how we feel it should be used clinically (ex: long term care, outpatient infusion clinics, hospital, etc).

third party [redacted]

- [redacted]

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

Privacy Office; Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

July 5, 2021

Sent via e-mail

Re: No Responsive Records – OUR FILE# NSHA-2021-072

On June 4, 2021 Nova Scotia Health (NSH) received your request under the *Freedom of Information and Protection of Privacy Act* (*FOIPOP Act*).

We understand your application to be for a copy of the following:
All records relating to:

1. *Decisions of NSHA intended to or with the effect of making it more difficult, impossible, or to delay the booking of appointments to get vaccinated against Covid-19 for non-residents of Nova Scotia who are in Nova Scotia whether on an extended stay in Nova Scotia or otherwise;*
2. *The process for booking appointments for Covid-19 vaccination and the differences for residents of Nova Scotia versus non-residents who are in Nova Scotia whether on an extended stay or not;*
3. *The fact that, and why, Nova Scotia makes the process different or more difficult (relative to residents) for, non-residents to book appointments for COVID-19 vaccinations in Nova Scotia whether here for an extended stay or otherwise;*
4. *Second shot COVID-19 vaccination appointment bookings for non-residents while in Nova Scotia whether on an extended stay or otherwise; and*
5. *How Nova Scotia's vaccination appointment booking process for non-residents in Nova Scotia in connection with COVID-19 vaccinations meets or does not meet Nova Scotia's obligations under inter provincial agreements and under the Canada Health Act.*

"Records" includes minutes/notes of meetings, emails, presentations etc. and all elements set out in definition of "records" in the Freedom of Information and Protection of Privacy Act.

We have conducted a thorough search of our records, but we were not able to find any records responsive to your request. We are now closing your file.

Should you have any questions, please do not hesitate to contact me.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review. Notwithstanding, within 30 days you have the right to appeal directly to the Supreme Court if there is no third party notified pursuant to section 22 of the *FOIPOP Act*.

Sincerely,
Katie Smith
Freedom of Information Officer
Nova Scotia Health Authority
Halifax, Nova Scotia

Privacy Office: Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

August 25, 2021

Sent via e-mail

Re: Full Disclosure – OUR FILE# NSHA-2021-074

On June 8, 2021 Nova Scotia Health (NSH) received your request under the *Freedom of Information and Protection of Privacy Act* (*FOIPOP Act*).

We understand your application to be for a copy of the following:
Records relating to potential and or approved pharmacological treatments for SARS-CoV-2 and Covid-19. Records which document in and outpatient treatment protocols. Records which describe the basis for approval, disqualification or ongoing consideration of Ivermetcin and Hydroxychloroquine.

Please find a copy of the records located in response to your request. We are providing these records to you in their entirety. The items marked unrelated refer to other pharmacological treatments for SARS-CoV-2 and COVID-19.

We are now closing your file.

Should you have any questions, please do not hesitate to contact me.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review.

Sincerely,
Katie Smith
Freedom of Information Officer
Nova Scotia Health Authority
Halifax, Nova Scotia

Agenda / Action Items

MEETING DETAILS			
Meeting Title	COVID-19 Network Meeting		
Location	Zoom		
Meeting Date	Tuesday, April 6, 2021	**Meeting Time**	4:30 to 6:30 p.m.
Purpose	A bi-weekly update meeting that provides an opportunity for clinical and medical leaders to discuss current pandemic strategies.		

PARTICIPANTS			
Co-chairs	Shelly McNeil	Alyson Lamb	
Participants	Marika Warren	Brett MacDougall	Angela Keenan
	Kimberley Anderson	Andrew Heighton	Cynthia Stockman
	Lisa Barrett	s.20(1)	Vickie Sullivan
	Darlene Davis	Lynn Johnston	Wanda Matthews
	Kate Mercer	Tamara Gilley	Heather Wolfe
	Tasha Ramsey	Maria Alexiadis	Ryan Sommers
	Tammy MacDonald	Christine Short	Jeannette Comeau
	Debbie Burris	s.20(1)	Melanie DiQuinzio
	Lynn Edwards	Janice Chisholm	Cheryl Pugh
	Tanya Munroe	Tania Sullivan	Todd Howlett
	Sam Hodder	Andrew Harris	Lois Bowden
	Todd Hatchette	Tara Sampalli	Christy Bussey
	Dylana Arsenault	Amy MacDonald	Glenn Patriquin
	Lorianne MacLean	Kirk McGee	Gary O'Toole
	Leah MacDonald	Annette Elliot Rose	Noella Whelan
	Nancy MacConnell-Maxner	Jennifer MacDougall	Cathy Ann Casault
	Carla MacDonald	Michelle DePodesta	
Guest(s)			
Regrets	Susan Stevens	Aaron Smith	Paul Hernandez
	Cindy MacQuarrie	Nicki Doyle	Ian Davis
	Katie MacLeod	Deborah Purvis	Scott Mawdsley
	Chris Lata	Cheryl Tschupruk	Tanya Penney
	Tony O'Leary	David Henderson	Greg Hirsch
	Doris Grant	Kris Srivatsa	Cindy Connolly

Item	Description	Lead
1.0	unrelated	unrelated
2.0	unrelated unrelated	unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
	unrelated unrelated	unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
3.0	unrelated	unrelated
4.0	unrelated	unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
	unrelated	unrelated
5.0	unrelated	unrelated
6.0	unrelated	• unrelated
7.0	unrelated	unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
	unrelated	unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
	unrelated	unrelated
8.0	unrelated	unrelated
9.0	unrelated	unrelated
10.0	unrelated	unrelated
11.0	unrelated	unrelated

Agenda / Action Items

MEETING DETAILS			
Meeting Title	COVID-19 Network Meeting		
Location	Zoom		
Meeting Date	Tuesday, April 27, 2021	**Meeting Time**	4:30 to 6:30 p.m.
Purpose	A bi-weekly update meeting that provides an opportunity for clinical and medical leaders to discuss current pandemic strategies.		

PARTICIPANTS			
Co-chairs	Shelly McNeil	Alyson Lamb	Cindy MacQuarrie
Participants	Marika Warren	Steve Button	Angela Keenan
	Kimberley Anderson	Andrew Heighton	Cynthia Stockman
	Paul Hernandez	s.20(1)	Ian Davis
	Darlene Davis	Lynn Johnston	Katie MacLeod
	Kate Mercer	Theresa Hawkesworth	Heather Wolfe
	Tasha Ramsey	Anita Muise	Andre Bernard
	Tammy MacDonald	Christine Short	Jeannette Comeau
	Scott Mawdsley	s.20(1)	Melanie DiQuinzio
	Chris Lata	Natalie Cheng	Maria Alexiadis
	Lynn Edwards	Janice Chisholm	Cheryl Tschupruk
	Leah MacDonald	Tania Sullivan	Tony O'Leary
	Sam Hodder	Kirk McGee	Gary O'Toole
	Todd Hatchette	Tara Sampalli	Greg Hirsch
	Doris Grant	Amy MacDonald	Glenn Patriquin
	Cindy Connolly	Annette Elliot Rose	Noella Whelan
	Nancy MacConnell-Maxner	Jennifer MacDougall	Cathy Ann Casault
	Carla MacDonald	Michelle DePodesta	Vickie Sullivan
	Lorianne MacLean	Dylana Arsenault	Lois Bowden
	Tanya Munroe	Todd Howlett	Cheryl Pugh
	Debbie Burris	Brett MacDougall	
Regrets	Susan Stevens	Tamara Gilley	Lisa Barrett
	Ryan Sommers	Robert Zwicker	David Henderson
	Andrew Harris	Kris Srivatsa	Christy Bussey
	Nicki Doyle		

Item	Description	Lead
1.0	unrelated	unrelated
2.0	unrelated	unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
	unrelated	• unrelated
3.0	unrelated	unrelated
4.0	unrelated	unrelated
5.0	unrelated	unrelated
6.0	unrelated	unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
	[redacted]	unrelated
7.0	unrelated	unrelated
8.0	unrelated	unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
9.0	unrelated	unrelated
10.0	unrelated	unrelated
11.0	unrelated	unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
12.0	**Therapeutics Update** (Tasha Ramsey)	unrelated
13.0	unrelated	unrelated
14.0	unrelated	unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
	unrelated	unrelated
15.0	unrelated	• unrelated

Agenda / Action Items

MEETING DETAILS			
Meeting Title	COVID Network Meeting		
Location	Skype		
Meeting Date	Tuesday, December 8, 2020	**Meeting Time**	4:00 to 6:00 p.m.
Purpose	A weekly update meeting that provides an opportunity for clinical and medical leaders to discuss current pandemic strategies.		

PARTICIPANTS			
Co-chairs	Shelly McNeil	Alyson Lamb	Lois Bowden
Participants	Christy Bussey	Nicki Doyle	Dylana Arsenault
	Kimberley Anderson	Andrew Heighton	Cynthia Stockman
	Lisa Barrett	s.20(1)	Ian Davis
	Darlene Davis	Lynn Johnston	Katie MacLeod
	Andrew Harris	Gary O'Toole	Heather Wolfe
	Tasha Ramsey	Cheryl Pugh	Ryan Sommers
	Tammy MacDonald	Carmel Turpin	Jeannette Comeau
	Bethany McCormick	Shauna Thompson	Melanie DiQuinzio
	Chris Lata	Maria Alexiadis	Rick Gibson
	Lynn Edwards	Janice Chisholm	Cheryl Tschupruk
	Tanya Penney	Tania Sullivan	Tanya Munroe
	Sam Hodder	Sandy Cantwell Kerr	David Henderson
	Todd Hatchette	Tara Sampalli	s.20(1)
	Paul Hernandez	Sally Loring	Glen Patriquin
	Aaron Smith	Kirk McGee	Christine Short
	Cindy Connolly	Annette Elliot Rose	Noella Whelan
	Nancy MacConnell-Maxner	Wendy McVeigh	Cathy Ann Casault
	Carla MacDonald	Jason LeBlanc	
Regrets	Cindy MacQuarrie	Angela Keenan	Kate Mercer
	Tony O'Leary	Susan Stevens	Kris Srivatsa
	Jennifer MacDougall	Michelle DePodesta	Lorianne MacLean
	Todd Howlett	Greg Hirsch	Marika Warren
	Deborah Purvis		
Guest	Doris Grant	Lewis Bedford	Susan Dunn
	Andrea Rose		

Item	Description	Lead
1.0	unrelated	unrelated
2.0	unrelated	unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
	unrelated	unrelated
3.0	unrelated	unrelated
4.0	unrelated	unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
5.0	unrelated	unrelated
6.0	Therapeutics Update (Tasha Ramsey/Lisa Barrett)	unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
7.0	unrelated	unrelated
8.0	unrelated	unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
	unrelated	unrelated
9.0	unrelated	unrelated
10.0	unrelated	unrelated
11.0	unrelated	• unrelated
12.0	unrelated	• unrelated

Agenda / Action Items

MEETING DETAILS			
Meeting Title	COVID Network Meeting		
Location	Skype		
Meeting Date	Tuesday, December 22, 2020	**Meeting Time**	4:30 to 6:30 p.m.
Purpose	A weekly update meeting that provides an opportunity for clinical and medical leaders to discuss current pandemic strategies.		

PARTICIPANTS			
Co-chairs	Shelly McNeil	Alyson Lamb	
Participants	Marika Warren	Noella Whelan	Angela Keenan
	Kimberley Anderson	Andrew Heighton	Christine Short
	Lisa Barrett	s.20(1)	Kirk McGee
	Darlene Davis	Lynn Johnston	Susan Stevens
	Kate Mercer	Gary O'Toole	Heather Wolfe
	Tasha Ramsey	Deborah Purvis	Ryan Sommers
	Tammy MacDonald	Carmel Turpin	Jeannette Comeau
	Cheryl Pugh	Shauna Thompson	Melanie DiQuinzio
	Todd Howlett	Maria Alexiadis	Rick Gibson
	Lynn Edwards	Janice Chisholm	Cheryl Tschupruk
	Ruth Harding	Michelle DePodesta	Christy Bussey
	Carla MacDonald	Andrew Harris	David Henderson
	Todd Hatchette	Nancy MacConnell-Maxner	s.20(1)
	Dylana Arsenault	Annette Elliot Rose	Glen Patriquin
	Doris Grant	Greg Hirsch	
Regrets	Ian Davis	Nicki Doyle	Cynthia Stockman
	Sally Loring	Cathy Ann Casault	Kris Srivatsa
	Paul Hernandez	Tara Sampalli	Lois Bowden
	Cindy MacQuarrie	Lorianne MacLean	Tanya Munroe
	Aaron Smith	Bethany McCormick	Chris Lata
	Cindy Connolly	Tanya Penney	Katie MacLeod
	Jennifer MacDougall	Tania Sullivan	Tony O'Leary
	Sam Hodder		

Item	Description	Lead
1.0	unrelated	• unrelated
2.0	unrelated	unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
3.0	unrelated	unrelated
4.0	unrelated	unrelated unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
5.0	Therapeutics Update (Tasha Ramsey/Lisa Barrett)	unrelated

Agenda / Action Items

Item	Description	Lead
	Therapeutics Update Cont'd	• Interim Recommendations: will be reviewed on a monthly basis by the NS Therapeutics and Prophylactics Advisory Group (review date: January 21, 2021). [redacted] unrelated

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Agenda / Action Items

Item	Description	Lead
	Therapeutics Update Cont'd	unrelated
6.0	unrelated	unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
7.0	unrelated	unrelated
8.0	unrelated	unrelated

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Agenda / Action Items

MEETING DETAILS			
Meeting Title	COVID-19 Network Meeting		
Location	Zoom		
Meeting Date	Tuesday, February 16, 2021	**Meeting Time**	4:30 to 6:30 p.m.
Purpose	A weekly update meeting that provides an opportunity for clinical and medical leaders to discuss current pandemic strategies.		

PARTICIPANTS			
Co-chairs	Shelly McNeil	Cindy MacQuarrie	Alyson Lamb
Participants	Carla MacDonald	Kate Mercer	Angela Keenan
	Kimberley Anderson	Andrew Heighton	Cynthia Stockman
	Lisa Barrett	s.20(1)	Ian Davis
	Darlene Davis	Lynn Johnston	Katie MacLeod
	Theresa Hawkesworth	Vivian Tan	Heather Wolfe
	Tasha Ramsey	Marika Warren	Ryan Sommers
	Tammy MacDonald	Michelle DePodesta	Jeannette Comeau
	Tanya Munroe	Shauna Thompson	Vickie Sullivan
	Todd Howlett	Maria Alexiadis	Dylana Arsenault
	Lynn Edwards	Janice Chisholm	Debbie Burris
	Tanya Penney	Tania Sullivan	Christy Bussey
	Sam Hodder	Andrew Harris	Amy MacDonald
	Todd Hatchette	Doris Grant	Greg Hirsch
	Paul Hernandez	Sally Loring	Glenn Patriquin
	s.20(1)	Kirk McGee	Cheryl Pugh
	Cindy Connolly	Annette Elliot Rose	Wanda Matthews
	Nancy MacConnell-Maxner	Brett MacDougall	Cathy Ann Casault
Guest			
Regrets	Susan Stevens	Christine Short	Deborah Purvis
	Chris Lata	Tara Sampalli	David Henderson
	Aaron Smith	Kris Srivatsa	Lorianne MacLean
	Lois Bowden	Jennifer MacDougall	Noella Whelan
	Gary O'Toole	Tony O'Leary	Cheryl Tschupruk
	Scott Mawdsley	Melanie DiQuinzio	Nicki Doyle
	Tamara Gilley		

Item	Description	Lead
1.0	unrelated	unrelated
2.0	unrelated	unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
	unrelated	unrelated
3.0	unrelated	unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
	unrelated	unrelated
4.0	unrelated	unrelated
5.0	unrelated	unrelated
6.0	unrelated	unrelated

Agenda / Action Items

Item	Description	Lead
7.0	**Therapeutics Recommendations** (Tasha Ramsey/Lisa Barrett)	• **Ivermectin:** Do not recommend for the treatment or prophylaxis of COVID-19 as part of routine care or in the context of research at this time. **Rationale:** ○ **Level of Evidence:** Published peer reviewed literature is limited to a retrospective study. Other agents recommended by the advisory group for use in routine care or the context of research have peer-reviewed phase 2 or RCT data ○ **Lack of Federal Support:** unrelated unrelated ivermectin is not being pursued by the federal government, it does not have a conditional approval or a Health Canada interim order, and will not be provided free of charge from the federal government. ○ **Guideline Recommendations:** Canadian PHAC/AMMI endorsed guidelines and other international guidelines do not recommend use at this time. ○ **Lack of Interest Locally to Explore Context of Research:** COVID-19 trials in NS do not have interest in exploring at this time. ○ **Global Supply:** Current Ivermectin shortage. Potential to deplete supply for established anti-parasitic indications.

unrelated

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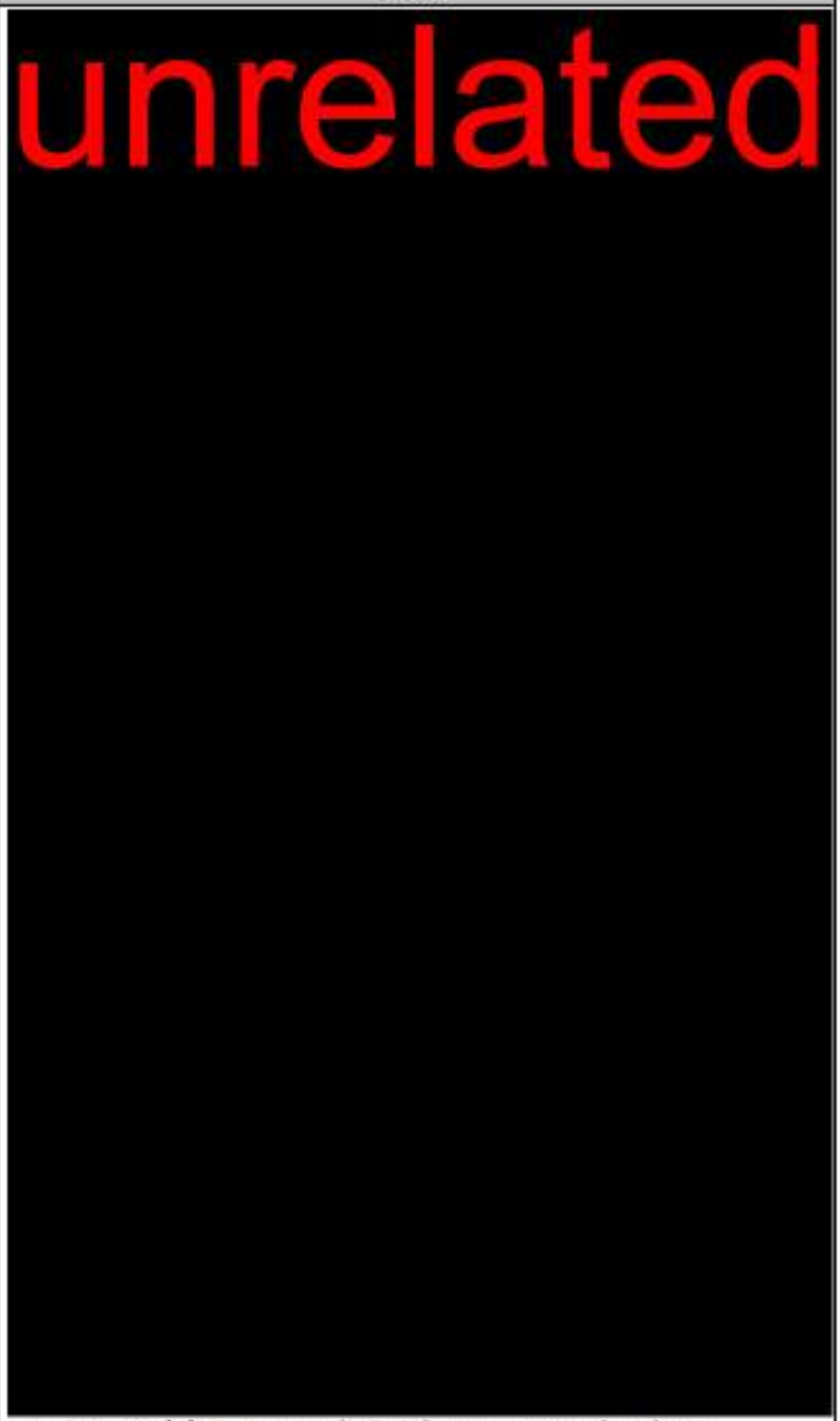
Agenda / Action Items

Item	Description	Lead
	Therapeutics Recommendations Cont'd	

- Key Decision: Network Members support the above recommendations. Network Co-Leads will bring forward to ELT for approval.

nova scotia health

Agenda / Action Items

Item	Description	Lead
8.0	unrelated [redacted]	unrelated [redacted]
9.0	unrelated [redacted]	• unrelated [redacted]
10.0	unrelated [redacted]	• unrelated [redacted]

nova scotia health

Agenda / Action Items

MEETING DETAILS			
Meeting Title	COVID-19 Network Meeting		
Location	Zoom		
Meeting Date	Tuesday, March 23, 2021	**Meeting Time**	4:30 to 6:30 p.m.
Purpose	A bi-weekly update meeting that provides an opportunity for clinical and medical leaders to discuss current pandemic strategies.		

PARTICIPANTS			
Co-chairs	Shelly McNeil	Cindy MacQuarrie	Alyson Lamb
Participants	Marika Warren	Amy MacDonald	Angela Keenan
	Kimberley Anderson	Andrew Heighton	Cynthia Stockman
	Lisa Barrett	[redacted]	Ian Davis
	Debbie Burris	Vickie Sullivan	Theresa Hawkesworth
	Kate Mercer	Cheryl Pugh	Heather Wolfe
	Tasha Ramsey	Todd Howlett	Maureen Carew
	Tammy MacDonald	Christine Short	Jeannette Comeau
	Andre Bernard	Maria Alexiadis	Melanie DiQuinzio
	Michelle DePodesta	Tanya Munroe	Christy Bussey
	Carla MacDonald	Janice Chisholm	Cathy Ann Casault
	Dylana Arsenault	Tania Sullivan	Nancy MacConnell-Maxner
	Sam Hodder	Andrew Harris	David Henderson
	Todd Hatchette	Annette Elliot Rose	Greg Hirsch
	Paul Hernandez	Noella Whelan	Glenn Patriquin
	Cindy Connolly	Kirk McGee	Gary O'Toole
	Yossry Hussein		
Guest(s)	Barbara Goodall		
Regrets	Susan Stevens	Tamara Gilley	[redacted]
	Ryan Sommers	Shauna Thompson	Jennifer MacDougall
	Scott Mawdsley	Nicki Doyle	Doris Grant
	Darlene Davis	Lynn Johnston	Katie MacLeod
	Deborah Purvis	Chris Lata	Cheryl Tschupruk
	Lynn Edwards	Tanya Penney	Tony O'Leary
	Tara Sampalli	Sally Loring	Wanda Matthews
	Kris Srivatsa	Brett MacDougall	Lois Bowden
	Aaron Smith	Lorianne MacLean	

Item	Description	Lead
1.0	[redacted]	• [redacted]
2.0	[redacted]	[redacted]

nova scotia health

Agenda / Action Items

Item	Description	Lead
	[redacted]	[redacted]

nova scotia health

Agenda / Action Items

Item	Description	Lead
		unrelated
3.0	unrelated	unrelated
4.0	unrelated	unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
	unrelated	unrelated
5.0	unrelated	unrelated
6.0	unrelated	unrelated

nova scotia health

Agenda / Action Items

Item	Description	Lead
7.0	**Therapeutics Update** (Lisa Barrett/Tasha Ramsey/Barbara Goodall)	unrelated
8.0	unrelated	• unrelated
9.0	unrelated	• unrelated
10.0	unrelated	• unrelated

To:	NS Health COVID Network
Date:	9 February 2021
From:	Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group
Subject:	Recommendations

The Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group has the following new recommendations for the COVID Network to consider for approval:

Ivermectin: Do not recommend for the treatment or prophylaxis of COVID-19 as part of routine care or in the context of research at this time.

The following recommendations were approved by the COVID Network on December 22, 2020. The Advisory Group reviewed them as part of our monthly review of previous recommendations. We have no revisions to the recommendations at this time.

Note: Recommendations will be reviewed on a monthly basis by the NS Therapeutics and Prophylactics Advisory Group

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group

April 8, 2021

Agenda

- Minutes
- unrelated [redacted]
- Review recommendations:
  - unrelated [redacted]
  - Ivermectin
  - unrelated [redacted]

Minutes

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	March 11, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, Amanda Porter, Gabrielle Richard, Lisa Grandy Allen, Barbara Goodall, Kenneth Rockwood		

Items	Discussion
- **Minutes**	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Review recommendations: - [redacted]	[redacted]


unrelated

unrelated

unrelated

unrelated

unrelated

unrelated

unrelated

unrelated

unrelated

Recommendation Review

COVID-19 Therapeutics and Prophylactics Advisory Group: Recommendations

Recommendation	Medication	Notes
unrelated	[redacted]	[redacted]
unrelated	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
Do NOT Recommend	Ivermectin	
	unrelated	
	[redacted]	
	[redacted]	

unrelated

unrelated

unrelated

unrelated

unrelated

unrelated

COVID-19 Therapeutics and Prophylactics Advisory Group: Recommendations

Recommendation	Medication	Notes
unrelated	[redacted]	[redacted]
unrelated	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
Do NOT Recommend	Ivermectin	
	unrelated	
	[redacted]	
	[redacted]	

unrelated

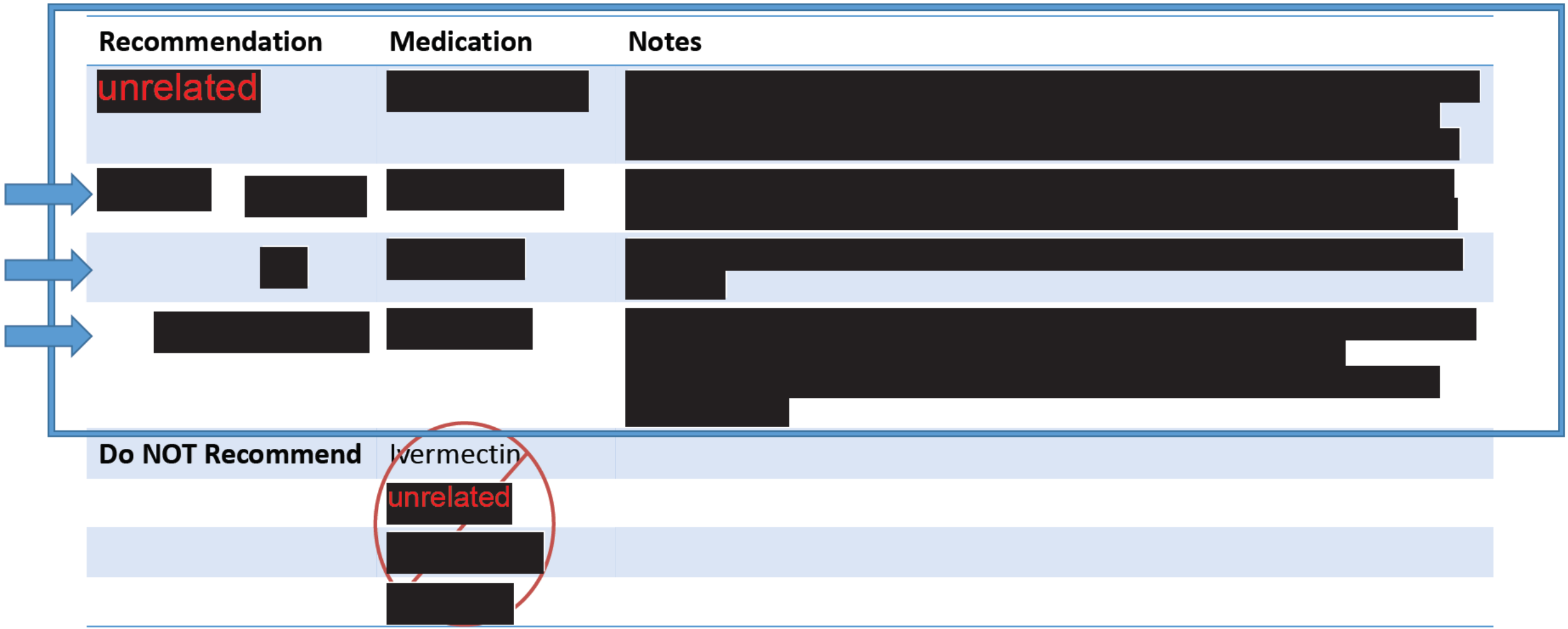
unrelated

COVID-19 Therapeutics and Prophylactics Advisory Group: Recommendations

Recommendation	Medication	Notes
unrelated	[redacted]	[redacted]
unrelated	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
Do NOT Recommend	Ivermectin	
	unrelated	
	[redacted]	
	[redacted]	

unrelated

NS Health COVID-19 Medication Recommendations



Recommendation	Medication	Notes
unrelated	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Do NOT Recommend	Ivermectin	
	unrelated	
	[redacted]	
	[redacted]	

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group

April 22, 2021

Agenda

- Minutes
- unrelated [redacted]
- Review recommendations:
  - unrelated [redacted]
    - Ivermectin
    - unrelated [redacted]

Minutes

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	April 8, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Kathleen Coleman, Emma Reid, Amanda Porter, Gabrielle Richard, Lisa Grandy Allen, Barbara Goodall, Kenneth Rockwood		

Items	Discussion
- **Minutes**	unrelated [redacted]
unrelated [redacted]	[redacted]
Review recommendations: - unrelated [redacted] **ivermectin,** unrelated [redacted]	unrelated [redacted]
	unrelated [redacted]
	[redacted]


unrelated

unrelated

unrelated

unrelated

unrelated

[redacted]

Recommendation Review

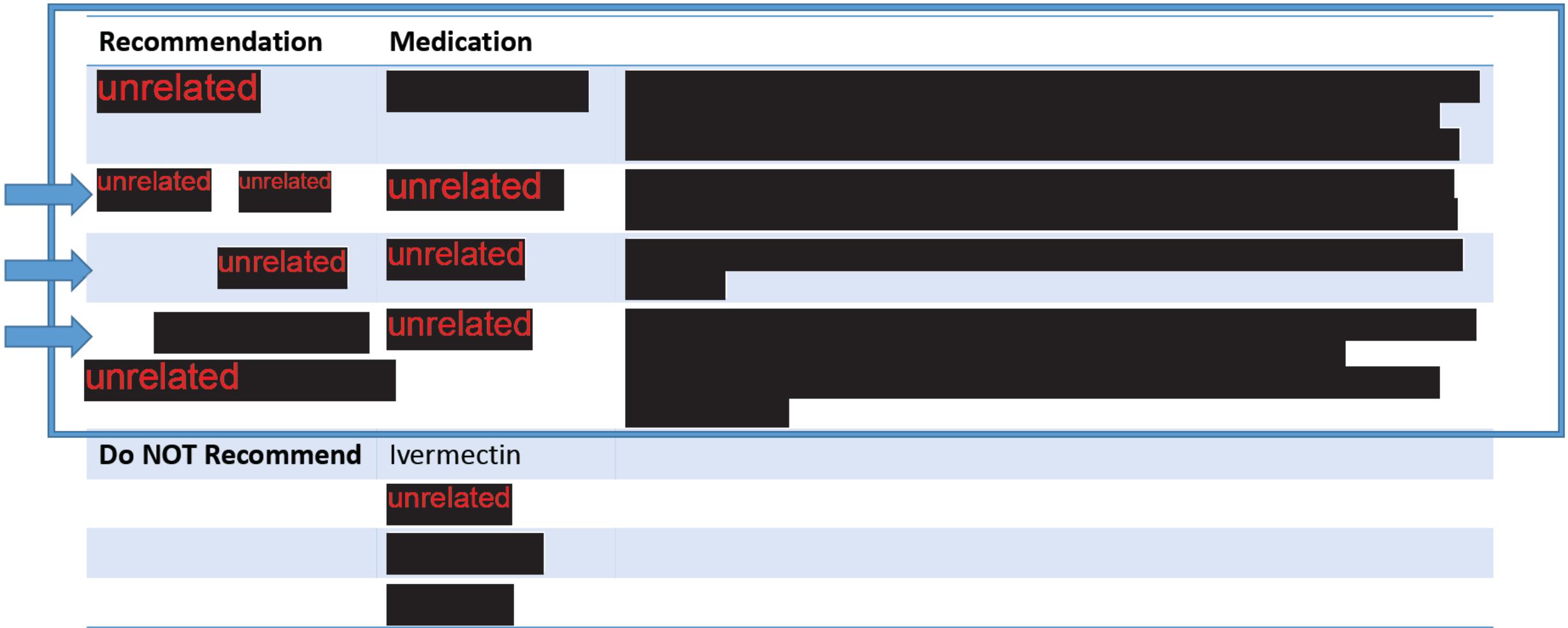
COVID-19 Therapeutics and Prophylactics Advisory Group: Recommendations

Recommendation	Medication	
unrelated	[redacted]	[redacted]
Research	unrelated	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
Do NOT Recommend	Ivermectin	
	unrelated	
	[redacted]	
	[redacted]	

unrelated

unrelated

COVID-19 Therapeutics and Prophylactics Advisory Group: Recommendations



Recommendation	Medication	
unrelated	[redacted]	[redacted]
unrelated unrelated	unrelated	[redacted]
unrelated	unrelated	[redacted]
[redacted] unrelated	unrelated	[redacted]
Do NOT Recommend	Ivermectin	
	unrelated	
	[redacted]	
	[redacted]	

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group

February 4, 2021

Agenda

- Minutes
- Conflict of interest
- Ivermectin, unrelated Memo
- unrelated
- Recommendation review process
- unrelated

Minutes

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	January 28, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, Barbara Goodall, Glenn Cox, Amanda Porter, Kenneth Rockwood, Lisa Grandy Allen		

Items	Discussion
- **Minutes**	unrelated
-	unrelated
-	
- **Ivermectin: Recommendation**	Reviewed updated recommendation for ivermectin (minor wordsmithing submitted and incorporated since last meeting): *Do not recommend ivermectin for the treatment or prophylaxis of COVID-19 as part of routine care or in the context of research at this time.* Reviewed updated rationale for ivermectin (qualified supporting evidence in terms of published peer review and where it fits in hierarchy, also added comment

unrelated

To:	NS Health COVID Network
Date:	4 February 2021
From:	Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group
Subject:	Ivermectin, unrelated [redacted]

***Ivermectin Recommendation*: Do not recommend ivermectin for the treatment or prophylaxis of COVID-19 as part of routine care or in the context of research at this time.**

[redacted]
unrelated

Note: Recommendations will be reviewed on a monthly basis by the NS Therapeutics and Prophylactics Advisory Group (review date: Feb 25, 2021).

unrelated

unrelated

[redacted]

Recommendation Review Process

unrelated
unrelated

Recommendation Review

unrelated

[redacted]

[redacted]

- unrelated

[redacted]

MSSU Review
CADTH Advice

unrelated

unrelated

unrelated

unrelated

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group

February 25, 2021

Agenda

- Minutes
- unrelated
- Review recommendations:
  - unrelated
  - Ivermectin
  - unrelated

Minutes

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	February 4, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, Barbara Goodall, Glenn Cox, Amanda Porter, Kenneth Rockwood, Lisa Grandy Allen, Gabrielle Richard		

Items	Discussion
- **Minutes**	unrelated [redacted]
- unrelated [redacted]	[redacted]
[redacted]	[redacted]
- **Ivermectin, unrelated [redacted]: Memo**	Reviewed the drafted memo Tasha had distributed. No suggestions/changes provided – group agreed to formatting and final wording of the recommendations. In order to streamline information presented to COVID Network, suggested to finalize unrelated recommendation and include in same memo.
- unrelated [redacted]	[redacted] k.
- **Recommendation: review process**	Discussed the Advisory Group's procedures for reviewing previous recommendations. The MSSU has been engaged and agreed to complete an evidence review for each medication discussed by the advisory group. They will also complete an updated review every 4 weeks (as long as given sufficient notice). Discussed that

unrelated

COVID-19 Therapeutics and Prophylactics Advisory Group: Recommendations

Recommendation	Medication	Notes
unrelated	[redacted]	[redacted]
unrelated	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
Do NOT Recommend	Ivermectin	
	unrelated	
	[redacted]	
	[redacted]	

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Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group

January 28, 2021

Agenda

- Minutes
- unrelated
- Ivermectin: Recommendation
- unrelated

Ivermectin

Ivermectin: Recommendation

- Do NOT recommend for the treatment or prophylaxis of COVID-19 as part of routine care or in the context of research at this time.
- The advisory group will continue to monitor clinical trials.

Ivermectin: Rationale for decision

- Level of evidence:
  - Published peer reviewed literature is limited to a retrospective observational study. Other agents recommended by the advisory group for use in routine care or in the context of research have peer-reviewed phase 2 or 3 RCT data.
- Lack of federal support:
  - unrelated [redacted]., ivermectin is not being pursued by the federal government, it does not have a conditional approval or a Health Canada interim order, and will not be provided free of charge from the federal government.
- Guideline recommendations:
  - Canadian PHAC/AMMI endorsed guidelines and other international guidelines do not recommend use at this time (e.g.: NIH: The COVID-19 Treatment Guidelines Panel recommends against the use of ivermectin for the treatment of COVID-19, except in a clinical trial).
- Lack of interest locally to explore in the context of research:
  - There are hundreds of agents being investigated for COVID-19. To our knowledge, COVID-19 clinical trials in NS, e.g.: CATCO and CO-VIC, do not have interest in exploring ivermectin use at this time.
- Global supply:
  - Current ivermectin shortage. Potential to deplete supply for established anti-parasitic indications.

unrelated

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Recommendation Review

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group

May 6, 2021

Agenda

- Minutes

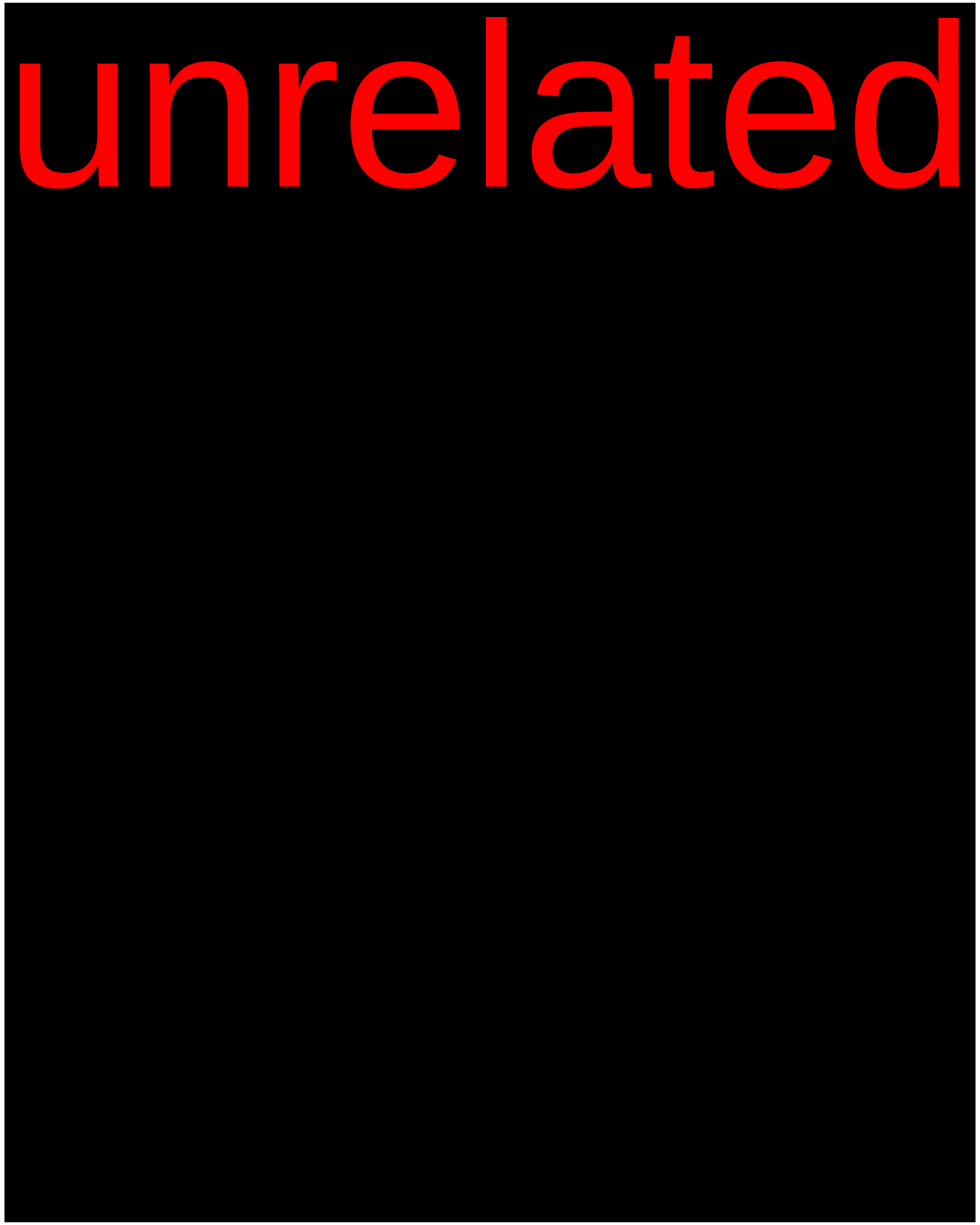
- unrelated

Minutes

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	April 22, 2021	**Meeting Time**	0800-0900
Present	**Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, , Gabrielle Richard, Lisa Grandy Allen, Kenneth Rockwood**		

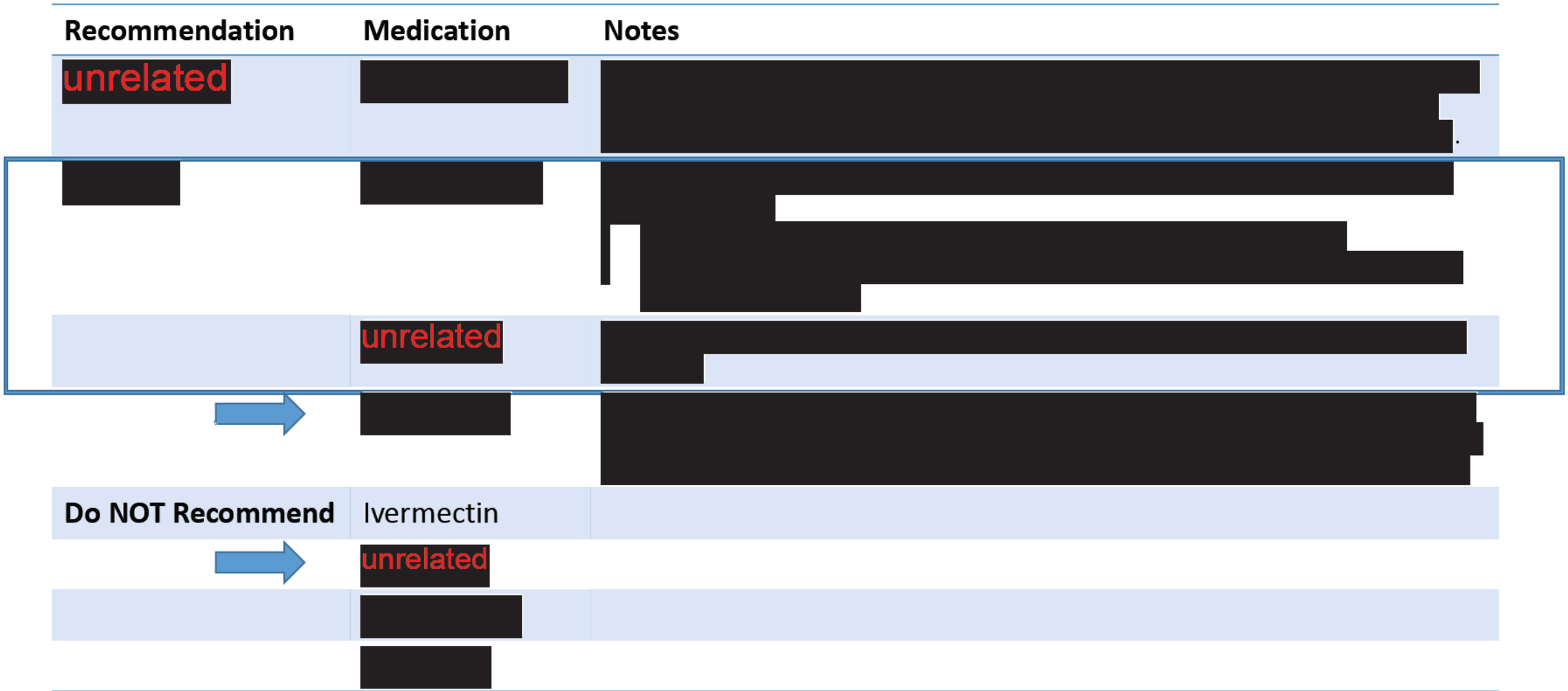
Items	Discussion
[redacted]	[redacted]
Review recommendations: - unrelated - Ivermectin - unrelated	unrelated [redacted] **ivermectin, unrelated** – group agreed no changes to current recommendations necessary.

unrelated



Recommendation Review

NS Health COVID-19 Medication Recommendations



unrelated

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[redacted]

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[redacted]

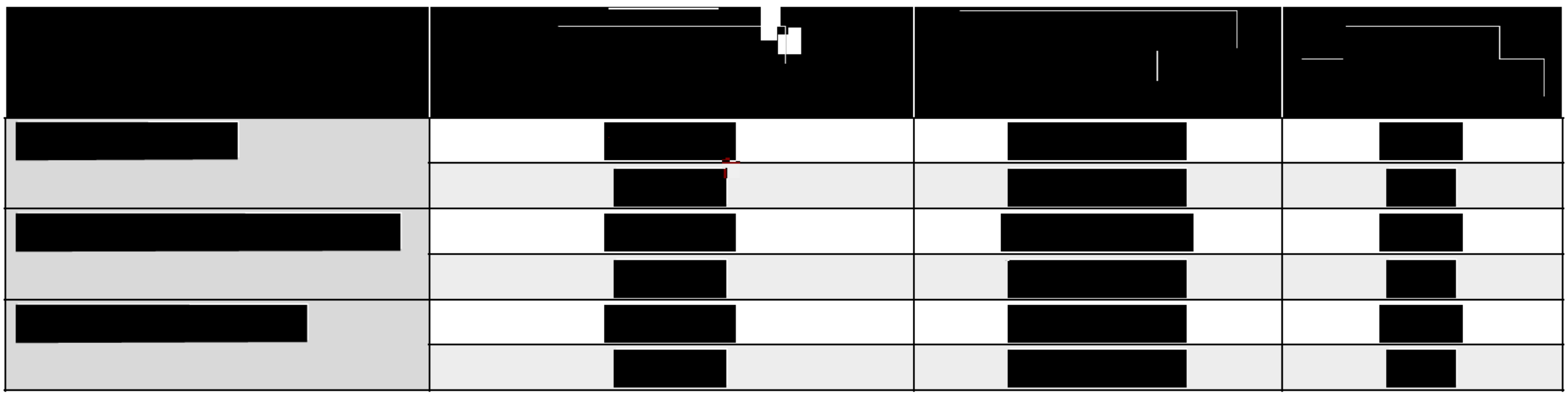
unrelated [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

unrelated

[redacted]



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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

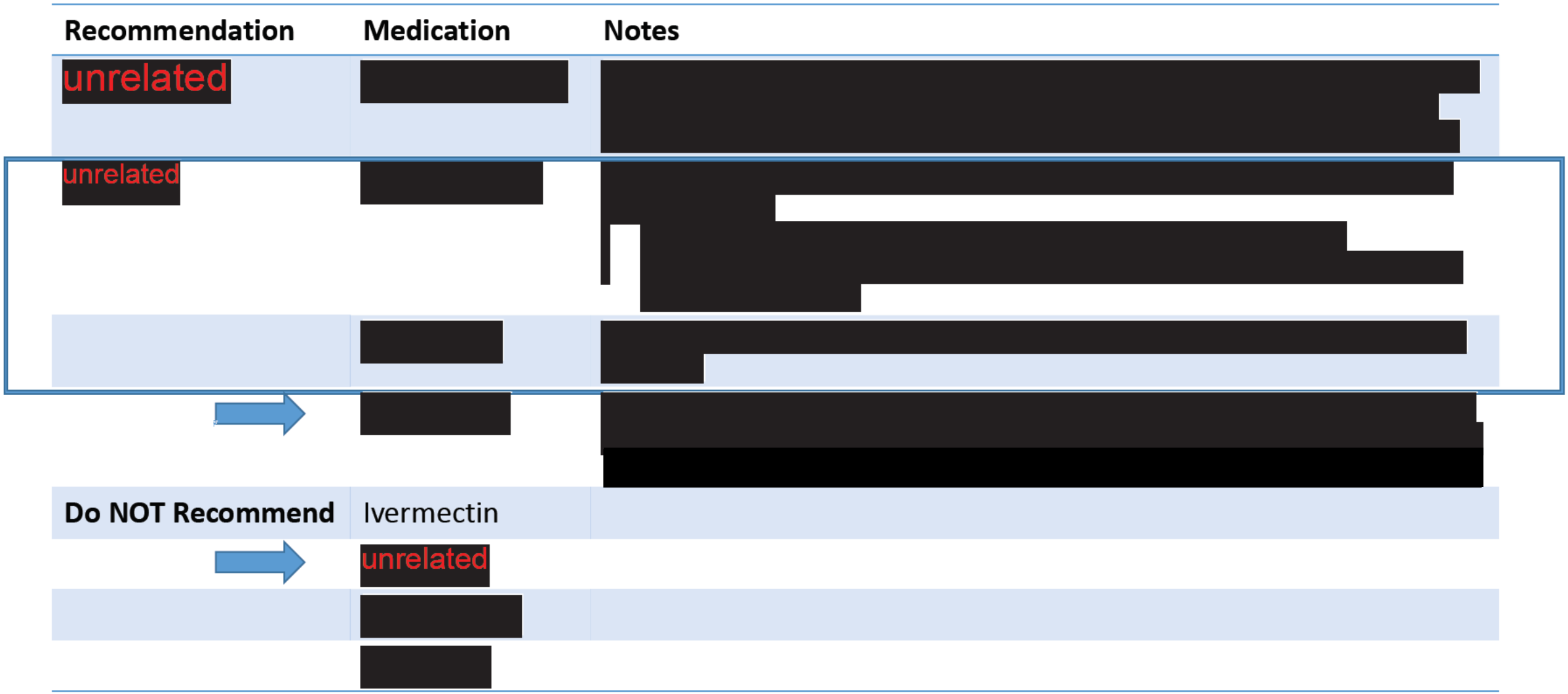
[redacted]


unrelated


unrelated


unrelated

NS Health COVID-19 Medication Recommendations



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NS Health COVID-19 Medication Recommendations

Recommendation	Medication	Notes
Routine Care	unrelated	[redacted]
unrelated	[redacted]	unrelated [redacted]
unrelated	[redacted]	[redacted]
unrelated	unrelated	[redacted]
Do NOT Recommend	Ivermectin	
	unrelated	
	[redacted]	
	[redacted]	

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	December 17, 2020	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Gabrielle Richard, Emma Reid, Barbara Goodall, Glenn Cox, Lisa Grandy Allen		

Items	Discussion
- **Review Minutes**	unrelated [redacted]
- unrelated [redacted]	[redacted]
- unrelated [redacted]	[redacted]
- **Ivermectin**	Will be moved to Dec 18 agenda.

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group

March 11, 2021

Agenda

- Minutes
- unrelated
- Review recommendations:
  -

Minutes

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	February 25, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, Amanda Porter, Gabrielle Richard, Lisa Grandy Allen		

Items	Discussion
- **Minutes**	unrelated [redacted]
[redacted]	[redacted]
- **Review recommendations** - unrelated [redacted], **ivermectin,** unrelated [redacted]	Advisory group due to review recommendations for [redacted] drugs today unrelated [redacted], ivermectin, unrelated [redacted]. MSSU provided summaries for unrelated [redacted], ivermectin unrelated [redacted] (distributed). Members had opportunity to discuss. Kathleen mentioned CADTH Health Technology Review for ivermectin is another helpful summary. No requests or suggestions to change recommendations for unrelated ivermectin, unrelated [redacted] Group agreed to renew current recommendations for these [redacted] agents. unrelated [redacted]

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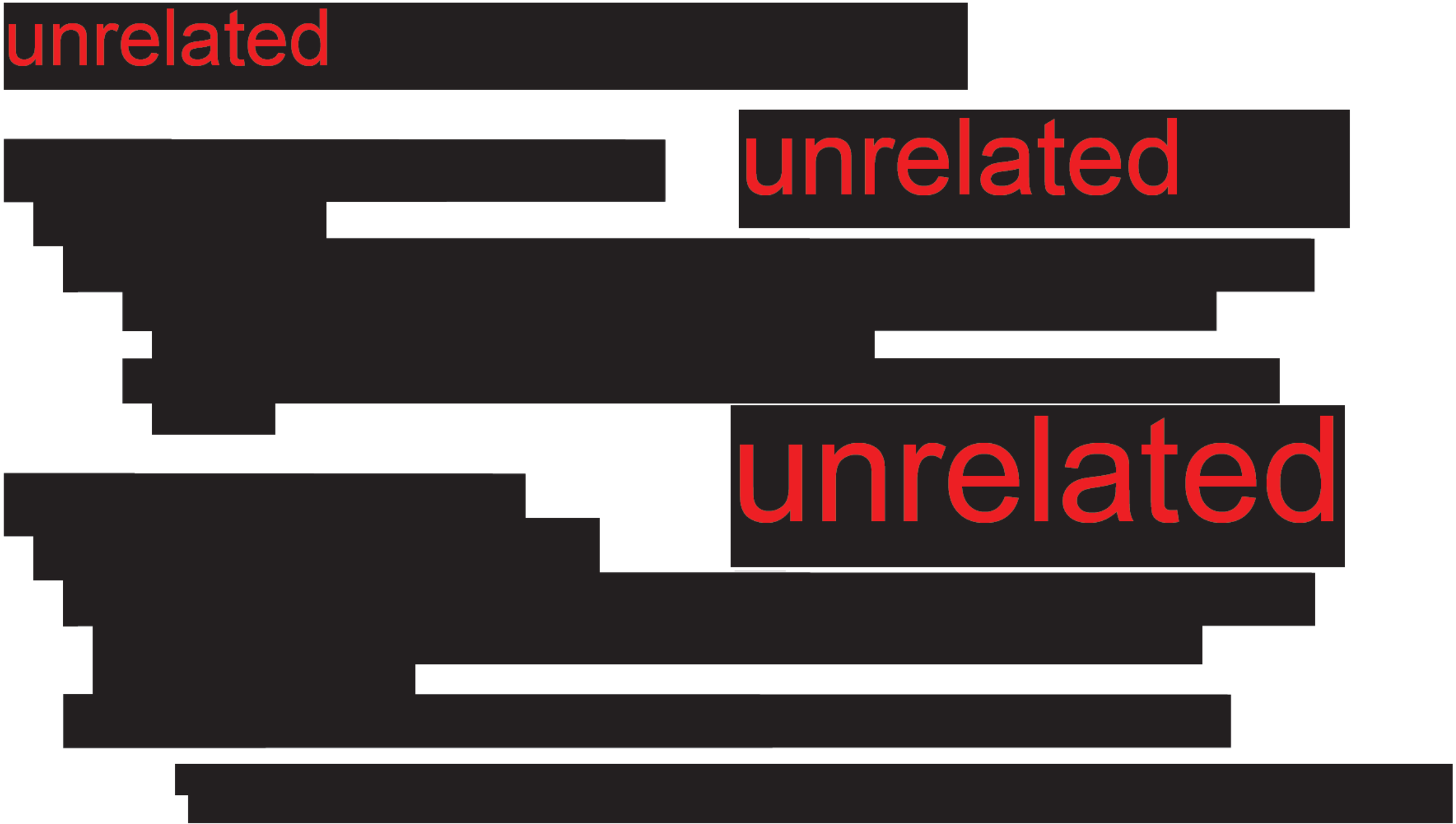
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COVID-19 Therapeutics and Prophylactics Advisory Group: Recommendations

Recommendation	Medication	Notes
unrelated	[redacted]	[redacted]
unrelated	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
Do NOT Recommend	Ivermectin	
	unrelated	
	[redacted]	
	[redacted]	

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	December 17, 2020	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Gabrielle Richard, Emma Reid, Barbara Goodall, Glenn Cox, Lisa Grandy Allen		

Items	Discussion
- **Review Minutes**	unrelated [redacted]
- unrelated [redacted]	[redacted]
[redacted]	[redacted]
- **Ivermectin**	Will be moved to Dec 18 agenda.

OVID-19 Drugs and Biologics Clinical Practice Guidelines Working Group

crobial and Immunomodulatory Therapy in Adult Patients with COVID-19

mendations in this document apply to patients ars of age. Click the medication names in the table the associated science briefs.

Recommendations are based on the best available data and may change as additional data becomes available.

Infectious diseases consultation (where available) is recommended before any investigational treatment is offered to a patient with COVID-19 outside of a clinical trial.

Click for dosing and pharmacologic for medications approved or under management of COVID-19.

F ILLNESS

RECOMMENDATIONS

Patients

ventilatory support, nasal oxygen, ation, invasive tion, or ECMO. usually ensive care

ill Patients

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tients

ot require supplemental baseline status, or other ort. These y managed in an tient setting.

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- **Ivermectin:** There is **insufficient evidence** to support the use of ivermectin in the treatment of critically ill COVID-19 outside of clinical trials or where other indications would justify its use. Individuals who require other established non-COVID indications may use it if they develop COVID-19.

unrelated

- **Ivermectin:** There is **insufficient evidence** to support the use of ivermectin in the treatment of moderately COVID-19 outside of clinical trials or where other indications would justify its use. Individuals who require other established non-COVID indications may use it if they develop COVID-19.

unrelated

- **Ivermectin:** There is **insufficient evidence** to support the use of ivermectin in the treatment of mildly ill p COVID-19 outside of clinical trials or where other indications would justify its use. Individuals who require other established non-COVID indications may use it if they develop COVID-19.

unrelated

ENDED for any patient severity: Hydroxychloroquine or chloroquine

unrelated

Version 2.0 | Upd
https://doi.org/10.4732

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	December 17, 2020	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Gabrielle Richard, Emma Reid, Barbara Goodall, Glenn Cox, Lisa Grandy Allen		

Items	Discussion
- **Review Minutes**	unrelated [redacted]
- [redacted]	unrelated [redacted]
[redacted]	[redacted]
- **Ivermectin**	Will be moved to Dec 18 agenda.

Background Summary

Ivermectin for COVID-19

What is ivermectin?

Ivermectin is an anti-parasite medication that is indicated for use in humans and animals. It has potential antiviral effects against SARS-CoV-2. The FDA issued a special alert in April 2020 warning people about taking ivermectin products intended for animals. Brand name: Stromectol [1]

New in this update (March 16, 2021)

Since the last background summary on remdesivir was completed (Feb 16), the following information is new. New information is also highlighted in blue below.

- The US FDA released a warning statement advising consumers not to use ivermectin as a self-prescribed COVID-19 treatment
- CADTH published a health technology review on ivermectin for COVID-19 on February 17, 2021 (report completed February 8)
- An RCT on ivermectin for COVID-19 was published in JAMA on March 4, 2021 – the first report in a major journal

No formal approval of ivermectin for COVID-19

Ivermectin was approved by Health Canada in 2018 for use in **parasitic infections** [2], but it is **not** currently approved for treating COVID-19. NIH does not currently recommend ivermectin as a COVID-19 treatment, citing insufficient evidence [3]. This perspective is shared by the FDA [4].

On February 4, 2021, Merck (producer of Stromectol) issued a statement advising against the use of ivermectin for COVID-19, due to insufficient evidence. As per Merck: "We do not believe that the data available support the safety and efficacy of ivermectin beyond the doses and populations indicated in the regulatory agency-approved prescribing information." [5]

The US FDA also released a statement on March 5, 2021 advising consumers not to use ivermectin as a self-prescribed COVID-19 treatment. [6]

Evidence syntheses

Alberta Health Services published a very thorough, high-quality rapid evidence report on ivermectin for COVID-19 on February 2, 2021. They concluded that "The studies evaluating ivermectin **treatment** are not high enough quality to properly decide if ivermectin is useful or not. Most studies did not clearly describe the effect of the other medications given to patients or what other factors might influence their findings ("confounding"), did not have an adequate comparator group to assess if there was a difference in patients given ivermectin, or were too small to be sure that any effect of ivermectin seen was real. With respect to ivermectin's ability to **prevent** infection with COVID-19, four low quality studies showed that ivermectin may reduce the risk of COVID-19 infection; however, there were several confounding factors and we don't know what else the study participants were doing that might have influenced their risk of infection. More studies are needed to show if ivermectin can be used to prevent infection." [7]

CADTH published a health technology review on ivermectin for COVID-19 on February 17, 2021 (report completed February 8). It includes one systematic review, one RCT, two non-randomized studies, and two evidence-based guidelines. It does not present strong conclusions. [8]

Epistemonikos lists 16 systematic reviews on ivermectin for COVID-19, most of which are preprints.

Clinical trials

Epistemonikos lists 119 reports of RCTs, of which only 41 have reported data. Almost all of the latter are preprints. A thorough table of 38 ongoing clinical trials (as of February 2, 2021) of ivermectin against COVID-19 is found in Table 7 of the Alberta Health Services rapid evidence report [7].

A **new RCT publication** in JAMA on March 4, 2021 is featured in the study spotlight. [9]

STUDY SPOTLIGHT

RCT in JAMA: Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19 – Mar 4, 2021 [9]

Summary

- Double-blind RCT
- Single site in Colombia
- Treatment: ivermectin, 300 μ g/kg of body weight per day for 5 days or placebo
- Primary outcome: time to resolution of symptoms within a 21-day follow-up period
- 200 patients received treatment vs. 200 in placebo group
- Results: "Among 400 patients who were randomized in the primary analysis population (median age, 37 years [interquartile range {IQR}, 29-48]; 231 women [58%]), 398 (99.5%) completed the trial. The median time to resolution of symptoms was 10 days (IQR, 9-13) in the ivermectin group compared with 12 days (IQR, 9-13) in the placebo group (hazard ratio for resolution of symptoms, 1.07 [95% CI, 0.87 to 1.32]; P = .53 by log-rank test). By day 21, 82% in the ivermectin group and 79% in the placebo group had resolved symptoms. The most common solicited adverse event was headache, reported by 104 patients (52%) given ivermectin and 111 (56%) who received placebo. The most common serious adverse event was multiorgan failure, occurring in 4 patients (2 in each group)."

Conclusions

- **"Among adults with mild COVID-19, a 5-day course of ivermectin, compared with placebo, did not significantly improve the time to resolution of symptoms. The findings do not support the use of ivermectin for treatment of mild COVID-19, although larger trials may be needed to understand the effects of ivermectin on other clinically relevant outcomes."**

Please note: This summary reflects evidence up to and including March 16, 2021 only.

Search Methods

Date searched: 2021-03-16

- Google for news items and clinical trials in progress
- Epistemonikos L·OVE on COVID-19 (manual search)
- Ovid MEDLINE search with built-in COVID-19 filter: (ivermectin or stromectol).ti,ab.

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https://www.merck.com/news/merck-statement-on-ivermectin-use-during-the-covid-19-pandemic/

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Background Summary

Ivermectin for COVID-19

What is ivermectin?

Ivermectin is an anti-parasite medication that is indicated for use in humans and animals. It has potential antiviral effects against SARS-CoV-2. The FDA issued a special alert in April 2020 warning people about taking ivermectin products intended for animals. Brand name: Stromectol [1]

New in this update (April 12, 2021)

Since the last background summary on ivermectin was completed (Mar 16), the following information is new. New information is also highlighted in blue below.

- The European Medicines Agency released a statement that ivermectin not be used to treat COVID-19 due to the limited availability of data
- The World Health Organization released a statement that ivermectin only be used to treat COVID-19 in clinical trials

No formal approval of ivermectin for COVID-19

Ivermectin was approved by Health Canada in 2018 for use in **parasitic infections** [2], but it is **not** currently approved for treating COVID-19. NIH does not currently recommend ivermectin as a COVID-19 treatment, citing insufficient evidence [3]. This perspective is shared by the FDA [4].

The US FDA and the European Medicines Agency also advise consumers not to use ivermectin as a self-prescribed COVID-19 treatment due to the limited availability of data [5, 6]. On March 31, 2021, the World Health Organization (WHO) released a similar statement, noting that ivermectin ought to only be used to treat COVID-19 in clinical trials [7].

On February 4, 2021, Merck (producer of Stromectol) issued a statement advising against the use of ivermectin for COVID-19, due to insufficient evidence. As per Merck: "We do not believe that the data available support the safety and efficacy of ivermectin beyond the doses and populations indicated in the regulatory agency-approved prescribing information." [8]

Evidence syntheses

Epistemonikos lists 19 systematic reviews on ivermectin for COVID-19, most of which are preprints. Notable evidence syntheses are listed below.

1.	Alberta Health Services published a very thorough, high-quality rapid evidence report on ivermectin for COVID-19 on February 2, 2021.	**Conclusions** "The studies evaluating ivermectin **treatment** are not high enough quality to properly decide if ivermectin is useful or not. Most studies did not clearly describe the effect of the other medications given to patients or what other factors might influence their findings ("confounding"), did not have an adequate comparator group to assess if there was a difference in patients given ivermectin, or were too small to be sure that any effect of ivermectin seen was real. With respect to ivermectin's ability to **prevent** infection with COVID-19, four low quality studies showed that ivermectin may reduce the risk of COVID-19 infection; however, there were several confounding factors and we don't know what else the study participants were doing that might have influenced their risk of infection. More studies are needed to show if ivermectin can be used to prevent infection." [9]

2.	CADTH published a health technology review on ivermectin for COVID-19 on February 17, 2021 (report completed February 8). [10]	**Summary** • Health technology review includes evidence from one systematic review, one RCT, two non-randomized studies, and two evidence-based guidelines. **Conclusions** This summary does not present strong conclusions.

Clinical trials

Epistemonikos lists 124 reports of RCTs, of which only 45 have reported data. Almost all of the latter are preprints. A thorough table of 38 ongoing clinical trials (as of February 2, 2021) of ivermectin against COVID-19 is found in Table 7 of the Alberta Health Services rapid evidence report [9].

A **RCT publication** in JAMA on March 4, 2021 is featured in the study spotlight. [11]

STUDY SPOTLIGHT

RCT in JAMA: Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19 – Mar 4, 2021 [11]

Summary

- Double-blind RCT
- Single site in Colombia
- Treatment: ivermectin, 300 μ g/kg of body weight per day for 5 days or placebo
- Primary outcome: time to resolution of symptoms within a 21-day follow-up period
- 200 patients received treatment vs. 200 in placebo group
- Results: "Among 400 patients who were randomized in the primary analysis population (median age, 37 years [interquartile range {IQR}, 29-48]; 231 women [58%]), 398 (99.5%) completed the trial. The median time to resolution of symptoms was 10 days (IQR, 9-13) in the ivermectin group compared with 12 days (IQR, 9-13) in the placebo group (hazard ratio for resolution of symptoms, 1.07 [95% CI, 0.87 to 1.32]; P = .53 by log-rank test). By day 21, 82% in the ivermectin group and 79% in the placebo group had resolved symptoms. The most common solicited adverse event was headache, reported by 104 patients (52%) given ivermectin and 111 (56%) who received placebo. The most common serious adverse event was multiorgan failure, occurring in 4 patients (2 in each group)."

Conclusions

- **"Among adults with mild COVID-19, a 5-day course of ivermectin, compared with placebo, did not significantly improve the time to resolution of symptoms. The findings do not support the use of ivermectin for treatment of mild COVID-19, although larger trials may be needed to understand the effects of ivermectin on other clinically relevant outcomes."**

Please note: This summary reflects evidence up to and including April 12, 2021 only.

Search Methods

Date searched: 2021-04-12

- Google for news items and clinical trials in progress
- Epistemonikos L·OVE on COVID-19 (manual search)
- Ovid MEDLINE search with built-in COVID-19 filter: (ivermectin or stromectol).ti,ab.

References

1. Drugs.com. Ivermectin (systemic) [Internet]. 2020 May 6 [cited 2021 Feb 12]. Available from:

https://www.drugs.com/monograph/ivermectin-systemic.html
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4. U.S. Food & Drug Administration. FAQ: COVID-19 and ivermectin intended for animals [Internet]. 2020 Dec 16 [cited 2021 Feb 12]. Available from: https://www.fda.gov/animal-veterinary/product-safety-information/faq-covid-19-and-ivermectin-intended-animals
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10. Tran K, Loshak H. Ivermectin for the treatment and prevention of COVID-19 [Internet]. Ottawa: CADTH; 2021 Feb 8 [cited 2021 Mar 16]. Available from: https://cadth.ca/sites/default/files/covid-19/RC1336%20-%20Ivermectin%20for%20COVID-19%20v6.4.pdf
11. López-Medina E, López P, Hurtado IC, Dávalos DM, Ramirez O, Martínez E, Díazgranados JA, Oñate JM, Chavarriaga H, Herrera S, Parra B, Libreros G, Jaramillo R, Avendaño AC, Toro DF, Torres M, Lesmes MC, Rios CA, Caicedo I. Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: a randomized clinical trial. JAMA. 2021 Mar 4. doi: 10.1001/jama.2021.3071. Epub ahead of print. PMID: 33662102.

CHEST

Use of Ivermectin Is Associated With Lower Mortality in Hospitalized Patients With Coronavirus Disease 2019

The ICON Study

Juliana Cepelowicz Rajter, MD; Michael S. Sherman, MD, FCCP; Naaz Fatteh, MD; Fabio Vogel, PharmD, BCPS; Jamie Sacks, PharmD; and Jean-Jacques Rajter, MD

BACKGROUND: Ivermectin was shown to inhibit severe acute respiratory syndrome coronavirus 2 replication in vitro, which has led to off-label use, but clinical efficacy has not been described previously.

RESEARCH QUESTION: Does ivermectin benefit hospitalized coronavirus disease 2019 (COVID-19) patients?

STUDY DESIGN AND METHODS: Charts of consecutive patients hospitalized at four Broward Health hospitals in Florida with confirmed COVID-19 between March 15 and May 11, 2020, treated with or without ivermectin were reviewed. Hospital ivermectin dosing guidelines were provided, but treatment decisions were at the treating physician's discretion. The primary outcome was all-cause in-hospital mortality. Secondary outcomes included mortality in patients with severe pulmonary involvement, extubation rates for mechanically ventilated patients, and length of stay. Severe pulmonary involvement was defined as need for $Fio_2 \geq 50\%$, noninvasive ventilation, or invasive ventilation at study entry. Logistic regression and propensity score matching were used to adjust for confounders.

RESULTS: Two hundred eighty patients, 173 treated with ivermectin and 107 without ivermectin, were reviewed. Most patients in both groups also received hydroxychloroquine, azithromycin, or both. Univariate analysis showed lower mortality in the ivermectin group (15.0% vs 25.2%; OR, 0.52; 95% CI, 0.29-0.96; $P = .03$). Mortality also was lower among ivermectin-treated patients with severe pulmonary involvement (38.8% vs 80.7%; OR, 0.15; 95% CI, 0.05-0.47; $P = .001$). No significant differences were found in extubation rates (36.1% vs 15.4%; OR, 3.11; 95% CI, 0.88-11.00; $P = .07$) or length of stay. After multivariate adjustment for confounders and mortality risks, the mortality difference remained significant (OR, 0.27; 95% CI, 0.09-0.80; $P = .03$). One hundred ninety-six patients were included in the propensity-matched cohort. Mortality was significantly lower in the ivermectin group (13.3% vs 24.5%; OR, 0.47; 95% CI, 0.22-0.99; $P < .05$), an 11.2% (95% CI, 0.38%-22.1%) absolute risk reduction, with a number needed to treat of 8.9 (95% CI, 4.5-263).

INTERPRETATION: Ivermectin treatment was associated with lower mortality during treatment of COVID-19, especially in patients with severe pulmonary involvement. Randomized controlled trials are needed to confirm these findings. CHEST 2020; ■(■):■-■

KEY WORDS: hospitalized COVID-19; in-hospital mortality; ivermectin; mechanical ventilation; number needed to treat; severe pulmonary involvement; survival

ABBREVIATIONS: COVID 19 coronavirus disease 2019; IQR interquartile range; MAP mean arteria pressure; SARS CoV 2 severe acute respiratory syndrome coronavirus 2

AFFILIATIONS: From the Broward Health Medical Center, Fort Lauderdale, FL (J. C. R., N. F., F. V., J. S., and J. J. R.); the Drexel University College of Medicine (M. S. S.),

FLA 5.6.0 DTD ■ CHEST3692_proof ■ 27 October 2020 ■ 4:10 am ■ EO: CHEST 20 3168

Take-home Point

STUDY QUESTION: Is ivermectin associated with lower mortality rate in patients hospitalized with coronavirus disease 2019 (COVID-19)?

RESULTS: A retrospective cohort study of consecutive patients hospitalized with confirmed severe acute respiratory syndrome coronavirus 2 infection at a four-hospital consortium in South Florida. Analysis showed statistically significant lower mortality rates in the group treated with ivermectin as compared with the group treated with usual care (15.0% vs 25.2%).

INTERPRETATION: Ivermectin was associated with lower mortality during treatment of COVID-19 patients, especially in patients who required higher inspired oxygen or ventilatory support.

Ivermectin previously was studied as a therapeutic option for viral infections, with data showing some in vitro activity against a broad range of viruses, including HIV, dengue, influenza, and Zika virus, likely through inhibition of IMP α/β1-mediated nuclear import of viral proteins.[1,2] Wagstaff et al[3] demonstrated that ivermectin was a potent in vitro inhibitor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), showing a 99.8% reduction in viral RNA after 48 h. Reports can be found on the Internet of physicians worldwide treating Coronavirus disease 2019 (COVID-19) empirically with ivermectin since late April 2020.

According to ClinicalTrials.gov, currently 37 studies are investigating the usefulness of ivermectin in COVID-19. However, in vivo efficacy of ivermectin in SARS-CoV-2 infection in humans has not been reported previously.

In the late 1970s, ivermectin was developed as a new class of drug to treat parasitic infections. Initially used in veterinary medicine, it soon was found to be safe and effective in humans. It has been used successfully to treat onchocerciasis and lymphatic filariasis in millions of people worldwide as part of a global drug donation program. About 3.7 billion doses of ivermectin have been distributed in mass drug administration campaigns globally over the past 30 years. Presently, ivermectin is approved for use in humans in several countries to treat onchocerciasis, lymphatic filariasis, strongyloidiasis, and scabies.[4]

Based on the data drug safety sheet for ivermectin (New Drug Application Identifier: 50-742/S-022), side effects were uncommon and limited. Reported side effects with more than 1% occurrence included elevation in alanine aminotransferase and aspartate aminotransferase (2%), nausea (2%), diarrhea (2%), decreased leukocyte count (3%), peripheral edema (3%), tachycardia (3%), dizziness (3%), and pruritus (3%). A pharmacokinetic study of 166 patients reported side effects of headache (6%), dysmenorrhea (5.5%), upper respiratory infection symptoms (1.8%), and diarrhea (1.8%).[5]

Methods

Patients

Sequentially consecutive hospitalized patients at four Broward Health associated hospitals in South Florida with laboratory confirmed infection with SARS CoV 2 during their admission were reviewed in this study. The list of confirmed cases was provided by the hospitals' epidemiology departments. Enrollment dates ranged from March 15, 2020, through May 11, 2020. Confirmatory testing was performed by nasopharyngeal swab using a Food and Drug Administration Emergency Use Authorized COVID 19 molecular assay for the detection of SARS CoV 2 RNA. Patients younger than 18 years and those who were pregnant or incarcerated were excluded from data collection based on institutional review board requirements. Patients who had at least two separate admissions placing them in both groups also were excluded.

Study Procedures

Records were abstracted by four of the authors, and all data were reviewed subsequently and confirmed by the lead author. Baseline data were collected at the time of ivermectin administration for the ivermectin group; for the usual care group, baseline was either the time of administration of hydroxychloroquine or, if not used, at the time of admission. Information collected included COVID 19 testing results, patient demographics, pre existing comorbid conditions, initial vital signs, laboratory results, and the use of corticosteroids, hydroxychloroquine, and azithromycin to describe the cohort and to identify potential confounders between groups. Severity of pulmonary involvement was assessed at the time of baseline data collection and was

Philadelphia, PA; and the Florida International University (J. J. R.), Miami, FL.

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CORRESPONDENCE TO: Jean Jacques Rajter, MD; e mail: covid19@pcflorida.com

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categorized as severe or nonsevere. Patients were considered to have severe pulmonary involvement if they required an F_{IO_2} of 50% or more, high flow nasal oxygen, noninvasive ventilation, or intubation and mechanical ventilation. The nonsevere pulmonary criteria encompassed patients who required no supplemental oxygen or low F_{IO_2} (ie, venturi mask 40% or less or up to 6 L/min of low flow nasal cannula), independent of laboratory findings.

Patients were categorized into two treatment groups based on whether they received ivermectin at any time during the hospitalization. Patients in the ivermectin group received at least one oral dose of ivermectin at 200 μg/kg in addition to usual clinical care. A second dose could be given at the discretion of the treating physician at day 7 of treatment. Ivermectin is not currently approved by the Food and Drug Administration for COVID 19 treatment. The decision to prescribe ivermectin, hydroxychloroquine, azithromycin, or other medications was at the discretion of the treating physicians; however, hospital guidelines were established for the safe use and dosing of these agents. These guidelines included a baseline ECG and mandatory cardiac and QTc monitoring for patients receiving hydroxychloroquine (alone or in combination with azithromycin), avoidance of azithromycin if patient's baseline QTc was more than 460 msec, and discontinuation of hydroxychloroquine if a concerning elevation in QTc occurred or if the patient's cardiologist recommended discontinuation. Oxygen and ventilatory support were applied per the customary care. Empiric use of ivermectin was given explicitly for COVID 19.

Outcomes

The primary outcome was all cause in hospital mortality. A patient was considered a survivor if he or she left the hospital alive or if his or her status in the hospital changed from active care to awaiting transfer to a skilled facility. Two consecutive nasopharyngeal swab specimens showing negative results for SARS CoV 2, collected ≥ 24 h apart, were necessary for a patient to be accepted to the local skilled nursing facilities.

Secondary outcomes included subgroup mortality of patients with severe pulmonary involvement, extubation rates for patients requiring mechanical ventilation, and length of hospital stay. Length of stay was calculated from day of admission to either the day of discharge or to patient death.

Statistical Analysis

Univariate analysis of the primary mortality outcome and comparisons between treatment groups were determined by the Student t test for parametric continuous variables or the Mann Whitney U test for nonparametric continuous variables as appropriate, and by the Pearson χ^2 test for categorical variables. The method of Hodges Lehman was used to estimate median differences with 95% CIs.

To adjust for confounders and between group differences, a multivariate analysis was performed using stepwise binary logistic regression. Patient variables included in the analysis were age, sex, comorbidities of diabetes, chronic lung disease, cardiovascular disease, and hypertension, smoking status, severity of pulmonary involvement, need for mechanical ventilation at study entry, BMI, peripheral white blood count, absolute lymphocyte count, and use of corticosteroids based on bivariate associations within our data, a priori plausibility, and documented associations with mortality from previous studies. Adjusted ORs with 95% CIs were computed to show level of certainty. Analyses were based on nonmissing data, and missing data were not imputed. Missingness of 1% was found for peripheral WBC count, 5% for smoking status, and 7% for absolute lymphocyte count.

We performed a secondary analysis using propensity score matching to reduce the effects of confounding and the likelihood of selection bias. Propensity matching was performed using a nearest neighbor algorithm with 1:1 matching without replacement and a caliper distance of less than 0.2. Variables for propensity scoring included those variables from the univariate between groups analysis of the unmatched cohort that had a P value of less than .2 (age, sex, pulmonary condition, hypertension , HIV status, severe pulmonary presentation, and exposure to corticosteroids, hydroxychloroquine, or azithromycin). Race, WBC count, absolute lymphocyte count, and need for mechanical ventilation before or on the day of study entry also were added as potential clinical confounders.

All tests were two sided and a P value $< .05$ was considered statistically significant. Statistical analyses were conducted using IBM SPSS version 26.0 software, R version 3.5.3 software (R Foundation for Statistical Computing), and SPSS PS matching software (sourceforge.net).

This study was conducted in accordance with tenets of the amended Declaration of Helsinki. The protocol was approved by the institutional review board for the Broward Health Hospital System (Identifier: 2020 034 BHMC). The authors assume responsibility for the accuracy and completeness of the data and analyses, as well as for the fidelity of the study.

Results

Characteristics of the Patients

Three hundred seven patients were admitted for COVID-19 during the period studied. Four patients were not reviewed because of multiple admissions, 11 did not have COVID-19 confirmed at the time of the study, and 12 were excluded because their age was younger than 18 years, they were pregnant, or they were incarcerated. The remaining cohort of 280 patients comprised 173 treated with ivermectin and 107 in the usual care group. Most patients received a single dose of ivermectin; however, 13 patients received a second dose of ivermectin for ongoing signs or symptoms on day 7 of treatment. Follow-up data for all outcomes were available through May 19, 2020. No patients were lost to follow-up for the primary outcome. At the time of analysis, all patients in both groups had met the end point of death, discharge alive, or awaiting transfer to a skilled facility. Of those awaiting transfer, in the control group, one patient was awaiting transfer to hospice because of an unrelated terminal illness and one patient was awaiting negative COVID-19 test results to proceed with unrelated surgery. In the ivermectin group, five patients were in stable condition, awaiting transfer to skilled facility or rehabilitation, and one patient was improving clinically.

Baseline characteristics and between-group comparisons for unmatched and propensity-matched cohorts are shown in Table 1. Before matching, hypertension and

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TABLE 1] Patient Characteristics by Treatment Group

Demographic Characteristic	Unmatched Cohort				Matched Cohort			
	Total (N = 280)	Usual Care (n = 107)	Ivermectin (n = 173)	*P* Value	Total (N = 196)	Usual Care (n = 98)	Ivermectin (n = 98)	*P* Value
Age, y	59.6 ± 17.9	58.6 ± 18.5	60.2 ± 17.6	.45	59.6 ± 17.5	59.04 ± 17.7	60.07 ± 17.4	.68
Female sex	127 (45.4)	43 (41.2)	84 (48.6)	.17	78 (39.8)	39 (39.8)	39 (39.8)	1.0
Race or ethnicity			.36				1.0	
Black	153 (54.6)	55 (51.4)	98 (56.6)		108 (55.1)	54 (55.1)	54 (55.1)	
White	76 (27.1)	35 (32.7)	41 (23.7)		55 (28.1)	27 (27.6)	28 (28.6)	
Hispanic	33 (11.7)	12 (11.2)	21 (12.1)		23 (11.7)	12 (12.5)	111 (11.2)	
Other or not identified[a]	13 (4.6)	5 (4.7)	13 (7.5)		10 (5.1)	5 (5.1)	5 (5.1)	
Current or former smoker	46/255 (18.0)	22/99 (22.3)	24/156 (15.6)	.40	31/180 (22.2)	20/90 (22.2)	11/90 (12.2)	.11
No. of comorbidities	1.66 ± 1.34	1.60 ± 1.46	1.70 ± 1.27	.57	1.56 ± 1.33	1.58 ± 1.43	1.53 ± 1.22	.79
Diabetes	90 ± 32.1	31 ± 29.0	59 ± 34.1	.37	59 ± 30.1	30 ± 30.6	29 ± 29.6	.88
Cardiac	43 ± 15.4	18 ± 16.8	25 ± 14.5	.59	27 ± 13.8	16 ± 16.3	11 ± 11.2	.30
Pulmonary	28 ± 10.0	14 ± 13.1	14 ± 8.9	.18	18 ± 10.1	10 ± 10.2	8 ± 8.2	.62
Obesity	114 ± 40.7	42 ± 39.3	72 ± 41.6	.70	79 ± 40.3	39 ± 39.8	40 ± 40.1	.88
Renal	24 ± 8.6	10 ± 9.4	14 ± 8.1	.72	16 ± 8.2	9 ± 9.2	7 ± 7.1	.60
Cancer	17 ± 6.1	8 ± 7.5	9 ± 5.2	.44	14 ± 7.1	7 ± 7.1	7 ± 7.1	1.00
Hypertension	50 ± 17.9	13 ± 12.2	37 ± 21.4	.05	26 ± 13.2	12 ± 12.2	14 ± 14.3	.67
Neurologic	28 ± 10.0	8 ± 7.5	20 ± 11.6	.27	17 ± 8.7	8 ± 8.2	9 ± 9.2	.80
HIV infection	9 ± 3.2	1 ± 1	8 ± 4.6	.09	3 ± 1.5	1 ± 1.0	2 ± 2.0	.56
Thyroid	23 ± 8.2	7 ± 6.6	16 ± 9.3	.42	15 ± 7.7	7 ± 7.1	8 ± 8.2	.79
BMI	30.0 ± 7.8	29.8 ± 7.2	30.1 ± 8.2	.81	29.4 ± 6.6	29.4 ± 6.3	29.4 ± 6.9	.95
Pulmonary severity				.46				
Severe	75 (26.8)	26 (24.3)	49 (28.3)	.12	47 (24.0)	22 (22.4)	25 (25.5)	.62
Intubated at study entry	38 (13.6)	15 (14.0)	23 (13.3)	.86	25 (12.8)	11 (11.2)	14 (14.3)	.52
Heart rate	86.0 (75.0-98.0)	86.0 (74.0-97.0)	86.0 (75.5-98.0)	.65	85.5 (74.0-98.0)	86.0 (73.0-97.5)	85.0 (74-98.0)	.88
MAP (mm Hg)	93 (82.3-103.0)	90 (81.0-103.0)	94 (83-103)	.24	92.5 (82.0-103.0)	91.0 (81.0-103.2)	93.0 (82.0-103.0)	.74
MAP ≤ 70 mm Hg	13/260 (5.0)	6/89 (6.7)	7/171 (4.1)	.35	7 (3.6)	4 (4.1)	3 (3.1)	.70
Corticosteroid	90 (32.1)	21 (19.6)	69 (39.8)	.001	46 (23.2)	21 (21.4)	25 (25.5)	.5

(Continued)

TABLE 1 (*Continued*)

Demographic Characteristic	Unmatched Cohort				Matched Cohort			
	Total (N = 280)	Usual Care (n = 107)	Ivermectin (n = 173)	*P* Value	Total (N = 196)	Usual Care (n = 98)	Ivermectin (n = 98)	*P* Value
Hydroxychloroquine	260 (92.9)	104 (97.2)	156 (90.2)	.03	190 (96.9)	95 (96.9)	95 (96.9)	1.00
Azithromycin	243 (86.7)	99 (92.5)	144 (83.2)	.03	177 (90.3)	90 (91.8)	87 (88.7)	.47
Peripheral WBC count (× 10^9/L)	7.3 (5.6-10.2; n = 277)	7.0 (5.7-8.9; n = 106)	7.6 (5.5-11.1; n = 171)	.41	6.9 (5.3-9.3)	7.0 (5.8-9.0)	6.9 (5.2-9.8)	.69
Lymphocyte count (× 10^9/L)	1.15 (0.78-1.56; n = 260)	1.14 (0.84-1.49; n = 102)	1.20 (0.77-1.67; n = 158)	.62	1.13 (0.77-1.52)	1.15 (0.87-1.45)	1.19 (0.75-1.57)	.88

Data are presented as No. (%), mean ± SD, or median (interquartile range), unless otherwise indicated. MAP = mean arterial pressure.
[a]Asian, Native American, Pacific Islander, or not identified.

corticosteroid use were more prevalent in the ivermectin group, whereas the use of hydroxychloroquine and hydroxychloroquine plus azithromycin were higher in the usual care group.

Propensity score matching created a total of 98 matched pairs. After matching, no statistically significant differences were found between the two groups. Eight patients in the propensity-matched group received a second dose of ivermectin on day 7.

Outcomes

Unadjusted outcomes for the unmatched cohort and outcomes in the propensity-matched cohort are shown in Table 2. For the unmatched cohort, overall mortality was significantly lower in the ivermectin group than in the usual care group (15.0% vs 25.2% for ivermectin and usual care, respectively; $P = .03$). Mortality also was lower for ivermectin-treated patients in the subgroup of patients with severe pulmonary involvement (38.8% vs. 80.7% for ivermectin and usual care, respectively; $P = .001$). On univariate analysis, patients receiving corticosteroids showed a higher mortality than those who did not receive corticosteroids (30.0% vs 13.7%; OR, 2.7; 95% CI, 1.47-4.99; $P = .001$); however, corticosteroids were more likely to have been prescribed for severe patients (58.6% vs 22.4% for severe and nonsevere, respectively; OR, 4.91; 95% CI, 2.78-8.63; $P < .001$).

Results were similar, with lower mortality in the ivermectin-treated patients for the matched cohort for the group as a whole and for the subgroup with severe pulmonary involvement (Table 2). In the matched cohort, ivermectin was associated with an absolute risk reduction of 11.2% (95% CI, 0.38%-22.1%) and a corresponding number needed to treat of 8.9 (95% CI, 4.5-263) to prevent one death. We found no difference in median hospital length of stay or in extubation rates in either the unmatched or matched cohorts. Of note, 1 of the 13 patients who received a second dose of ivermectin died; this patient was not in the propensity-matched cohort.

Multivariate analysis was performed on the unmatched cohort, adjusting for demographic factors and between-group differences in mortality risks. Independent predictors of in-hospital mortality included treatment group, age, severe pulmonary disease category, and reduced lymphocyte count (Table 3). Because race was not a significant predictor after adjustment, a further analysis was performed that showed that White patients were significantly older than Black patients (mean age,

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TABLE 2] Univariate Clinical Outcomes by Treatment Group

Outcome	Unmatched Cohort				Matched Cohort			
	Control Subjects (n = 107)	Ivermectin (n = 173)	OR or Difference (95% CI)	*P* Value	Control Subjects (n = 98)	Ivermectin (n = 98)	OR or Difference (95% CI)	*P* Value
Mortality	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
Total	27 (25.2)	26 (15.0)	0.52 (0.29-0.96)	0.03	24 (24.5)	13 (13.3)	0.47 (0.22-0.99)	0.045
Severe	21/26 (80.7)	19/49 (38.8)	0.15 (0.05-0.47)	0.001	18/22 (81.8)	8/25 (32.0)	0.27 (0.08-0.92)	0.002
Nonsevere	6/81 (7.4)	7/124 (5.6)	0.75 (0.24-2.3)	0.61	6/76(7.9)	4/74 (5.4)	0.97 (0.61-1.54)	0.78
Successful extubation	4/26 (15.4)	13/36 (36.1)	3.11 (0.88-11.00)	0.07	3/22 (15.4)	7/18 (38.9)	1.91 (0.43-8.46)	0.14
Length of stay	7.0 (4.0-10.0)	7.0 (4.0-13.3)	0 (-1 to 2)	0.34	7.0 (4.0-10.0)	7.0 (3.0-13.0)	0 (-2 to 1)	0.88

Data are presented as No./Total No. (%) or median (interquartile range) unless otherwise indicated

66.8 vs 59.1 y; mean difference, 7.7 y; 95% CI, 3.0-12.4 y; $P = .001$) and that Hispanic patients (mean age, 49.8 y; mean difference, 17.0 y; 95% CI, 9.6-24.4 y; $P < .001$).

Discussion

In this multihospital retrospective cohort study, we observed a significant association of ivermectin with improved survival for patients admitted with COVID-19. This association also was seen in the subset of patients with severe pulmonary disease. These findings were confirmed after multivariate adjustment for comorbidities and differences between groups, and also in a propensity score-matched cohort. Similar to other studies, we noted that older age, cardiac disease, current or former smoking, more severe pulmonary involvement at presentation, higher WBC counts, and lower lymphocyte counts emerged as risk markers for in-hospital mortality.

The overall mortality, and mortality in intubated patients, in our usual care group was similar to what was reported in previous studies. Richardson et al[6] reported an overall mortality of 21% in a New York City cohort, with a mortality of 88% in intubated patients. Zhou et al[7] reported 28.2% mortality in a cohort of hospitalized patients in Wuhan, China; the intubated patients showed a mortality of 96.9%. In contrast to Magagnoli et al,[8] we did not see a higher mortality effect Q13 for hydroxychloroquine. This may have been because of the small number of patients who were not treated with this agent; thus, our study was underpowered to detect a difference in mortality from hydroxychloroquine treatment. We also hypothesize that precautionary measures in the hospitals' protocol for hydroxychloroquine use could have prevented fatal arrhythmias from developing. These included baseline electrocardiography and daily QTc monitoring by telemetry for any patient receiving hydroxychloroquine or combination therapy, avoidance of azithromycin if patient's baseline QTc was more than 460 msec, and discontinuation of hydroxychloroquine if a concerning elevation in QTc occurred or if the patient's cardiologist recommended discontinuation. In contrast to Horby et al,[9] we did not find a mortality benefit for patients who were prescribed corticosteroids in our multivariate analysis, which included several severity covariates. These findings are likely explainable by physicians' choice to reserve use of corticosteroids for the most seriously ill patients, because the study was performed before the results of the RECOVERY trial were Q14 published.[9]

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TABLE 3] Multivariate Analysis of Factors Associated With Mortality

Variable	OR (95% CI)	*P* Value
Treatment group	. . .	. . .
Ivermectin	0.27 (0.09-0.80)	.03
Control subject	Reference	. . .
Age	1.05 (1.02-1.09)	.003
Sex	. . .	. . .
Female	0.42 (0.24-1.82)	.42
Male	Reference	. . .
Smoking status	. . .	. . .
Current or former smoker	3.49 (0.71-17.32)	.13
Nonsmoker	Reference	. . .
Race	. . .	.18
Black	0.64 (0.21-1.94)	.43
Hispanic	0.14 (0.02-1.22)	.08
Other	0.62 (0.05-7.92)	.71
White	Reference	. . .
Comorbidities	. . .	. . .
Diabetes	1.17 (0.39-3.55)	.78
Cardiac	1.51 (0.43-5.22)	.52
Pulmonary	0.15 (0.20-1.84)	.15
Hypertension	0.72 (0.17-3.08)	.66
No comorbidities	Reference	. . .
BMI	0.97 (0.89-1.07)	.58
Severe presentation	11.41 (3.42-38.09)	< .001
Intubated at study entry	2.96 (0.73-12.06)	.13
MAP ≤ 70 mm Hg	1.82 (0.17-19.1)	.62
Corticosteroid treatment	1.71 (0.57-5.16)	.34
Peripheral WBC count	1.08 (0.96-1.23)	.22
Lymphocyte count	3.65 (1.25-10.60)	.02

MAP = mean arterial pressure.

We also did not confirm a higher risk of mortality in Black patients in comparison with White patients after controlling for age. Prior reports showed lower survival rates among Black and Hispanic patients[10]; however, Price et al[11] also found no racial differences in mortality. In our hospital population, White patients were significantly older, which is reflective of our catchment area and may be responsible for the discrepancy.

We did not observe a significant difference in hospital length of stay between the groups (median, 7 days for both groups) despite the lower mortality. Possible explanation could include delay in discharging patients to other facilities (skilled nursing facilities, inpatient rehabs, and so forth) because of a delay in obtaining required repeat COVID-19 testing results. Patients who died were included in length-of-stay measurements.

Use of mechanical ventilation was not adopted as an outcome of interest, because guidelines and practice patterns for intubation criteria changed throughout the length of the study. We were unable to determine ICU length of stay and ventilatory-free days in the ICU because overflow conditions during the pandemic placed critically ill patients in the emergency room and other non-ICU environments, and therefore, we could not determine ICU stay accurately. We did not find a lower mortality in the subgroup of nonsevere patients treated with ivermectin; however, our study was not powered to assess these differences because the overall mortality in nonsevere patients was low. Similarly, the study was not powered to determine whether extubation rates were higher in the ivermectin group. These should be investigated further with a larger randomized controlled trial.

Interpretation

Our study has several limitations. Because of the retrospective observational nature of the study, despite adjustment for known confounders and propensity score matching, we cannot exclude the possibility of unmeasured confounding factors. Although more of the control group was enrolled in the first weeks of the study, suggesting the possibility of timing bias, this may be offset by preferential treatment of more severe patients with ivermectin early in the study because of low initial availability. We also did not find consistently different mortality outcomes with time over the short duration of this study. We also did not find evidence of immortal time bias, because only one of the control patients died fewer than 5 days from admission, the average time from admission to death was 11 days, and the vast majority of patients received ivermectin in 2 days or fewer. If we omit the patient with potential immortal time from the analysis, the mortality difference remains significant in both unmatched (15.0% vs 24.5% for ivermectin and usual care, respectively; $P < .05$) and matched (12.4% vs 25.0% for ivermectin and usual care, respectively; $P < .03$) cohorts. Most of the studied patients received hydroxychloroquine with or without azithromycin, and we are unable to determine whether these medications had an added benefit or whether mortality would have been better in both groups without these agents.

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We showed that ivermectin administration was associated significantly with lower mortality among patients with COVID-19, particularly in patients with more severe pulmonary involvement. Interpretation of these findings are tempered by the limitations of the retrospective design and the possibility of confounding. Appropriate dosing for this indication is not known, nor are the effects of ivermectin on viral load or in patients with milder disease. Further studies in appropriately designed randomized trials are recommended before any conclusions can be made.

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Effectiveness of Ivermectin as add-on Therapy in COVID-19 Management

(Pilot Trial)

Faiq I Gorial [1*], Sabeeh Mashhadani [2] , Hend M Sayaly [3], Basim Dhawi Dakhil [4], Marwan M.AlMashhadani[5] , Adnan M Aljabory [6] , Hassan M Abbas [7] , Mohammed Ghanim 8, Jawad I Rasheed [9]

[1, 2, 6] Department of Medicine, College of Medicine, University of Baghdad, Baghdad, Iraq
[3,4,5,7,8,9] Medical City Teaching Hospital, Baghdad, Iraq

- Corresponding author email: faiqig@gmail.com

Abstract

Background: To date no effective therapy has been demonstrated for COVID-19. In vitro, studies indicated that ivermectin (IVM) has antiviral effect.

Objectives: To assess the effectiveness of ivermectin (IVM) as add-on therapy to hydroxychloroquine (HCQ) and azithromycin (AZT) in treatment of COVID-19.

Methods: This Pilot clinical trial conducted on hospitalized adult patients with mild to moderate COVID-19 diagnosed according to WHO interim guidance. Sixteen Patients received a single dose of IVM 200Mcg /kg on admission day as add on therapy to hydroxychloroquine (HCQ)and Azithromycin (AZT) and were compared with 71 controls received HCQ and AZT matched in age, gender, clinical features, and comorbidities.

The primary outcome was percentage of cured patients, defined as symptoms free to be discharged from the hospital and 2 consecutive negative PCR test from nasopharyngeal swabs at least 24 hours apart. The secondary outcomes were time to cure in both groups and evaluated by measuring time from admission of the patient to the hospital till discharge.

Results: Of 87 patients included in the study,t he mean age ± SD (range) of patients in the IVM group was similar to controls [44.87 ± 10.64 (28-60) vs 45.23 ± 18.47 (8-80) years, p=0.78] Majority of patients in both groups were male but statistically not significant [11(69%) versus 52 (73%), with male: female ratio 2.21 versus 2.7-, p=0.72)

All the patients of IVM group were cured compared with the controls [16 (100 %) vs 69 (97.2 %)]. Two patients died in the controls. The mean time to stay in the hospital was significantly lower in IVM group compared with the controls (7.62 ± 2.75 versus 13.22 ±5.90 days, p=0.00005, effect size= 0.82). No adverse events were observed

Conclusions : Add-on use of IVM to HCQ and AZT had better effectiveness, shorter hospital stay, and relatively safe compared with controls. however, a larger prospective study with longer follow up may be needed to validate these results.

Keywords: Ivermectin, hydroxychloroquine, azithromycin, COVID-19,

Introduction

A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in December 2019 as the cause of a respiratory illness designated coronavirus disease 2019, or Covid-19 with significant public health impact (1). Several therapeutic agents have

been evaluated for the treatment of Covid-19, however, none have yet been shown to be effective (2,3)

Recently some reports on HCQ [4-6], Azithromycin [7] and Ivermectin [8] have shown therapeutic effects against novel coronavirus infection. Ivermectin is an antiparasitic drug with a broad spectrum antiviral effect Recently, in vitro study showed reduction of viral RNA in Vero-hSLAM cells 2 hours postinfection with SARS-CoV-2 clinical isolate Australia/VIC01/2020 (8). The authors hypothesized that the effect was likely due to the inhibition of IMP α/β1- mediated nuclear import of viral proteins.

Because of the broad spectral antiviral activities of IVM and it is safety profile, It may offer a therapeutic potential to COVID-19. This study was designed to assess effectiveness and safety of add-on use of IVM to HCQ and AZT in COVID 19 patients.

Patients and Methods

Study design

This pilot interventional single center study with a synthetic controlled arm (SCA) was conducted at Al-Shifa'a Hospital Center from first of April to the end of May 2020. Synthetic controlled arm was used due to difficulty of using placebo for our patients and the strong preference for the investigational product in this pandemic Covid-19 disease to improve drug development and reduce patients burden. SCA is an external control constructed from patient-level data from previous patients records to match the baseline characteristics of the patients in an investigational group and augment a single-arm trial to estimate treatment effects. The SCA in this trial included previous patients who were treated by HCQ and AZT according to the Iraqi Ministry of Health protocols for treatment of covid-19.

Ethical approval of the study was taken in accordance with the Declaration of Helsinki and its amendments and the Guidelines for Good Clinical Practices issued by the Committee of Propriety Medicinal Product of the European Union from Iraqi ministry of health and the study was registered with No. 497 at April 2020. Also, this study was registered in ClinicalTrials.gov website under identifier number: NCT04343092. Informed consent was obtained from the participants to admit the study.

Participants

Inclusion criteria

Inclusion criteria were the following: 1) men and women with age at least 18 years 2) mild to moderate COVID-19 diagnosed by positive polymerase chain reaction (PCR) testing <=3 days from enrollment 3)Patient acceptance and willingness to comply with planned study procedures and to complete the follow up. 4) hospital admission 5) no participation in other clinical trials, such as antiviral trials, during the study period. 6) Able to provide informed consent

Mild and moderate COVID-19 were defined according to World Health Organization (WHO) interim guidance (16). Mild COVID-19 was defined as symptomatic patients meeting the case

definition for COVID-19 without evidence of viral pneumonia or hypoxia. The symptoms included: fever, cough, fatigue, anorexia, shortness of breath, myalgias. Other non specific symptoms such as soar throat, nasal congestion, headache, diarrhea nausea, vomiting, loss of smell, loss of taste, Older people and immunosuppressed patients in particular may present with atypical symptoms such as fatigue, reduced alertness, reduced mobility, diarrhea, loss of appetite, delirium, and absence of fever. Moderate COVID-19: included adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including SpO2 ≥ 90% on room air.

Exclusion criteria

Exclusion criteria were the following: 1) severe COVID-19 defined as respiratory distress (≥30 breaths/min; in resting state, oxygen saturation of 93% or less on room air; or arterial partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FIO2) of 300 or less. 2) Life threatening COVID-19 was defined as respiratory failure requiring mechanical ventilation; shock; or other organ failure (apart from lung) requiring intensive care unit (ICU) monitoring. 3) hypersensitivity or severe adverse events to IVM, 4) Alanine Aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 X upper limit of normal (ULN) 4) pregnancy 5) breast feeding.
6) history of severe asthma.

Intervention

Patients received IVM 200 Mcg single dose at the admission day as add on therapy to Iraqi Ministry of Health protocol for treatment of mild to moderate COVID-19 [HCQ 400mg BID for the first day then 200mg BID for 5 days plus AZT 500mg single dose in the first day then 250mg for 5 days]. We evaluated these patients for cure by clinical assessment and PCR swab testing. Nasopharyngeal or oropharyngeal swabs specimens were collected on days 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21 , and 23 for viral RNA detection and quantification till two successive days of negative PCR swab testing at least 24hrours apart. Virological testing was done at Alshifa'a Hospital Laboratory Center using ABI 7500Dx Real-Time PCR System instruments (Applied Biosystems), USA.

Outcomes

The primary outcome was percentage of the cured patients within 23 days. Cure of the patients was defined by assessing proportion of patients who were symptoms free to be discharged from the hospital and included body temperature returned to normal for longer than 3 days, respiratory symptoms significantly improved, and 2 consecutive negative PCR test results from nasopharyngeal swabs at least 24 hours apart. The secondary outcomes were time to cure in both groups. Time to cure is evaluated by measuring time from admission of the patient to the hospital till discharge after being free of symptoms and negative PCR swab. Once nasopharyngeal and oropharyngeal swab viral PCR testing yielded negative results 2 times consecutively, no further testing was performed. Also safety outcomes included treatment-emergent adverse events, serious adverse events, and premature discontinuations of study were recorded if present.

Sampling method and sample size calculation

A convenient consecutive sample of patients were enrolled in the study. The sample size calculated for this pilot trial was 30 patients : 15 in the active arm (IVM group) and 15 in the controls (SCA) according to pilot study sample size rule of thumb to get medium effect size of $0.3 \leq \delta/\sigma < 0.7$ with a statistical power of 90%. (9)

Statistical analysis

Statistical analysis was done using R packages software for IOS. The normality of continuous variables was analyzed using Shapiro Wilk test. Continuous variables were expressed as mean ± standard deviation (SD) if were normally distributed and median (interquartile range) if not normally distributed. Categorical variables were presented as number and percentages. Difference between normally distributed continuous variables was measured using Student's t-test and Mann-Whitney U test if not normally distributed. Effect size for non normally distributed variables was measured using Vargha and Delany A test. Kaplan Meier survival curve analysis with and log rank testing was used. The standardized mean difference effect size is small if value 0.2- 0.5; medium if value 0.5-0.8, and large effect size if value 0.8-1.4 P value less than 0.05 was considered statistically significant.

Results

Population characteristics

Participant flow

A total of 20 patients were screened for IVM add on group. Of those 4 patients were excluded: 2 of them due to severe COVID-19 and 2 had incomplete data and diagnosis. For comparison with the SCA, a total of 84 patients were screened for eligibility, of them 13 patients were excluded due to having severe COVID-19. The eligible patients in the controls were 71 patients. Two of them died during follow up and 69 completed their standard protocol of therapy according to the Iraqi ministry of health protocol of treatment of COVID-19 as shown in figure 1.

Baseline characteristics

Table 1 shows that mean age ± SD of patients in the IVM group was 44.87 ± 10.64 years with a range of (28-60) years and for the controls was 45.23 ± 18.47 years with a range of (8-80) years. Majority of patients of IVM and controls were male [11(69%) versus 52 (73%), with male: female ratio 2.21 versus 2.7-1 respectively. Most cases of COVID-19 were mild in both groups [9(65%) in IVM versus 40(56%) In non IVM]. The most common clinical features in IVM group were cough 13(81 %), next fever 11(685) , then shortness of breath 9(56%). Similarly, in non IVM group, the most common clinical features were: cough 55 (77 %), next fever 53 (74 %), then shortness of breath 44 (61%). Four patients in IVM group had underlying diseases: of them three had diabetes mellitus and hypertension and 1 had asthma, while in the non IVM, 29 (45%) had underlying diseases, of them 15 had diabetes mellitus, 14 had hypertension, and seven had asthma. There was no statistical significant difference between IVM group and the controls indicating no signiant sociodemographic and clinical confounders affected the study ($p>0.05$)

Outcomes and estimation

In Table 2, All the patients 16 (100 %) of IVM group were cured compared to 69 (97.2%) in the non IVM group. There were two patients died in the non IVM group.

The mean time to stay in the hospital was lower in IVM group compared with the controls and was statistically significant and clinically relevant (7.62 ± 2.75 versus 13.22 ±5.90 days, p=0.00005) with large effect size = 0.82) as in figure 2.

The percentage of positive PCR patients with IVM group had significantly shorter time to become negative PCR compared to the controls. The median days of positive PCR in the IVM group was significantly lower than that of controls [7 (95% CI 6-11) vs 12 (95% CI 10-15), log rank test p<0.001 respectively] as in figure 3.

No side effects have been found in the IVM group.

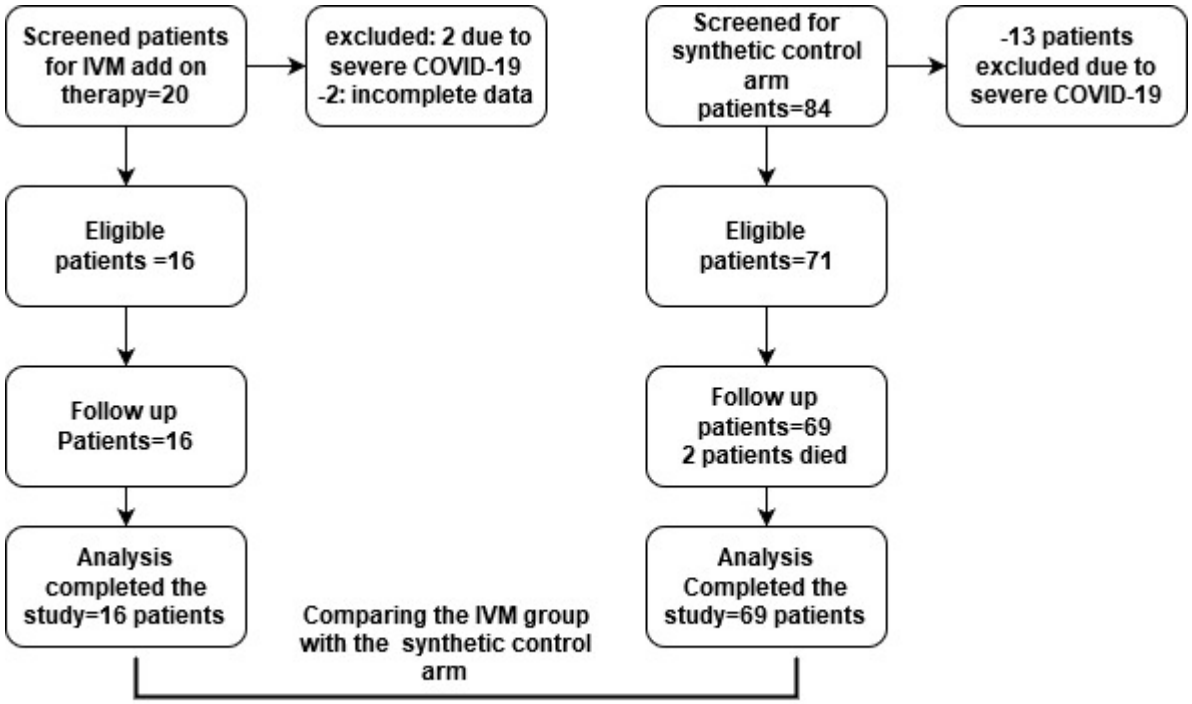


Figure 1: Flow chart of the study group.

Table1: Baseline characteristics of IVM and Non IVM group

Variables	**Total=87**	**IVM Group = 16**	**Controls=71**	**P value**
Age in years, Mean ± SD (range)	45.17±17.25(8-80)	44.87 ± 10.64 (28-60)	45.23 ± 18.47 (8-80)	0.78
Gender Male n ((%) Female n (%) Ratio male: female	 63(72) 24(28)	 11(69) 5 (31) 2.21	 52 (73) 19 (27) 2.7-1	 0.72
Severity Mild n (%) Moderate n(%) Ratio	 49(56) 38(44)	 9 (56) 7 (44) 1.2=1	 40(56) 31 (44) 1.2:1	 1.00
Clinical Features n(%) Cough Fever Shortness of breath Myalgia Sor throat Underlying diseases	 68(78) 64(73) 53(61) 61(70) 21(24) 33(38) Diabetes melitus:18 Hypertension17 Asthma: 8	 13(81) 11(68) 9(56) 8(50) 4 (25) 4 (25) Diabetes melitus:3 Hypertension3 Asthma: 1	 55 (77) 53 (74) 44 (61) 53 (74) 17 (23) 29 (40) Diabetes mellitus:15 Hypertension:14 Asthma:7	 0.74 0.63 0.67 0.10 0.82 0.83 0.79 0.65

IVM, Ivermectin; SD, standard deviation; n, number; %, percentage

Table 2: Percentage of cure rate IVM group and Non IVM group Cure rate

Outcome	**IVM**	**Controls**
Cure n (%)	16(100)	69(97.2)
Mortality n (%)	zero%	2 (2.8%)

IVM, ivermectin; N, number; %, percentage

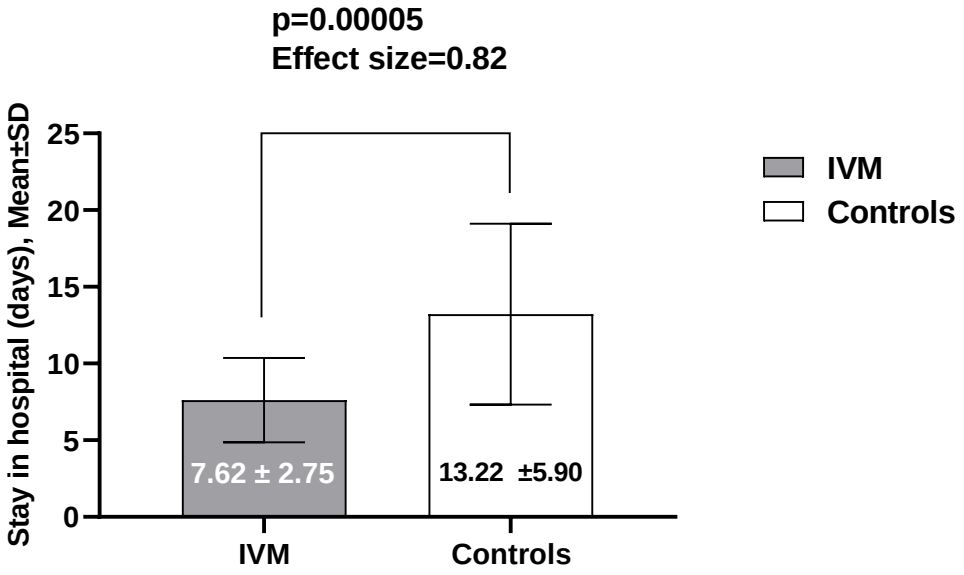
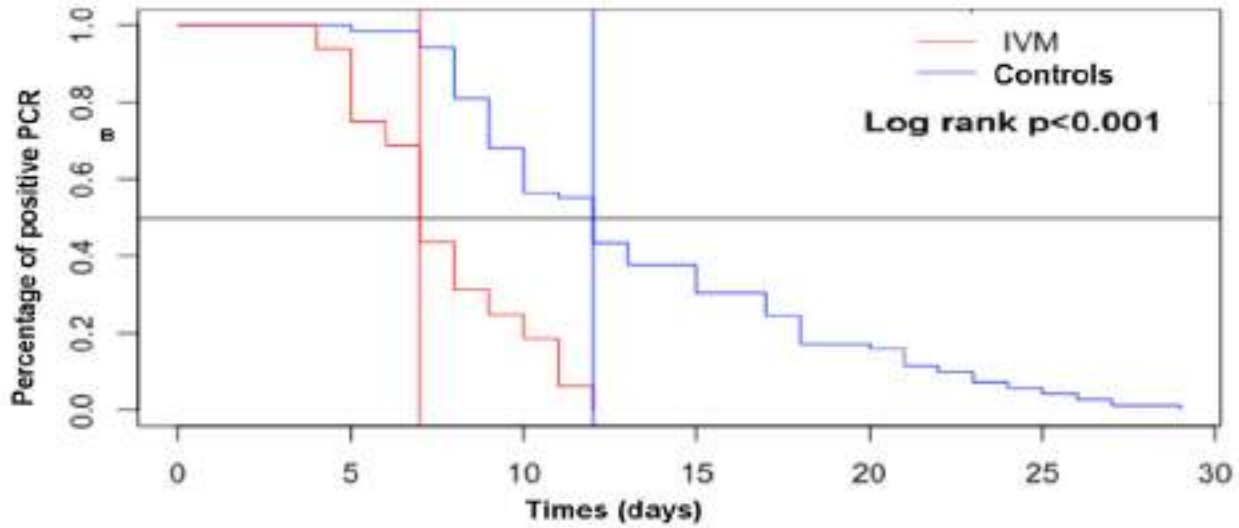


Figure 2: Mean stay days in hospital in IVM group compared with controls



Group	Number of Events	Median days	95% Lower CI	95% Upper CI
Controls	69	12	10	15
IVM	16	7	6	11

Figure 3: Kaplan Meier survival analysis curve for time to percentage of positive PCR in IVM group (n=16) versus controls (n= 69) (p<0.001, Log rank test). PCR, polymerase chain reaction; IVM, ivermectin; CI, confidence interval. The vertical red line represents the median days of IVM; The vertical blue line, represent the median days for controls.

Discussion

To date, no effective therapy has been shown for patients with COVID-19. This preliminary pilot study demonstrated for the first time that add-on use of IVM to HCQ and AZT had obvious higher cure rate, shorter hospital stay days compared with controls. In addition, there was no obvious reported adverse events.

Although data from several ongoing randomized controlled trials (RCT) for IVM will soon provide more informative evidence regarding safety and effectiveness IVM for COVID-19. The outcomes observed in this study with synthetic controls are the best available data regarding IVM use for COVID-19. In addition, during a pandemic with a potential death outcome, RCT become difficult to conduct and may be unethical. Randomization to placebo could carry a risk of serious consequences and even Food and Drug Administration (FDA) is encouraging the use of synthetic control for more innovative approaches (10).

According to the results of this study, all the patients 16 (100%) in the IVM group were cured compared to 69 (97.2%) in the controls. No similar study to compare with.

A Pilot observational study conducted by Gautret et al to assess the clinical and microbiological effect of a combination of HCQ and AZT in 80 COVID-19 patients with at least

a six-day follow up reported that all patients recovered except three patients, one of them died and the other two admitted to the intensive care unit (11).

Another open label non randomized trial evaluated six patients taking HCQ and AZT compared with 14 patients on HCQ and 16 untreated patients from another center and cases refusing the protocol were included as negative controls reported 100 % cure rate for those on combined HCQ and AZT , 57.1 % on HCQ only, and 12.5% ($p<0.001$) (12)

Recently, in a large international, multicenter, observational propensity-score matched case-controlled study in 1,408 patients (704 received IVM in a dose of 150 mcg/kg and 704 that did not) showed that fewer patients of those requiring mechanical ventilation died in the IVM group (7.3% versus 21.3%) and overall death rates were lower with IVM (1.4% versus 8.5% with a corresponding HR 0.20, CI 95% 0.11-0.37, $p<0.0001$).They concluded an association of IVM use with lower in-hospital mortality and suggested a potential survival benefit of IVM in COVID 19 (13)

In contrast, Molina et al reported in a letter to editor that no evidence of rapid antiviral clearance or clinical benefit with the combination of HCQ and AZT in patients with severe COVID-19 infection despite a reported antiviral activity of HCQ against COVID-19 in vitro and suggested ongoing randomized clinical trials with HCQ to provide a definitive answer regarding the alleged effectiveness and its safety (14). The variation in the results in those studies may be related to their study design, included severe patients, small sample sizes, inaccurate sampling method, and short follow up with repeated qualitative PCR assay.

In a randomized, controlled trial of lopinavir-ritonavir in adults hospitalized patients with severe COVID-19 reported no significant benefit was observed with lopinavir-ritonavir treatment beyond the standard care. However, in the modified intention to-treat analysis, which excluded three patients with early death, the between-group difference in the median time to clinical improvement (median,15 days vs. 16 days) was significant, albeit modest. The overall cure rate was 77.9% in that trial. The explanation of high mortality rate possibly was related to the severely ill population enrolled in that study (15)

Moreover, in another recent trial, a preliminary report of compassionate use of remdesivir for small cohort of patients with severe COVID-19 showed an observed clinical improvement in 36 of 53 patients (68%) and overall mortality was 13% over a median follow-up of 18 days . The relatively high mortality rate and less cure in their results may be related to the sever type of COVID-19 in their patients. (16).

Another noteworthy observation in this study was the time to stay in the hospital. The results revealed that the mean time to stay in the hospital in IVM group was 7.62 ± 2.75 days compared with 13.22 ± 5.90 days for the controls which was statistically significant ($p=0.00005$) and clinically relevant with large effect size (Effect size=0.82). This mean shorter time to recovery and early time to discharge patient to home in those taking IVM which will help to provide more beds for another patients who need it and this is practically important in this pandemic disease. Up to our knowledge there is no other study to compare with it.

The time of rapid and full viral clearance was controversial in literatures regarding combination of HCQ and AZT. One study reported that a 100% viral clearance in nasopharyngeal swabs in 6 patients after 5 and 6 days of the combination of HCQ and AZT (17). Another study observed that 10 patients (not done on patient who died) out of 11patients were still positive at day 6 after initiation of treatment on repeated nasopharyngeal swab using a qualitative PCR assay (nucleic

acid extraction using Nuclisens Easy Mag®, Biomerieux and amplification with RealStar SARS CoV-2®, Altona) (13).

In addition, a new study from China in individuals with COVID -19 found no difference in duration of hospitalization at 7 days with or without HCQ (18). The difference in the study design and short follow up with repeated PCR may related to the variation in the day of cure in those studies.

On comparing the mean cure days of patients in our study to the mean recovery of other medications, we found two recent studies. The first study reported the median duration of recovery with 95% CI of patients receiving remdesivir compared with PBO was of variable ranges from 11 (9–12) days in remdesivir versus 15 (13-19) days in PBO to unestimated days in remdesivir versus 28 days in PBO (16). This variation can be explained according to the severity score of the disease on the ordinal scale of intention to treat analysis they used in their study, those patients with score four or less had less duration of cure compared to those with score seven which was an expected finding. The second study compared lopinavir/ritonavir to the standard care and showed that the median time to clinical improvement in days (interquartile range) was 16.0 (13.0 to 17.0) days in lopinavir/ritonavir group versus 16.0 (15.0 to 18.0) in the standard care group which was not significant (15).

In the current short-term study, no new safety signals were detected apart from patients' manifestations on hospital admission. There were no obvious immediate or late adverse events that occurred during treatment, and no serious adverse events that necessitate discontinuation of treatment However it is challenging to attribute any new abnormal complications in the patients whether due to IVM use or the disease itself.

The age, gender, severity of the disease, and the comorbid diseases in the IVM group were not statistically significantly different from the controls. This indicate that these variables were not significant confounders that affect our results and the findings we got were mostly due to the effect of IVM rather than those confounders.

The mechanism of better response in IVM group compared with the controls in this study may be due to the possible synergistic action of these three drugs (IVM, HCQ, and AZT). It was reported that HCQ and IVM were known to act by creating the acidic environment and inhibiting the importin (IMPα/β1) mediated viral import. AZT was found to act similar to the HCQ as an acidotropic lipophilic weak base. All the three categories of drugs seemed to potentially act against COVID 19. infection (19).

This study had some strengths. It is the first externally controlled pilot trial; performed in a public hospital, strict exclusion and inclusion criteria, and presented for the first time assessment of the effectiveness and safety of add on use of IVM to HCQ and AZT. However, this study has some limitations, including its small sample size; single center design, short time for the study, and being nonrandomized.

In conclusion, this study showed that adding IVM to HCQ and AZT had a better cure rate and shorter time to stay in the hospital compared with controls. In addition, it was relatively safe without observable safety signals. These findings may suggest using IVM as an add on therapy to protocols used for treatment of COVID-19. However, these results are needed to be validated in a larger prospective follow up study. The results of the study must not be considered conclusive since unknown confounders cannot always be reliably accounted and we recommend further

studies. A national multicenter randomized study is planned to perform in different provinces of Iraq using IVM alone since HCQ is temporary withdrawn from the COVID 19 therapy according to the WHO advice.

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ICON (Ivermectin in COvid Nineteen) study: Use of Ivermectin is Associated with Lower Mortality in Hospitalized Patients with COVID19

Juliana Cepelowicz Rajter, M.D. [1]
Michael S. Sherman, M.D.[2]
Naaz Fatteh, M.D. [1]
Fabio Vogel, Pharm. D. , BCPS[1]
Jamie Sacks, Pharm. D. [1]
Jean-Jacques Rajter, M.D.[1,3]

1. Broward Health Medical Center, Fort Lauderdale, FL
2. Emeritus Professor, Drexel University College of Medicine
3. Assistant Professor, Florida International University

Corresponding author: Jean-Jacques Rajter, MD
covid19@pscflorida.com

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Abstract

Importance:

No therapy to date has been shown to improve survival for patients infected with SARS-CoV-2. Ivermectin has been shown to inhibit the replication of SARS-CoV-2 in vitro but clinical response has not been previously evaluated.

Objective:

To determine whether Ivermectin is associated with lower mortality rate in patients hospitalized with COVID-19.

Design and Setting:

Retrospective cohort study of consecutive patients hospitalized at four Broward Health hospitals in South Florida with confirmed SARS-CoV-2. Enrollment dates were March 15, 2020 through May 11, 2020. Follow up data for all outcomes was May 19, 2020.

Participants:

280 patients with confirmed SARS-CoV-2 infection (mean age 59.6 years [standard deviation 17.9], 45.4% female), of whom 173 were treated with ivermectin and 107 were usual care were reviewed. 27 identified patients were not reviewed due to multiple admissions, lack of confirmed COVID results during hospitalization, age less than 18, pregnancy, or incarceration.

Exposure:

Patients were categorized into two treatment groups based on whether they received at least one dose of ivermectin at any time during the hospitalization. Treatment decisions were at the discretion of the treating physicians. Severe pulmonary involvement at

study entry was characterized as need for either FiO2 ≥50%, or noninvasive or invasive mechanical ventilation.

Main Outcomes and Measures:

The primary outcome was all-cause in-hospital mortality. Secondary outcomes included subgroup mortality in patients with severe pulmonary involvement and extubation rates for patients requiring invasive ventilation.

Results:

Univariate analysis showed lower mortality in the ivermectin group (15.0 % versus 25.2%, OR 0.52, 95% CI 0.29-0.96, P=.03). Mortality was also lower among 75 patients with severe pulmonary disease treated with ivermectin (38.8% vs 80.7%, OR 0.15, CI 0.05-0.47, P=.001), but there was no significant difference in successful extubation rates (36.1% vs 15.4%, OR 3.11 (0.88-11.00), p=.07). After adjustment for between-group differences and mortality risks, the mortality difference remained significant for the entire cohort (OR 0.27, CI 0.09-0.85, p=.03; HR 0.37, CI 0.19-0.71, p=.03).

Conclusions and Relevance:

Ivermectin was associated with lower mortality during treatment of COVID-19, especially in patients who required higher inspired oxygen or ventilatory support. These findings should be further evaluated with randomized controlled trials.

Introduction

As of May 24th, 2020, the CDC recorded nearly 100,000 people having died of Covid-19 with at least 1,639,099 confirmed infections having been reported in the US and its territories. Covid-19 presents an unprecedented challenge to identify effective therapy for prevention and treatment. Currently, there is no evidence from randomized controlled trials of any potential therapy improving survival outcomes in patients with confirmed disease.

In the late 1970s Ivermectin was developed as a new class of drug to treat parasitic infections. Initially used in veterinary Medicine, it was soon found to be safe and effective in humans. It has successfully been used to treat onchocerciasis and lymphatic filariasis in millions of people worldwide as part of a global drug donation program. About 3.7 billion doses of Ivermectin have been distributed in mass drug administration campaigns globally over the past 30 years. Presently, Ivermectin is approved for use in humans in several countries to treat onchocerciasis, lymphatic filariasis, strongyloidiasis and scabies.[1]

Ivermectin has previously been studied as a therapeutic option for viral infections with in vitro data showing some activity against a broad range of viruses, including HIV, Dengue, Influenza and Zika virus.[2,3] In a recent study, Wagstaff et al, demonstrated that Ivermectin was a potent in-vitro inhibitor of SARS-CoV-2, showing a 99.8% reduction in viral RNA after 48 hours.[4] However, in-vivo efficacy of ivermectin in SARS-CoV-2 infection in humans has not previously been reported.

Methods:

Patients

Sequentially consecutive hospitalized patients at four Broward Health associated hospitals in South Florida with laboratory-confirmed infection with SARS-CoV-2 during their admission were reviewed in this study. The list of confirmed cases was provided by the epidemiology department. Enrollment dates ranged from March 15, 2020 through May 11, 2020. Confirmatory testing was performed by nasopharyngeal swab using an FDA Emergency Use Authorized COVID-19 molecular assay for the detection of SARS-CoV-2 RNA. Patients younger than 18 years old, pregnant, or incarcerated were excluded from the data collection based on IRB requirements. Patients who had at least 2 separate admissions placing them in both groups were also excluded.

Trial procedures

Records were abstracted by four of the authors and all data was subsequently reviewed and confirmed by the lead author. Baseline data was collected at the time of ivermectin administration for the ivermectin group; for the usual care group baseline was either at the time of administration of hydroxychloroquine or, if not used, at the time of admission. Information collected included COVID-19 testing results, patient demographics, pre-existing comorbid conditions, initial vital signs, chest imaging studies, laboratory results, and the use of hydroxychloroquine with and without azithromycin in order to describe the cohort and to identify potential cofounders between groups. Severity of pulmonary involvement was assessed at the time of initiation of therapy ("onset") and categorized as severe or non-severe. Patients were considered to have severe pulmonary involvement if they required an FiO2 of 50% or greater, high-flow

nasal oxygen, noninvasive ventilation, or intubation and mechanical ventilation. The non-severe pulmonary criteria encompassed patients who required no supplemental oxygen, or "low FIO2" (ie: Venturi mask 40% or less, or any amount of low flow nasal cannula), independent of radiographic or laboratory findings.

Patients were categorized into two treatment groups based on whether they received ivermectin at any time during the hospitalization. Patients in the Ivermectin group received at least one oral dose of ivermectin at 200 micrograms/kilogram in addition to usual clinical care. The decision to prescribe ivermectin, hydroxychloroquine, azithromycin or other medications was at the discretion of the treating physicians, however hospital guidelines were established for the use of these agents as well as for cardiac and QT monitoring for patients receiving hydroxychloroquine. Oxygen and ventilatory support were applied per the customary care.

Outcomes

The primary outcome was all-cause in-hospital mortality. Patient was considered a "survivor" if they left the hospital alive, or if their status in the hospital changed from active care to awaiting transfer to a skilled facility. The latter outcome was necessitated by the requirement that two consecutive negative nasopharyngeal swab specimens for SARS-CoV-2, collected equal to or greater than 24 hours apart, were necessary for a patient to be accepted to a skilled nursing facility.

Secondary outcomes included subgroup mortality of patients with severe pulmonary involvement, extubation rates for patients requiring mechanical ventilation, and length of hospital stay.

Statistical analysis

Univariate analysis of the primary mortality outcome, and comparisons between treatment groups were determined by Student's t test or Mann-Whitney U test for continuous variables as appropriate, and by Pearson Chi Square test for categorical variables. The method of Hodges-Lehman was used to estimate median differences with 95% confidence intervals.

To adjust for confounders and between-group differences, a multivariate analysis was performed using stepwise binary logistic regression. Patient variables included in the analysis were age, sex, comorbidities of diabetes, chronic lung disease, cardiovascular disease, and hypertension, smoking status, severity of pulmonary involvement, BMI, peripheral white blood count, absolute lymphocyte count, and use of hydroxychloroquine and azithromycin based on bivariate associations within our data, a priori plausibility, and documented associations with mortality from previous studies. Adjusted odds ratio with 95% confidence intervals were computed to show level of certainty. Hazard ratios for the primary outcome of mortality with 95% confidence intervals were calculated by means of the Cox regression with the same covariates. Analyses were based on nonmissing data and missing data were not imputed. Missingness of 1% was found for peripheral white blood cell count, 5% for smoking status, and 7% for absolute lymphocyte count. Secondary analyses were thus also performed on the entire cohort. All tests were 2-sided and a p value <.05 was considered statistically significant. All statistical analyses were conducted using IBM SPSS v 24.0 software.

Oversight

The protocol was approved by the institutional review board for the Broward Health hospital system. The authors assume responsibility for the accuracy and completeness of the data and analyses, as well as for the fidelity of the trial.

Results

Characteristics of the patients

307 patients were admitted for COVID-19 during the time period studied. 4 patients were not reviewed due to multiple admissions, 11 had no confirmed COVID testing at the time of the study, and 12 were excluded due to age younger than 18 years old, pregnancy, or incarceration. The remaining cohort of 280 patients was comprised of 173 treated with ivermectin and 107 in the usual care group. Follow up data for all outcomes were available through May 19th, 2020. No patients were lost to follow-up for the primary outcome. At the time of analysis, all patients in the cohort had met the endpoint of death, discharge alive, or awaiting transfer to a skilled facility.

Baseline characteristics and between group comparisons are shown in Table 1. Characteristics were similar between groups, however hypertension was more prevalent in the Ivermectin group, whereas the use of hydroxychloroquine and hydroxychloroquine plus azithromycin were higher in the usual care group. No other significant between-group differences were found among baseline characteristics or comorbidities, including age, race, cardiac comorbidities, or smoking status.

Outcomes

Unadjusted outcomes for both groups are shown in Table 2. Overall mortality was significantly lower in the ivermectin group than in the usual care group (15.0% vs 25.2%, for ivermectin and usual care respectively, p=.03). Mortality was also lower for ivermectin treated patients in the subgroup of patients with severe disease (38.8% vs. 80.7%, p=.001). Differences in extubation rates between groups were not significant and there was also no difference in length of hospital stay.

Univariate analysis found that patients dying with COVID-19 infection were older, had higher white blood cell counts and lower absolute lymphocyte counts (Table 3a) than survivors. Patients who died were also more likely to have been current or former smokers and have comorbid cardiac conditions, and were more likely to have severe pulmonary involvement and hypotension at study entry (Table 3b). In comparison to Caucasians, Blacks and Hispanics had lower odds of mortality in this cohort.

In the multivariate analysis, adjusting for demographic factors, between-group differences in mortality risks, and concomitant use of hydroxychloroquine (with or without azithromycin), independent predictors of in-hospital mortality included treatment group, age, severe pulmonary disease category, and reduced lymphocyte count (Table 4). Similarly, the Cox regression showed ivermectin was associated with a significantly lower hazard ratio for mortality of 0.37 (CI 0.19 - 0.70, p=.003). Complete case analysis on the entire cohort without missing data was similar (HR 0.40, 0.22- 0.74), p=.003).

Discussion

In this multihospital retrospective cohort study, we observed a significant association with ivermectin on survival for patients admitted with Covid-19. This association was also seen in the subset of patients with severe pulmonary disease.

Similar to other studies, we noted that older age, cardiac disease, current or former smoking, more severe pulmonary involvement at presentation, higher white blood cell counts, and lower lymphocyte counts emerged as risk markers for in-hospital mortality. The overall mortality, and mortality in intubated patients, in our usual care group was similar to what was reported in previous studies. Richardson et al reported an overall mortality of 21% in their New York City cohort, with a mortality of 88% in intubated patients.[5] Fei Zhou et al reported a 28.2% mortality in their cohort of hospitalized patients in Wuhan, China; their intubated patients had a mortality of 96.9%.[6] In contrast to Mehra et al, we did not see a mortality effect for hydroxychloroquine, with or without the addition of azithromycin.[7] This may have been due to the small number of patients who were not treated with these agents; our study was underpowered to detect a difference. We also hypothesize that precautionary measures in the hospitals' protocol for hydroxychloroquine use could have prevented them from developing fatal arrhythmias. These included baseline EKG and daily QT monitoring by telemetry for any patient receiving hydroxychloroquine or combination therapy, avoidance of azithromycin if patient's baseline QTc was greater than 460msec, and discontinuation of hydroxychloroquine if there was a concerning elevation in QTc or if the patient's cardiologist recommended discontinuation.

We did not confirm an increase risk of mortality in Blacks. This was likely due to difference in age; white patients were significantly older (66.8 vs 59.1 years; mean difference 7.7 years, CI 3.0 - 12.4, p=.001).

In the Ivermectin group, thirteen patients received a second dose of Ivermectin (200 mcg/kg) on day 7, since they were still hospitalized. Due to the low numbers, we did not perform any further analysis of the redosing. We also did not observe any significant side-effect from Ivermectin use.

We did not observe a significant difference in hospital length of stay between the groups (median 7 days for both groups). Possible explanation could include delay in discharging patients to other facilities (skilled nursing facilities, inpatient rehabs, etc) due to lag in obtaining required repeat COVID testing results.

Need for mechanical ventilation was not adopted as outcome of interest, as national guidelines and practice patterns for intubation criteria changed throughout the length of the study.

We did not find a lower mortality in the non-severe patients treated with ivermectin; however, our study was not powered to assess these differences as the overall mortality in non-severe patients was low. Similarly, the study was not powered to determine whether extubation rates were higher in the Ivermectin group. These should be investigated further with a larger randomized controlled trial.

Our study has several limitations. Due to the retrospective observational nature of the study, despite adjustment for known cofounders, we cannot exclude the possibility of unmeasured confounding factors. Although more of the control group was enrolled

earlier in the study, suggesting the possibility of timing bias, this may be offset by preferential treatment of more severe patients with ivermectin early in the study due to low initial availability. We also did not find consistently better mortality outcomes with time over the short duration of this study. Most of our patients studied received hydroxychloroquine with or without azithromycin and we are unable to determine whether these medications had an added benefit, or whether mortality would have been better in both groups without these agents.

We have shown that ivermectin administration was significantly associated with lower mortality among patients with COVID-19, particularly in patients with more severe disease. Interpretation of these findings are tempered by the limitations of the retrospective design and the possibility of confounding. Appropriate dosing for this indication is not known; nor are the effects of ivermectin on viral load, or in patients with milder disease. Further studies in appropriately designed randomized trials are recommended before any conclusions can be made.

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Conflicts of interest- including relevant financial interests, activities, relationships/affiliations

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Table 1: Patient Characteristics by Treatment Group

Demographic characteristics	Total (n=280)	Usual Care (n=107)	Ivermectin (n=173)	P value
Age, years[a]	59.6 (17.9)	58.6 (18.5)	60.2 (17.6)	.45
Female sex	127 (45.4)	43 (41.2)	84 (48.6)	.17
Race ethnicity				.36
Black	153 (54.6)	55 (51.4)	98 (56.6)	
White	76 (27.1)	35 (32.7)	41 (23.7)	
Hispanic	33 (11.7)	12 (11.2)	21 (12.1)	
Other or not identified[c]	13 (4.6)	5 (4.7)	13 (7.5)	
Smoking				.40
Current	16/255 (6.3)	7/99 (7.1)	9/156 (5.7)	
Former	30/255 (11.7)	15/99 (15.2)	15/151 (9.9)	
Never	209/255 (81.9)	77/99 (77.8)	132/151 (87.4)	
Number of comorbidities[a]	1.66 (1.34)	1.60 (1.46)	1.70 (1.27)	.57
Diabetes	90 (32.1)	31 (29.0)	59 (34.1)	.37
Cardiac	43 (15.4)	18 (16.8)	25 (14.5)	.59
Pulmonary	28 (10.0)	14 (13.1)	14 (8.9)	.18
Obesity	114 (40.7)	42 (39.3)	72 (41.6)	.70
Renal	24 (8.6)	10 (9.4)	14 (8.1)	.72
Cancer	17 (6.1)	8 (7.5)	9 (5.2)	.44
Hypertension	50 (17.9)	13 (12.2)	37 (21.4)	.05
Neurologic	28 (10.0)	8 (7.5)	20 (11.6)	.27
HIV	9 (3.2)	1 (1)	8 (4.6)	.09
Thyroid	23 (8.2)	7 (6.6)	16 (9.3)	.42
BMI[a]	30.0 (7.8)	29.8 (7.2)	30.1 (8.2)	.81
Severity				.46
Severe	75 (26.8)	26 (24.3)	49 (28.3)	.12
Non-severe	205 (73.2)	81 (75.7)	124 (71.7)	.55
HR[b]	86.0 (75.0, 97.0)	87.0 (73.5, 95.5)	85.5 (75.3, 98.0)	.65
MAP (mm Hg)[b]	93 (82.2, 103.0)	91 (81.5, 104)	94 (83, 103)	.66
MAP $\leq$ 70 mm Hg	13/260 (5.0%)	6/89 (6.7%)	7/171 (4.1%)	.35
Hydroxychloroquine	260 (92.9%)	104 (97.2)	156 (90.2)	.03
Hydroxychloroquine plus azithromycin	241 (86.1%)	98 (91.6)	143 (82.7)	.04
Peripheral white cell count (X 10^9/L)[b]	7.3 (5.6, 10.2) (n=277)	7.0 (5.7, 8.9) (n=106)	7.6 (5.5, 11.1) (n=171)	.41
Lymphocyte count (X 10^9/L)[b]	1.15 (0.78, 1.56) (n=260)	1.14 (.84, 1.49) (n=102)	1.20 (.77, 1.67) (n=158)	.62

[a] mean ($\pm$ SD)

[b] median (interquartile range)

[c] Asian, Native American, Pacific Islander, or not identified

Table 2: Univariate Clinical Outcomes by Treatment Group

	Number/total number (%)				
	Total (n=280)	Control (n=107)	Ivermectin (n=173)	OR (CI)	P value
Mortality					
Total	53 (18.9)	27 (25.2)	26 (15.0)	0.52 (0.29 to 0.96)	.03
Severe	40/75 (53.3)	21/26 (80.7)	19/49 (38.8)	0.15 (0.05 to 0.47)	.001
Non-severe	13/205 (6.3)	6/81 (7.4)	7/124 (5.6)	0.75 (0.24 to 2.3)	.61
Successful extubation	17/62 (27.4)	4/26 (15.4)	13/36 (36.1)	3.11 (0.88 to 11.00)	.07
Length of stay (median, IQR)	7.0 (4.0, 12.5)	7.0 (4.0, 10.0)	7.0 (4.0, 13.3)		.34

Abbreviations: IQR – interquartile range.

Table 3a: Univariate analysis of factors associated with mortality (continuous variables)

	Nonsurvivors	Survivors	Difference (CI)	P value
Age, years[a]	70.7 (15.1)	57.0 (17.6)	13.6 (8.5 to 18.8)	<.001
Number of comorbidities[a]	1.81 (1.49)	1.63 (1.31)	0.18 (-0.22 to 0.59)	.37
BMI[a]	28.3 (6.7)	30.3 (8.0)	-2.0 (-4.4 to -0.33)	.09
Peripheral white cell count (X 10^9/L)[b]	9.8 (6.1, 13.2)	7.2 (5.5, 9.25)	2.1 (0.8 to 3.6)	.001
Lymphocyte count (X 10^9/L)[b]	0.77 (0.47, 1.15)	1.29 (0.90, 1.68)	-0.46 (-0.63 to -0.30)	<.001

[a] mean (± SD)

[b] median (interquartile range)

Table 3b: Univariate analysis of factors associated with mortality (categorical variables)

	Mortality Number/total (percent)	OR (CI)	P value
Sex			
Female	24/127 (18.8)	1.00 (0.55 to 1.83)	.99
Male	29/153 (19.0)	Reference	
Smoking			
Current or former	18/46 (39.1)	2.75 (0.14 to 0.55)	<.001
Nonsmoker	28/209 (13.9)	Reference	
Race			.04
White	22/76 (28.9)	Reference	
Black	26/153 (17.0)	0.50 (0.26 to 0.96)	.04
Hispanic	3/33 (9.1)	0.24 (0.07 to 0.89)	.02
Other[a]	2/18 (11.1)	0.31 (0.07 to 1.45)	.12
Comorbidities			
Diabetes	19/90 (21.1)	1.23 (0.66 to 2.30)	.52
Cardiac	15/43 (34.9)	2.81 (1.37 to 5.75)	.004
Pulmonary	5/28 (17.9)	0.92 (0.33 to 2.55)	.88
Obesity	20/114 (17.5)	0.86 (0.46 to 1.59)	.62
Renal	6/24 (25.0)	1.48 (0.56 to 3.94)	.43
Cancer	5/17 (29.4)	1.87 (0.63 to 5.55)	.25
Hypertension	9/50 (18.0)	0.93 (0.42 to 2.05)	.85
Neurologic	7/28 (25.0)	1.49 (0.60 to 3.72)	.39
Thyroid	5/23 (21.7)	1.21 (0.43 to 3.42)	.72
Presentation severity			
Severe	40/75 (53.3)	16.88 (8.20 to 34.75)	<.001
Non-severe	13/192 (6.8)		
MAP $\leq$ 70	8/13 (38.5)	9.08 (2.82, 29.28)	<.001
Hydroxychloroquine	50/260 (19.2)	1.35 (0.38 to 4.78)	.64
Hydroxychoroquine plus azithromycin	47/241 (19.5)	1.33 (0.53 to 3.37)	.54

[a]Asian, Native American, Pacific Islander, or not identified

Table 4: Multivariate analysis of factors associated with mortality

	OR (CI)	P value
Treatment group:		
Ivermectin	0.27 (0.09, 0.85)	.03
Control	Reference	
Age	1.05 (1.02, 1.09)	.005
Female sex	0.69 (0.25, 1.91)	.48
Current or former smoker	3.43 (0.94, 12.48)	.06
Race		.165
Black	0.66 (0.22, 1.99)	.464
Hispanic	0.14 (0.02, 1.10)	.061
Other	0.77 (0.06, 9.88)	.843
Comorbidities		
Diabetes	1.13 (0.38, 3.36)	.83
Cardiac	1.62 (0.45, 5.83)	.46
Pulmonary	0.15 (0.17, 1.24)	.08
Hypertension	1.00 (0.22 to 4.56)	.99
BMI	0.99 (0.90, 1.08)	.77
Severe presentation	26.88 (8.11, 89.05)	<.001
MAP $\leq$ 70 mm Hg	2.10 (0.26, 7.04)	.73
Peripheral white cell count	1.09 (.958, 1.24)	.19
Lymphocyte count	4.04 (1.35, 12.09)	.01

Background Summary

Ivermectin for COVID-19

What is ivermectin?

Ivermectin is an anti-parasite medication that is indicated for use in humans and animals. It has potential antiviral effects against SARS-CoV-2. The FDA issued a special alert in April 2020 warning people about taking ivermectin products intended for animals. Brand name: Stromectol [1]

No formal approval of ivermectin for COVID-19

Ivermectin was approved by Health Canada in 2018 for use in **parasitic infections** [2], but it is **not** currently approved for treating COVID-19. NIH does not currently recommend ivermectin as a COVID-19 treatment, citing insufficient evidence [3]. This perspective is shared by the FDA [4].

On February 4, 2021, Merck (producer of Stromectol) issued a statement advising against the use of ivermectin for COVID-19, due to insufficient evidence. As per Merck: "We do not believe that the data available support the safety and efficacy of ivermectin beyond the doses and populations indicated in the regulatory agency-approved prescribing information." [5]

Evidence syntheses

Alberta Health Services published a very thorough, high-quality rapid evidence report on ivermectin for COVID-19 on February 2, 2021. They concluded that "The studies evaluating ivermectin **treatment** are not high enough quality to properly decide if ivermectin is useful or not. Most studies did not clearly describe the effect of the other medications given to patients or what other factors might influence their findings ("confounding"), did not have an adequate comparator group to assess if there was a difference in patients given ivermectin, or were too small to be sure that any effect of ivermectin seen was real. With respect to ivermectin's ability to **prevent** infection with COVID-19, four low quality studies showed that ivermectin may reduce the risk of COVID-19 infection; however, there were several confounding factors and we don't know what else the study participants were doing that might have influenced their risk of infection. More studies are needed to show if ivermectin can be used to prevent infection." [6]

Epistemonikos lists 15 systematic reviews on ivermectin for COVID-19, most of which are preprints. Here are two recent examples: one recent preprint focusing on ivermectin, and one peer-reviewed network meta-analysis comparing multiple treatments.

Source	Title	Date	Link	Conclusions	Quality
medRxiv	Outcomes of Ivermectin in the treatment of COVID-19: a systematic review and meta-analysis	Jan 27	Link	"There [is] insufficient certainty and quality of evidence to recommend the use of ivermectin to prevent or treat ambulatory or hospitalized patients with COVID-19." [7]	• Preprint • Not peer-reviewed • Good search strategy and critical appraisal methods
PLoS Medicine	Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: A systematic review and network meta-analysis	Dec 30	Link	"For ICU-based critically ill patients, corticosteroids reduced mortality from RCT evidence; high-dose IVIG, **ivermectin**, and tocilizumab may be associated with reduced mortality when including observational data." [8]	• Peer-reviewed • High-quality journal • Search methods not reported in full

Prepared by Leah Boulos, Evidence Synthesis Coordinator, Maritime SPOR SUPPORT Unit

February 16, 2020

Clinical trials

Epistemonikos lists 110 reports of RCTs, of which only 34 have reported data. Almost all of the latter are preprints. There are no reports of ivermectin trials in major medical journals (e.g. Nature, NEJM, JAMA, Lancet, etc.). A thorough table of 38 ongoing clinical trials (as of February 2, 2021) of ivermectin against COVID-19 is found in Table 7 of the Alberta Health Services rapid evidence report [6].

Please note: This summary reflects evidence up to and including February 16, 2021 only.

Search Methods

Date searched: 2021-02-16

- Google for news items and clinical trials in progress
- Epistemonikos L-OVE on COVID-19 (manual search)
- Ovid MEDLINE search with built-in COVID-19 filter: (ivermectin or stromectol).ti,ab.

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Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	December 3, 2020	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Lisa Grandy Allen, Glenn Cox, Gabrielle Richard, Emma Reid		

Items	Discussion
[redacted]	unrelated [redacted]
- Therapeutic agents being considered at Nova Scotia Health	unrelated [redacted]

Items	Discussion
- unrelated [redacted]	unrelated [redacted]
- Round Table	

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	December 10, 2020	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Gabrielle Richard, Emma Reid, Barbara Goodall, Glenn Cox, Lisa Grandy Allen		

Items	Discussion
- unrelated meeting minutes	unrelated [redacted]
- unrelated	[redacted]
- unrelated	unrelated [redacted]
- **Ivermectin**	Ivermectin was brought to the attention of the Advisory Group as a potential COVID-19 treatment to investigate. Discussed limited evidence, and plan moving forward addressing requests like this. Plan will be to distribute a more formal agenda two days in advance of our meetings to alert members of research/preparation in advance of the meetings. **Action items: Tasha to add ivermectin to agenda for next week's meeting.**

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	December 17, 2020	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Gabrielle Richard, Emma Reid, Barbara Goodall, Glenn Cox, Lisa Grandy Allen		

Items	Discussion
- unrelated [redacted]	[redacted]
- unrelated [redacted]	unrelated [redacted]
- unrelated [redacted]	unrelated [redacted]
- **Ivermectin**	Will be moved to Dec 18 agenda.

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	December 18, 2020	**Meeting Time**	0830-0930
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Gabrielle Richard, Emma Reid, Barbara Goodall, Glenn Cox, Lisa Grandy Allen		

Items	Discussion
- [redacted]	unrelated [redacted]
- unrelated [redacted]	unrelated [redacted]

	unrelated [redacted]
unrelated [redacted]	unrelated [redacted]
- **Ivermectin**	Evidence is limited to a pilot study and a retrospective observational study. Discussed that more succinct or summarized information may be useful to facilitate our group discussion before determining our recommendation for its role. **Action Item: L. Barrett will share an ivermectin summary prior to next meeting. T. Ramsey to add ivermectin discussion to next agenda.**
unrelated [redacted]	unrelated [redacted]
- **Next meeting**	Resume meetings January 7, 2021.

To:	NS Health COVID Network
Date:	22 December 2020
From:	Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group
Subject:	unrelated

unrelated

unrelated [redacted]

[redacted]

Note: Recommendations will be reviewed on a monthly basis by the NS Therapeutics and Prophylactics Advisory Group (review date: January 21, 2021)

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	January 7, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Gabrielle Richard, Emma Reid, Barbara Goodall, Glenn Cox, Lisa Grandy Allen		

Items	Discussion
- unrelated	unrelated [redacted]
- unrelated	unrelated [redacted]
- unrelated	unrelated [redacted]
- **Ivermectin**	Advisory Group had originally had received request from Brendan Carr to review. Lisa Barrett presented slides: - Ivermectin background: current role in therapy as anti-parasitic and rationale for investigating use in COVID-19, potential mechanism for anti-viral activity, pertinent pharmacokinetic considerations, in vitro evidence against SAR-COV-2 and limitations, proposed concentrations required for antiviral activity and safety considerations at standard and higher doses. - Reviewed spreadsheet of clinical trials of ivermectin in COVID-19, ongoing and completed (approx. 45): few randomized, many in combination with other interventions (especially doxycycline,

	hydroxychloroquine, and azithromycin). Some investigating prophylaxis and some investigating treatment. Many due to be completed but results not reported. Discussed consideration for publication bias amongst studies published and available as pre-prints. - Reviewed individual studies included in the Kalfas et al. ivermectin systematic review/meta-analysis including outcome data and interpretation. The advisory group discussed quality of study data available for ivermectin versus other agents authorized for use in COVID-19 by Health Canada – overall lower quality evidence (retrospective/observational published data), less rigorous than other approved agents, such as bamlanivimab and remdesivir, with Phase 2 or Phase 3 randomized control trials. High risk of confounding. Lack of proven biologic mechanism for antiviral activity with ivermectin, unclear anti-inflammatory mechanism. Discussed mindfulness around global supply of ivermectin - need to be aware of potential to deplete supply for established indications and ethical considerations. Agreement that as Advisory Group we will not recommend ivermectin for routine use in COVID-19 treatment nor prophylaxis, and will not recommend use in clinical research at this time. We will continue monitoring as evidence evolves and will revisit our recommendation accordingly. Discussion around how frequently we will revisit the ivermectin recommendation. Resources may not allow for a full review every 4 weeks for all agents discussed by Advisory Group. Potential solutions: can lean on other expert groups like CADTH for evidence reviews, other individuals/groups that have previously prepared evidence reviews (Leah Boulos from MSSU, Dr. Tara Sampalli). **Action items: T. Ramsey to draft official recommendation from Advisory Group regarding ivermectin for next meeting. L. Barrett to send materials from ivermectin presentation today to group. T. Ramsey to send agenda items two days before next meeting.**
- **Next meeting**	Jan 21st – next week cancelled.

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	January 21, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, Barbara Goodall, Glenn Cox, Amanda Porter, Kenneth Rockwood, Lisa Grandy Allen, Gabrielle Richard		

Items	Discussion
- unrelated	[redacted]
[redacted]	[redacted]
- unrelated	unrelated [redacted]
- **Ivermectin**	Reviewed draft recommendation and rationale distributed to group prior to meeting. Discussion focused primarily around content included in rationale: - Concern around stating lack of federal support as a reason to not recommend use at this time given that ivermectin is generic drug, maybe no sponsor to bring it forward for Health Canada approval. unrelated [redacted] level of evidence and recommendations from federal stakeholder groups inform the decision to pursue a COVID medication on the federal level. Discussed two federal groups that have not supported pursuing ivermectin: the Canadian Therapeutics Task Force and Clinical Pharmacology Working Group, the latter which has global representation (WHO member). - Readdressed concern about global supply of medication. Posted shortage of ivermectin currently. - Discussed citing guideline recommendations – maybe we should only providing our own conclusion independent of guideline recommendations? Felt it was alright to leave in the rationale in addition to comments about the literature to date. In interest of time further suggestions/updates to be made on the rationale for the recommendation will be

	sent to T. Ramsey via email. Voted via poll and there was unanimous support for overall ivermectin recommendation: • Do NOT recommend for the treatment or prophylaxis of COVID-19 as part of routine care or in the context of research. • The advisory group will continue to monitor clinical trials. Noted that we did not take meeting time to review WHO-sponsored ivermectin meta-analysis in depth (link was distributed to the group). Given time sensitivity of our group's recommendations we will not be able to formally review all content pertaining to drugs reviewed during meetings. Suggested that group members can volunteer to prepare a summary for the group for when ivermectin recommendation is reviewed again in 4 weeks. **Action item: T. Ramsey will distribute the finalized recommendation/rationale via email for next meeting.**
- unrelated [redacted]	unrelated [redacted]
[redacted]	[redacted]
- unrelated [redacted]	unrelated

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	January 28, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, Barbara Goodall, Glenn Cox, Amanda Porter, Kenneth Rockwood, Lisa Grandy Allen		

Items	Discussion
- [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
- **Ivermectin: Recommendation**	Reviewed updated recommendation for ivermectin (minor wordsmithing submitted and incorporated since last meeting): *Do not recommend ivermectin for the treatment or prophylaxis of COVID-19 as part of routine care or in the context of research at this time.* Reviewed updated rationale for ivermectin (qualified supporting evidence in terms of published peer review and where it fits in hierarchy, also added comment about global supply and ensuring we do not deplete supply for established parasitic indications). Discussed role of the rationale component along with the recommendation. Given that the Advisory Group discusses at length the rationale behind our drug recommendations during our meetings, the discussion is reflected in the minutes, and that we must be conscious of time with our weekly agendas, decided that the rationale will not accompany recommendations in the future. The rationale will be discussed verbally when the recommendations are formally presented and will reflect updates to our rationale as the recommendations are revisited at the pre-specified intervals. Discussed that our medication reviews should include a statement on whether the drug is procured through a pandemic supply if applicable. Tasha will incorporate recommendation into a memo which will be used to present to COVID Network. - **Action item: T. Ramsey to send memo to group.**
- unrelated [redacted]	unrelated [redacted]

	unrelated [redacted]
- unrelated [redacted]	[redacted]
- unrelated [redacted]	unrelated [redacted]

	unrelated [redacted]
- unrelated [redacted]	unrelated [redacted]
- unrelated [redacted]	unrelated [redacted]

To:	NS Health COVID Network
Date:	9 February 2021
From:	Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group
Subject:	Recommendations

The Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group has the following new recommendations for the COVID Network to consider for approval:

Ivermectin: Do not recommend for the treatment or prophylaxis of COVID-19 as part of routine care or in the context of research at this time.

unrelated [redacted]

The following recommendations were approved by the COVID Network on December 22, 2020. The Advisory Group reviewed them as part of our monthly review of previous recommendations. We have no revisions to the recommendations at this time.

unrelated [redacted]

Note: Recommendations will be reviewed on a monthly basis by the NS Therapeutics and Prophylactics Advisory Group

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	February 4, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, Barbara Goodall, Glenn Cox, Amanda Porter, Kenneth Rockwood, Lisa Grandy Allen, Gabrielle Richard		

Items	Discussion
- unrelated	[redacted]
- unrelated	unrelated [redacted]
- unrelated	[redacted]
- **Ivermectin, unrelated : Memo**	Reviewed the drafted memo Tasha had distributed. No suggestions/changes provided – group agreed to formatting and final wording of the recommendations. In order to streamline information presented to COVID Network, suggested to finalize unrelated recommendation and include in same memo.
- unrelated	unrelated [redacted]
- **Recommendation: review process**	Discussed the Advisory Group's procedures for reviewing previous recommendations. The MSSU has been engaged and agreed to complete an evidence review for each medication discussed by the advisory group. They will also complete an updated review every 4 weeks (as long as given sufficient notice). Discussed that

	sometimes we can predict (e.g., based on trial registries) that there will not be new publications or study results to impact current recommendation at each 4-week interval. Decided that despite this, as interim results may be released, we will continue to request the evidence overview from MSSU every four weeks and will add the corresponding drug recommendations to the agenda every four weeks. Group members and stakeholders can review the summaries on their own. If no update is required the existing recommendation can be quickly re-accepted by attendees at the corresponding meeting, and if further discussion is warranted this can be requested prior to the meeting.
- unrelated [redacted]	unrelated [redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	February 25, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, Amanda Porter, Gabrielle Richard, Lisa Grandy Allen		

Items	Discussion
- unrelated	[redacted]
- unrelated [redacted]	unrelated [redacted]
- **Review recommendations** - unrelated [redacted] **ivermectin,** unrelated [redacted]	Advisory group due to review recommendations for [redacted] drugs today unrelated [redacted], ivermectin, unrelated [redacted]. MSSU provided summaries for unrelated [redacted], ivermectin, unrelated [redacted] Members had opportunity to discuss. Kathleen mentioned CADTH Health Technology Review for ivermectin is another helpful summary. No requests or suggestions to change recommendations for unrelated, ivermectin, unrelated [redacted] Group agreed to renew current recommendations for these [redacted] agents. unrelated [redacted]

	[redacted]
- [redacted]	[redacted]
- **Next meeting**	Will cancel next week (March 4) unless extenuating circumstances arise. Next meeting: March 11, 2021.

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	March 11, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, Amanda Porter, Gabrielle Richard, Lisa Grandy Allen, Barbara Goodall, Kenneth Rockwood		

Items	Discussion
[redacted]	[redacted]
unrelated [redacted]	[redacted] unrelated [redacted]
[redacted]	unrelated [redacted]

	unrelated [redacted]
- unrelated [redacted]	unrelated [redacted]
- **Next meeting**	Will start scheduling meetings for every two weeks, with the option to host additional meetings or cancel meetings if needed. Next meeting: March 25.

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	April 8, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Kathleen Coleman, Emma Reid, Amanda Porter, Gabrielle Richard, Lisa Grandy Allen, Barbara Goodall, Kenneth Rockwood		

Items	Discussion
- [redacted]	[redacted]
unrelated [redacted]	[redacted]
Review recommendations: - unrelated [redacted] ivermectin, unrelated [redacted]	unrelated [redacted] unrelated [redacted] [redacted]

	unrelated [redacted] *Ivermectin recommendation:* Tasha reported the group had received a request from within NS Health to re-review ivermectin as prompted by the publication of a new RCT. This trial did not report any benefit regarding studied outcomes. Recommendation will remain unchanged at this time and review process will continue every four weeks as scheduled. Current recommendation: *Do not recommend for the treatment or prophylaxis of COVID-19 as part of routine care or in the context of research at this time.* unrelated [redacted]
- unrelated [redacted]	[redacted]
- **Next meeting**	Will occur in two weeks on April 22.

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	April 22, 2021	**Meeting Time**	0800-0900
Present	**Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, , Gabrielle Richard, Lisa Grandy Allen, Kenneth Rockwood**		

Items	Discussion
- unrelated	[redacted]
Review recommendations: - unrelated - **Ivermectin** - unrelated	unrelated [redacted] unrelated [redacted] unrelated, **ivermectin**, unrelated – group agreed no changes to current recommendations necessary.

unrelated	unrelated
unrelated	
- **Next meeting**	Will occur in two weeks on May 6.

To:	NS Health COVID Network
Date:	26 April 2021
From:	Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group
Subject:	unrelated [redacted]

The Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group has the following revised recommendations for the COVID Network to consider for approval:

unrelated [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted].

unrelated [redacted]

[redacted]

[redacted]

Note: Recommendations will be reviewed on a monthly basis by the NS Therapeutics and Prophylactics Advisory Group

Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group			
Meeting Date	May 6, 2021	**Meeting Time**	0800-0900
Present	Tasha Ramsey, Lisa Barrett, Kathleen Coleman, Emma Reid, Amanda Porter, Gabrielle Richard, Lisa Grandy Allen, Kenneth Rockwood, Kathryn Slayter, Glenn Cox		

Items	Discussion
- unrelated [redacted]	[redacted]
[redacted]	[redacted]
Review recommendations: - unrelated [redacted] - Ivermectin - unrelated [redacted]	unrelated [redacted]. Other recommendations to remain the same. unrelated unrelated [redacted]

	unrelated [redacted]
unrelated	unrelated [redacted] unrelated unrelated [redacted]
- **Next meeting**	Will occur in two weeks on May 20.

To:	NS Health COVID Network
Date:	4 February 2021
From:	Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group
Subject:	Ivermectin unrelated [redacted]

Ivermectin Recommendation: Do not recommend ivermectin for the treatment or prophylaxis of COVID-19 as part of routine care or in the context of research at this time.

unrelated [redacted]

[redacted]

[redacted]

Note: Recommendations will be reviewed on a monthly basis by the NS Therapeutics and Prophylactics Advisory Group (review date: Feb 25, 2021).

From: tasha.ramsey@nshealth.ca
To: Richard, Gabrielle; Barrett, Lisa L; Grandy Allen, Lisa; Coleman, Kathleen; Neale, Sionv; Cox, Glenn; Reid, Emma K; Goodall, Barbara; Rockwood, Kenneth; Amanda Porter
Cc: McNeil, Shelly
Subject: COVID-19 therapeutics and prophylactics
Date: Tuesday, April 20, 2021 10:56:50 PM
Attachments: 1. April 22 Full Slides.pdf
[redacted]
Barrett Ramsey_C-19 Therapeutics Ag_Summary_Ivermectin_2021-04-12.pdf
[redacted]

Hi everyone,

Here is the agenda for our April 22nd meeting:

- Minutes
- [redacted]
  - [redacted]
- Review recommendations:
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - Ivermectin
  - [redacted]
  - [redacted]
- [redacted]

You will find slides for our meeting, minutes from our last meeting, and MSSU reviews attached.

Feel free to let me know if you have any questions,
Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

From: tasha.ramsey@nshealth.ca
To: Richard, Gabrielle; Barrett, Lisa L; Grandy Allen, Lisa; Coleman, Kathleen; Neale, Sionv; Cox, Glenn; Reid, Emma K; Goodall, Barbara; Rockwood, Kenneth; Amanda Porter
Cc: McNeil, Shelly
Subject: COVID-19 therapeutics and prophylactics
Date: Tuesday, February 23, 2021 9:05:48 PM
Attachments: 1. Feb 25 Slides.pdf
2. Feb 4 Minutes.pdf
unrelated
Ivermectin_2021-02-16.pdf
unrelated

Hi everyone,

Here is the agenda for our Feb 25th meeting:

- Minutes
- unrelated
- Review recommendations:
  - unrelated
  - [redacted]
  - Ivermectin
  - unrelated
  - [redacted]
  - [redacted]
- [redacted]

Please review the attached slides and updated MSSU summary sheets in advance of the meeting.

Feel free to let me know if you have questions,

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

From: tasha.ramsey@nshealth.ca
To: Richard, Gabrielle; Barrett, Lisa L; Grandy Allen, Lisa; Coleman, Kathleen; Neale, Sionv; Cox, Glenn; Reid, Emma K; Goodall, Barbara; Rockwood, Kenneth; Amanda Porter
Cc: McNeil, Shelly
Subject: COVID-19 therapeutics and prophylactics
Date: Tuesday, February 2, 2021 7:14:08 PM
Attachments: 1. Feb 4 Slides.pdf
1. Jan 28 NS COVID-19 Therapeutics and Prophylactics Minutes.docx
unrelated
3. Memo 2 DRAFT Feb 2021.doc
unrelated [redacted]

Hi everyone,

Here is the agenda for our Feb 4th meeting:
- Minutes
unrelated [redacted]
- Ivermectin, unrelated [redacted] Memo
- unrelated [redacted]
- Recommendation review process
- unrelated [redacted]

Please review the attached items in advance of the meeting and feel free to let me know if you have questions,
Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

From: tasha.ramsey@nshealth.ca
To: Richard, Gabrielle; Barrett, Lisa L; Grandy Allen, Lisa; Coleman, Kathleen; Neale, Sionv; Cox, Glenn; Reid, Emma K; Goodall, Barbara; Rockwood, Kenneth; Amanda Porter
Cc: McNeil, Shelly
Subject: COVID-19 therapeutics and prophylactics
Date: Tuesday, January 26, 2021 9:49:45 PM
Attachments: 1. Jan 28 Slides.pdf
2. Jan 21 NS COVID-19 Therapeutics and Prophylactics Minutes.docx
[redacted]

Hi everyone,

Here is the agenda for our Jan 28th meeting:

- Minutes
- [redacted]
- [redacted]
- Ivermectin: Recommendation
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Please review the attached items in advance of the meeting and feel free to let me know if you have any questions,
Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

From:	tasha.ramsey@nshealth.ca
To:	Barrett, Lisa L; Grandy Allen, Lisa; Coleman, Kathleen; Neale, Siony; Cox, Glenn; Richard, Gabrielle; Reid, Emma K; Goodall, Barbara
Subject:	COVID-19 therapeutics and prophylactics
Date:	Tuesday, January 5, 2021 2:02:38 PM
Attachments:	3. Dec 17 NS COVID-19 Therapeutics and Prophylactics Minutes.docx 4. Dec 18 NS COVID-19 Therapeutics and Prophylactics Minutes.docx ivermectin mortality.pdf Ivermectin Pilot Study.pdf

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Hi everyone,

Here is the agenda for our Jan 7th meeting:

- Review minutes from Dec 17 and 18th (all)
- unrelated [redacted]
- Ivermectin (all)

For the ivermectin discussion, the pilot and retrospective studies are attached for those that wish to review them. Lisa (Barrett) may also have an ivermectin summary to send out to the group as well.

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

From: tasha.ramsey@nshealth.ca
To: Barrett, Lisa L; Grandy Allen, Lisa; Coleman, Kathleen; Neale, Siony; Cox, Glenn; Richard, Gabrielle; Reid, Emma K; Goodall, Barbara
Subject: COVID-19 therapeutics and prophylactics
Date: Tuesday, December 15, 2020 8:22:55 AM
Attachments: 2. Dec 10 2020 NS COVID-19 Therapeutics and Prophylactics Minutes.docx
unrelated
Ivermectin Pilot Study.pdf
Ivermectin Retrospective Observational Study.pdf

Hi everyone,

Here is the agenda for our December 17th Meeting:

- Review minutes (all)
- unrelated
- [redacted]
- Ivermectin (all)

unrelated
[redacted].

For the ivermectin discussion, the pilot and single retrospective study are attached for those that wish to review them. They are not peer reviewed and guidelines do not recommend use at this time.

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

From: Ramsey, Tasha on behalf of tasha.ramsey@nshealth.ca
To: Richard, Gabrielle; Barrett, Lisa L; Grandy Allen, Lisa; Coleman, Kathleen; Neale, Sionv; Cox, Glenn; Reid, Emma K; Goodall, Barbara; Rockwood, Kenneth; Amanda Porter
Cc: McNeil, Shelly
Subject: COVID-19 therapeutics and prophylactics
Date: Tuesday, April 6, 2021 10:13:40 PM
Attachments: 1. April 8 Full Slides.pdf
2. Mar 11 Minutes.pdf
unrelated
Barrett Ramsey_C-19 Therapeutics Ab_Summary_Ivermectin_2021-03-16[1].pdf
unrelated

Hi everyone,

Here is the agenda for our April 8th meeting:

- Minutes
- unrelated
  - [redacted]
- Review recommendations:
  - unrelated
  - [redacted]
  - [redacted]
  - [redacted]
  - Ivermectin
  - unrelated
  - [redacted]
- [redacted]

You will find the slides for our meeting, minutes from our last meeting, and MSSU reviews for the agents we are due to review attached.

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

unrelated [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

From: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>
Sent: November 12, 2020 8:42 AM
To: Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>
Cc: Neale, Siony <Siony.Neale@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics

Hello all.

I think most of you were on the call we have a couple of weeks ago about COVID therapeutics, and the desire to form a committee that helps inform provincial decisions around therapeutic and prophylactic evidence, usage and availability.

Is everyone on this group okay to be involved? And do people have time to meet on Monday Nov 16 at either 9 am or 5 pm to discuss ToR, membership, and the existing recommendations, as well as the long term care facility context for treatment?

Lisa

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: tasha.ramsey@nshealth.ca
To: Reid, Emma K
Subject: FW: Ivermectin and unrelated
Date: Monday, April 12, 2021 7:23:55 PM
Attachments: image001.png
image002.png
unrelated
[redacted]

FYI

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Monday, April 12, 2021 at 5:43 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Subject: FW: Ivermectin unrelated

nova scotia health

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Boulos, Leah M
Sent: Monday, April 12, 2021 3:05 PM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Cc: Farrell, Ashley M <Ashley.Farrell@nshealth.ca>
Subject: Ivermectin unrelated

Hi Barb,

Here's this week's ivermectin update, unrelated [redacted]

[redacted]

Have a good week!
Leah

Leah Boulos, MLIS

Evidence Synthesis Coordinator
Maritime SPOR SUPPORT Unit
Email: LeahM.Boulos@nshealth.ca

www.mssu.ca | @maritimespor
Sign up for our mailing list

From: tasha.ramsey@nshealth.ca
To: Reid, Emma K
Subject: FW: MSSU summaries
Date: Monday, April 12, 2021 10:06:13 AM
Attachments: unrelated [redacted]
unrelated

FYI- updated versions

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Thursday, April 8, 2021 at 9:58 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: FW: MSSU summaries

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Boulos, Leah M
Sent: Thursday, April 8, 2021 9:40 AM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Subject: RE: MSSU summaries

Hi Barb,

Here are the updated summaries. Since the ivermectin unrelated summaries just had typos, I didn't change the dates on them. unrelated [redacted]

We'll be in touch next week with the new ivermectin and unrelated [redacted].

Cheers,
Leah

From: tasha.ramsey@nshealth.ca
To: Reid, Emma K
Subject: Re: COVID-19 therapeutics and prophylactics
Date: Monday, February 1, 2021 12:39:23 PM

---

unrelated

[redacted].

T

From: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Date: Monday, February 1, 2021 at 10:53 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics

Hi Tasha,

See attached for minutes. Let me know if any feedback with regards to content/incorporation of recommendations. I realize that the minutes will be particularly important if the rationale piece is no longer provided.

unrelated [redacted]

Thanks,
Emma

From: Ramsey, Tasha
Sent: Tuesday, January 26, 2021 9:50 PM
To: Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Rockwood, Kenneth <Kenneth.Rockwood@nshealth.ca>; Amanda Porter <Amanda.Porter@dal.ca>
Cc: McNeil, Shelly <Shelly.McNeil@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics

Hi everyone,

Here is the agenda for our Jan 28th meeting:

- Minutes
- unrelated [redacted]

- unrelated [redacted]
- Ivermectin: Recommendation
- unrelated [redacted]
- [redacted]
- [redacted]
- [redacted]

Please review the attached items in advance of the meeting and feel free to let me know if you have any questions,
Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

From: tasha.ramsey@nshealth.ca
To: McNeil, Shelly; Milligan, Samantha
Cc: Barrett, Lisa L
Subject: Re: COVID-19 therapeutics and prophylactics
Date: Friday, January 29, 2021 8:41:28 AM

---

unrelated [redacted]

[redacted].

Tasha

From: "McNeil, Shelly" <Shelly.McNeil@nshealth.ca>
Date: Thursday, January 28, 2021 at 11:22 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Cc: "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>, "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Reid, Emma K" <EmmaK.Reid@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Rockwood, Kenneth" <Kenneth.Rockwood@nshealth.ca>, Amanda Porter <Amanda.Porter@dal.ca>, "Milligan, Samantha" <Samantha.Milligan@nshealth.ca>
Subject: Re: COVID-19 therapeutics and prophylactics

unrelated [redacted]

Sent from my iPhone

> On Jan 26, 2021, at 9:49 PM, Ramsey, Tasha <Tasha.Ramsey@nshealth.ca> wrote:
>
> Hi everyone,
>
> Here is the agenda for our Jan 28th meeting:
>
> - Minutes

- unrelated
- [redacted]
- Ivermectin: Recommendation
- unrelated [redacted]
- [redacted]
- [redacted]
- [redacted]

Please review the attached items in advance of the meeting and feel free to let me know if you have any questions,
Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

From:	Barrett, Lisa L
To:	Richard, Gabrielle; Ramsey, Tasha; Grandy Allen, Lisa; Coleman, Kathleen; Neale, Siony; Cox, Glenn; Reid, Emma K; Goodall, Barbara; Rockwood, Kenneth; Amanda Porter
Cc:	McNeil, Shelly
Subject:	RE: COVID-19 therapeutics and prophylactics
Date:	Wednesday, January 20, 2021 1:55:14 PM

Gabrielle
We can discuss tomorrow.
Lisa

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Richard, Gabrielle [Gabrielle.Richard@novascotia.ca]
Sent: Wednesday, January 20, 2021 1:16 PM
To: Ramsey, Tasha; Barrett, Lisa L; Grandy Allen, Lisa; Coleman, Kathleen; Neale, Siony; Cox, Glenn; Reid, Emma K; Goodall, Barbara; Rockwood, Kenneth; Amanda Porter
Cc: McNeil, Shelly
Subject: RE: COVID-19 therapeutics and prophylactics

Hi

I'm not sure how everyone else feels about this but I think personally I would be most comfortable for Ivermectin saying that there is no recommendation at this time so the recommendation is held pending more evidence. The reason I feel that way is because not having federal support is most likely because it doesn't have a pharmaceutical company applying to Health Canada [redacted] unrelated [redacted] I'd like us to remain open to the potential for research in Nova Scotia outside of CO-VIC and CATCO unless there is something here I don't understand (I might be missing something on eligibility of covid research).

So I don't want to recommend it or anything, but just give it no recommendation pending further evidence as we acknowledge that there are several trials on-going on this drug.

Just my 2 cents.
Thanks
Gabrielle

NOVA SCOTIA
Health and Wellness

Dr. Gabrielle Richard BSc (Pharm), Pharm D
Pharmacist Consultant
Pharmaceutical Services and Extended Health Benefits
gabrielle.richard@novascotia.ca

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: January 19, 2021 1:24 PM
To: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Rockwood, Kenneth <Kenneth.Rockwood@nshealth.ca>; Amanda Porter <Amanda.Porter@dal.ca>
Cc: McNeil, Shelly <Shelly.McNeil@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics

Hi everyone,

Here is the agenda for our Jan 21st advisory group meeting:
unrelated
)
- Minutes (attached)
- unrelated
- Ivermectin (see slides for draft recommendation)
unrelated

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

From:	tasha.ramsey@nshealth.ca
To:	Coleman, Kathleen; Barrett, Lisa L; Grandy Allen, Lisa; Neale, Siony; Cox, Glenn; Richard, Gabrielle; Reid, Emma K; Goodall, Barbara
Subject:	Re: COVID-19 therapeutics and prophylactics
Date:	Wednesday, January 6, 2021 11:03:43 AM
Attachments:	ivermectin mortality.pdf Ivermectin Pilot Study.pdf Protocol.pdf

Hi Kathleen,

I agree- it will be important to have an ivermectin advisory group recommendation as more people are talking about it and we will aim to have one by the end of our meeting tomorrow.

The published data is attached (ivermectin pilot study and retrospective trial). I received a few questions asking about an ivermectin RCT that was published yesterday, but it is just the protocol and the study is ongoing (see attached).

Lisa Barrett very kindly offered to summarize the proposed mechanism, data, and give the ivermectin presentation tomorrow. Her content will come later today.

Tasha

From: "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>
Date: Wednesday, January 6, 2021 at 8:55 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Reid, Emma K" <EmmaK.Reid@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics

Hi Tasha
We are starting to hear more around ivermectin and I suspect we will be receiving correspondence here at DHW that will need to be answered.

Are these the only two documents that address the ivermectin studies? I also thought we were going to have a bit of a presentation of the evidence (similar to bamlan)?

I reached out to CADTH and they are completing a rapid response re the evidence although it is not complete yet. I know PHAC is also monitoring the evidence, but not sure what committees are involved in that. I just think we need to ensure we are doing a very thorough review if we are going to issue any recommendations.

Thanks,
Kathleen

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: January 5, 2021 2:03 PM
To: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics

Hi everyone,

Here is the agenda for our Jan 7th meeting:

- Review minutes from Dec 17 and 18th (all)
- unrelated [redacted]
- Ivermectin (all)

For the ivermectin discussion, the pilot and retrospective studies are attached for those that wish to review them. Lisa (Barrett) may also have an ivermectin summary to send out to the group as well.

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

From:	Coleman, Kathleen
To:	Ramsey, Tasha; Barrett, Lisa L; Grandy Allen, Lisa; Neale, Siony; Cox, Glenn; Richard, Gabrielle; Reid, Emma K; Goodall, Barbara
Subject:	RE: COVID-19 therapeutics and prophylactics
Date:	Wednesday, January 6, 2021 8:55:42 AM

Hi Tasha
We are starting to hear more around ivermectin and I suspect we will be receiving correspondence here at DHW that will need to be answered.

Are these the only two documents that address the ivermectin studies? I also thought we were going to have a bit of a presentation of the evidence (similar to bamlan)?

I reached out to CADTH and they are completing a rapid response re the evidence although it is not complete yet. I know PHAC is also monitoring the evidence, but not sure what committees are involved in that. I just think we need to ensure we are doing a very thorough review if we are going to issue any recommendations.

Thanks,
Kathleen

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: January 5, 2021 2:03 PM
To: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics

Hi everyone,

Here is the agenda for our Jan 7th meeting:

- Review minutes from Dec 17 and 18th (all)
- unrelated [redacted]
- Ivermectin (all)

For the ivermectin discussion, the pilot and retrospective studies are attached for those that wish to review them. Lisa (Barrett) may also have an ivermectin summary to send out to the group as well.

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7

Mi'kma'ki—Unceded Mi'kmaq Territory
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Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

From: Goodall, Barbara
To: Ramsey, Tasha
Subject: RE: COVID-19 therapeutics and prophylactics
Date: Tuesday, January 5, 2021 3:19:37 PM
Attachments: image002.png

Thank you Tasha!

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Ramsey, Tasha
Sent: Tuesday, January 5, 2021 2:03 PM
To: Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics

Hi everyone,

Here is the agenda for our Jan 7th meeting:

- Review minutes from Dec 17 and 18th (all)
- unrelated [redacted]
- Ivermectin (all)

For the ivermectin discussion, the pilot and retrospective studies are attached for those that wish to review them. Lisa (Barrett) may also have an ivermectin summary to send out to the group as well.

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

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Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
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✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University

5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

From:	Richard, Gabrielle
To:	Ramsey, Tasha; Coleman, Kathleen; Barrett, Lisa L; Grandy Allen, Lisa; Neale, Siony; Cox, Glenn; Reid, Emma K; Goodall, Barbara; Rockwood, Kenneth; Amanda Porter
Cc:	McNeil, Shelly
Subject:	RE: COVID-19 therapeutics and prophylactics
Date:	Thursday, April 8, 2021 8:57:56 AM
Attachments:	image002.png ON COVID tx guidelines April 6, 2021.jpg

Hi all

In case you're interested, these are the ON guidelines for COVID-19 published April 6th, 2021.
Thanks
Gabrielle

NOVA SCOTIA
Health and Wellness

Dr. Gabrielle Richard BSc (Pharm), Pharm D (she/her)
Pharmacist Consultant
Pharmaceutical Services and Extended Health Benefits
gabrielle.richard@novascotia.ca

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: April 7, 2021 8:38 PM
To: Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Rockwood, Kenneth <Kenneth.Rockwood@nshealth.ca>; Amanda Porter <Amanda.Porter@dal.ca>
Cc: McNeil, Shelly <Shelly.McNeil@nshealth.ca>
Subject: Re: COVID-19 therapeutics and prophylactics

unrelated
Tasha

From: "Coleman, Kathleen" <Kathleen.Coleman@novascotia.ca>
Date: Wednesday, April 7, 2021 at 4:47 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Richard, Gabrielle" <Gabrielle.Richard@novascotia.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>, "Grandy Allen, Lisa" <Lisa.GrandyAllen@nshealth.ca>, "Neale, Siony" <Siony.Neale@nshealth.ca>, "Cox, Glenn" <Glenn.Cox@nshealth.ca>, "Reid, Emma K" <EmmaK.Reid@nshealth.ca>, "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>, "Rockwood, Kenneth" <Kenneth.Rockwood@nshealth.ca>, Amanda Porter <Amanda.Porter@dal.ca>

Cc: "McNeil, Shelly" <Shelly.McNeil@nshealth.ca>
Subject: RE: COVID-19 therapeutics and prophylactics

Hi everyone,

unrelated [redacted]

Talk tomorrow,
Kathleen

From: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>
Sent: April 6, 2021 10:14 PM
To: Richard, Gabrielle <Gabrielle.Richard@novascotia.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>; Grandy Allen, Lisa <Lisa.GrandyAllen@nshealth.ca>; Coleman, Kathleen <Kathleen.Coleman@novascotia.ca>; Neale, Siony <Siony.Neale@nshealth.ca>; Cox, Glenn <Glenn.Cox@nshealth.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>; Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Rockwood, Kenneth <Kenneth.Rockwood@nshealth.ca>; Amanda Porter <Amanda.Porter@dal.ca>
Cc: McNeil, Shelly <Shelly.McNeil@nshealth.ca>
Subject: COVID-19 therapeutics and prophylactics

Hi everyone,

Here is the agenda for our April 8th meeting:

- Minutes
- unrelated [redacted]
  - [redacted]
- Review recommendations:
  - unrelated [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - Ivermectin
  - unrelated [redacted]
  - [redacted]
- [redacted]

You will find the slides for our meeting, minutes from our last meeting, and MSSU reviews for the agents we are due to review attached.

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
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✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

From: tasha.ramsey@nshealth.ca
To: Goodall, Barbara; Barrett, Lisa L
Subject: Re: Ivermectin unrelated
Date: Monday, April 12, 2021 7:23:46 PM
Attachments: image001.png
image002.png

Thanks!

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Monday, April 12, 2021 at 5:43 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Subject: FW: Ivermectin unrelated

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Boulos, Leah M
Sent: Monday, April 12, 2021 3:05 PM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Cc: Farrell, Ashley M <Ashley.Farrell@nshealth.ca>
Subject: Ivermectin and bamlanivimab

Hi Barb,

Here's this week's ivermectin update, unrelated

Have a good week!
Leah

Leah Boulos, MLIS
Evidence Synthesis Coordinator

Maritime SPOR SUPPORT Unit
Email: LeahM.Boulos@nshealth.ca

www.mssu.ca | @maritimespor
Sign up for our mailing list

From: Goodall, Barbara
To: Ramsey, Tasha
Subject: RE: MSSU Rapid Review
Date: Tuesday, January 26, 2021 12:23:01 PM
Attachments: image001.png
image002.png

Thank you!!!

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Ramsey, Tasha
Sent: Tuesday, January 26, 2021 12:22 PM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Subject: Re: MSSU Rapid Review

Ideally she would have summaries ready the Tuesday before each meeting. So it would be great if she could send us a summary page by the date indicated and then update it for us every 4 weeks

- unrelated
- Ivermectin: ideally feb 16 then every 4 weeks afterwards (march 16, etc).
- unrelated

Tasha

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Tuesday, January 26, 2021 at 11:50 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: MSSU Rapid Review

I am trying to align dates to these to provide to Leah – do you have a record of what "date" would be the 4 week mark for those we have put forth recommendations and what "Date" the upcoming will be reviewed?

Barbara Goodall
Research Associate, Infectious Diseases

Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Ramsey, Tasha
Sent: Monday, January 25, 2021 4:51 PM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>; Barrett, Lisa L <Lisa.Barrett@nshealth.ca>
Subject: Re: MSSU Rapid Review

Perfect- unrelated ! I appreciate it may take a bit to catch up with the advisory group, but I would also appreciate if she can complete an initial document and rolling review (every 4 weeks) for the agents we have made recommendations on:

- unrelated
- Ivermectin

unrelated

Tasha

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Monday, January 25, 2021 at 1:32 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Subject: MSSU Rapid Review

Hello,

Had a meeting with Leah Boulos today, she did the rapid reviews for COVIC … she will do them for the COVID therapeutics advisory group starting this week. unrelated .

Thanks!
Barb

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: tasha.ramsey@nshealth.ca
To: Goodall, Barbara
Subject: Re: MSSU summaries
Date: Monday, April 12, 2021 10:06:00 AM
Attachments: image001.png

Thanks!

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Thursday, April 8, 2021 at 9:58 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: FW: MSSU summaries

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Boulos, Leah M
Sent: Thursday, April 8, 2021 9:40 AM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Subject: RE: MSSU summaries

Hi Barb,

Here are the updated summaries. Since the ivermectin and unrelated summaries just had typos, I didn't change the dates on them. unrelated [redacted]

We'll be in touch next week with the new ivermectin unrelated [redacted].

Cheers,
Leah

From: Barrett, Lisa L
To: Ramsey, Tasha; Reid, Emma K
Subject: Re: T and P Advisory Group Meeting
Date: Tuesday, February 16, 2021 1:53:37 PM

unrelated [redacted]

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Ramsey, Tasha
Sent: Tuesday, February 16, 2021 1:45 PM
To: Barrett, Lisa L; Reid, Emma K
Subject: Re: T and P Advisory Group Meeting

unrelated [redacted]

From: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Date: Tuesday, February 16, 2021 at 1:41 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>, "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Subject: Re: T and P Advisory Group Meeting

unrelated [redacted]

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Ramsey, Tasha
Sent: Tuesday, February 16, 2021 1:19 PM
To: Barrett, Lisa L; Reid, Emma K
Subject: Re: T and P Advisory Group Meeting

Sounds like we have a plan:
Feb 25: ivermectin, unrelated
[redacted]

[redacted]

Tasha

From: "Barrett, Lisa L" <Lisa.Barrett@nshealth.ca>
Date: Tuesday, February 16, 2021 at 11:46 AM
To: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>, "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: Re: T and P Advisory Group Meeting

unrelated [redacted]

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Reid, Emma K
Sent: Tuesday, February 16, 2021 11:12 AM
To: Barrett, Lisa L; Ramsey, Tasha
Subject: RE: T and P Advisory Group Meeting

unrelated [redacted]
.

unrelated [redacted]

[redacted]

[redacted]

Thanks!
Emma

From: Barrett, Lisa L
Sent: Tuesday, February 16, 2021 10:55 AM
To: Ramsey, Tasha <Tasha.Ramsey@nshealth.ca>; Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: Re: T and P Advisory Group Meeting

unrelated [redacted])

L.

Lisa Barrett MD PhD FRCPC
Clinician Scientist, Infectious Diseases
NSHA/Dalhousie University
Rm. 5076, Dickson Building
Halifax, NS
Lisa.Barrett@nshealth.ca
Ph. 902 473 8477
Cell 902 233 3795

From: Ramsey, Tasha
Sent: Tuesday, February 16, 2021 10:41 AM
To: Barrett, Lisa L; Reid, Emma K
Subject: T and P Advisory Group Meeting

Hi Lisa and Emma,

unrelated [redacted]

We only have the ivermectin re-review on the agenda. The MSSU summary (attached) does not provide any new info that we have not considered already.

Tasha

Tasha Ramsey (she/her), BSc (Pharm), ACPR, PharmD

Clinical Coordinator– Infectious Diseases and Internal Medicine
Pharmacy Department | Nova Scotia Health Authority
1796 Summer Street, Halifax, NS | Canada | B3H 3A7
Mi'kma'ki—Unceded Mi'kmaq Territory
☎902-473-6829
✉ Tasha.Ramsey@nshealth.ca

Assistant Professor– College of Pharmacy
Dalhousie University
5968 College Street, PO Box 15000| Halifax, NS | Canada | B3H 4R2
✉ Tramsey@dal.ca

From: Reid, Emma K
To: Ramsey, Tasha
Subject: unrelated [redacted]
Date: Wednesday, February 24, 2021 8:13:57 AM
Attachments: image001.png
image002.png

Sounds good to me! Thanks.

Emma

From: Ramsey, Tasha
Sent: Tuesday, February 23, 2021 9:09 PM
To: Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: Re: unrelated [redacted]

Hi Emma,

unrelated [redacted].

Tasha

From: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Date: Tuesday, February 23, 2021 at 3:39 PM
To: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Subject: Re: unrelated [redacted]

[redacted]

[redacted]

[redacted] I also agree with ivermectin, ultimately the quality of evidence (no matter how you put it together in a meta analysis) is low.

Tasha

From: "Reid, Emma K" <EmmaK.Reid@nshealth.ca>
Date: Tuesday, February 23, 2021 at 1:13 PM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: RE: unrelated [redacted]

Hey Tasha,

unrelated [redacted]

unrelated [redacted].

And even though the information isn't new per se, I do picture some people seeing the results of the network meta-analysis for ivermectin and the ICU mortality outcome getting excited. Just looked into that a tad further and turns out that outcome data is from one single observational study of very low GRADE quality. I don't think we need to address it specifically, though.

unrelated [redacted]

[redacted]

[redacted]

Emma

From: Ramsey, Tasha
Sent: Tuesday, February 23, 2021 12:26 PM
To: Reid, Emma K <EmmaK.Reid@nshealth.ca>
Subject: FW: unrelated [redacted]

Hi Emma,

unrelated [redacted], but am wondering if you can take a quick peek to see if there is anything in these MSSU documents you feel we should address in the meeting package that will be sent out today.

Tasha

From: "Goodall, Barbara" <Barbara.Goodall@nshealth.ca>
Date: Tuesday, February 23, 2021 at 11:56 AM
To: "Ramsey, Tasha" <Tasha.Ramsey@nshealth.ca>
Subject: FW: unrelated [redacted]

Barbara Goodall
Research Associate, Infectious Diseases
Rm. 322B, Centre for Clinical Research, VG Site, QEII
5790 University Ave., Halifax, NS B3H 1V7
Cell: (902) 292-0132
barbara.goodall@nshealth.ca

From: Boulos, Leah M
Sent: Tuesday, February 23, 2021 10:58 AM
To: Goodall, Barbara <Barbara.Goodall@nshealth.ca>
Subject: unrelated [redacted]

Hi Barb,

unrelated [redacted]

Cheers,
Leah

Leah Boulos, MLIS
Evidence Synthesis Coordinator
Maritime SPOR SUPPORT Unit
Email: LeahM.Boulos@nshealth.ca

www.mssu.ca | @maritimespor
Sign up for our mailing list

From: Reid, Emma K
To: Ramsey, Tasha
Subject: Slides for next week"s Therapeutics and Prophylactics
Date: Friday, February 19, 2021 11:22:12 AM
Attachments: unrelated [redacted]

Hi Tasha,

[redacted]

For next week's meeting (ivermectin [redacted]), unrelated [redacted]

unrelated [redacted]

Emma

Privacy Office; Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

June 30, 2021

Sent via e-mail

Re: Full Disclosure – OUR FILE# NSHA-2021-077

On June 10, 2021 Nova Scotia Health (NSH) received your request under the *Freedom of Information and Protection of Privacy Act* (*FOIPOP Act*).

We understand your application to be for a copy of the following:
My request is involving information about PCR testing in Nova Scotia as it relates to Covid-19 since April of 2021. For reference, I also submitted request NSH-2021-033 several months ago. The information I am now looking for is essentially the same, just with an updated date range and some slight changes to the PCR cycle threshold ranges I am looking for. I've attached a document that was provided with my last request.

1. *I would like an updated version of this document including any changes to the cycle threshold for each lab in NS for all tests performed in the updated date range (April 1 2021 to present).*
2. *What is the average number of PCR amplification cycles that has been required to determine a positive Covid-19 test in Nova Scotia to date, since April 1 2021?*
3. *Of the total positive Covid-19 tests in NS to date (approximately 3978 since April 1 2021), how many (or what percentage) of them fit into the following PCR cycle threshold ranges?*
   <20
   20-25
   25-30
   30-35
   >35
4. *Is the cycle threshold used to test a Vaccinated vs Unvaccinated person any different?*

(Date Range for Record Search: From 03/31/2021 To 06/08/2021).

Please find a copy of the records located in response to your request. We are providing these records to you in their entirety. We are now closing your file.

Should you have any questions, please do not hesitate to contact me.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review.

Sincerely,
Katie Smith
Freedom of Information Officer

Privacy Office; Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

Nova Scotia Health Authority
Halifax, Nova Scotia

1. *I would like an updated version of this document including any changes to the cycle threshold for each lab in NS for all tests performed in the updated date range (April 1 2021 to present). What is the average number of PCR amplification cycles that has been required to determine a positive Covid-19 test in Nova Scotia to date, since April 1 2021?*

The information has not changed since your previous request. Please see the table below.

Laboratory	SARS CoV 2 Test	Ct value
QEII	In house assay based on BCCDC primers for RdRp on ABI 7500 fast	Total cycles – 45 RdRp CT <35 = positive RdRp CT 35 -38 = indeterminate
	Hologic Panther Aptima SARS CoV 2 assay	Total cycles – not described by manufacturer Positive based on manufacturer's criteria. Assay does not produce a Ct value
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	Roche 6800 – Cobas SARS CoV 2 assay	Total cycles – not described by manufacturer Ct<38 = positive Ct ≥ 38 = indeterminate
IWK	Biofire Respiratory 2.1 panel	Total cycles – not described by manufacturer Positive based on manufacturer's criteria - Ct value not reported by the instrument and cut off not defined by manufacturer
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
Cape Breton Regional	Hologic Panther Aptima SARS CoV 2 assay	Total cycles – not described by manufacturer

		Positive based on manufacturer's criteria. Assay does not produce a Ct value
	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	Biofire Respiratory 2.1 panel	Positive based on manufacturer's criteria - Ct value not reported by the instrument and cut off not defined by manufacturer
St Martha's Hospital	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
Aberdeen Hospital	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
Colchester Regional	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
Cumberland Regional Health Care Center	Biofire Respiratory 2.1 panel	Positive based on manufacturer's criteria - Ct value not reported by the instrument and cut off not defined by manufacturer
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate

	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
Valley Regional Hospital	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	Biofire Respiratory 2.1 panel	Positive based on manufacturer's criteria - Ct value not reported by the instrument and cut off not defined by manufacturer
Yarmouth Regional Hospital	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate

2. *Of the total positive Covid-19 tests in NS to date (approximately 3978 since April 1 2021), how many (or what percentage) of them fit into the following PCR cycle threshold ranges?*
   <20
   20-25
   25-30
   30-35
   >35

PCR range	**Count of Cycle Thresholds**
<20	111
20-25	85
25-30	52
30-35	28
>35	1
Grand Total	307

3. *Is the cycle threshold used to test a Vaccinated vs Unvaccinated person any different? (Date Range for Record Search: From 03/31/2021 To 06/08/2021).*

The cycle threshold used to test a vaccinated and unvaccinated person is not different.

Privacy Office; Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

September 2, 2021

Sent via e-mail

Re: Full Disclosure – OUR FILE# NSHA-2021-081

On June 17, 2021 Nova Scotia Health (NSH) received your request under the *Freedom of Information and Protection of Privacy Act* (*FOIPOP Act*).

We understand your application to be for a copy of the following:
Please provide documentation on the number of canceled or postponed surgeries and health procedures due to COVID-19. Please also provide any notes or notices about changes in surgeries or services provided to the Minister's Office.

Please find a copy of the records located in response to your request. We are providing these records to you in their entirety. We are now closing your file.

Should you have any questions, please do not hesitate to contact me.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review.

Sincerely,
Katie Smith
Freedom of Information Officer
Nova Scotia Health Authority
Halifax, Nova Scotia

Surgery Reductions - ALL Notifications

	Zone Group	Start Date	Reassess Date	SiteMerge	Surg % Reduction	Surgery Change Desc	Surg Impact	Comments
1		2-May-2021		Dartmouth General Hospital Halifax Infirmary Victoria General Hospital	21-40%	Impacted surgical services may include general surgery, cardiac surgery, orthopedic, urology, neurosurgery, ENT and ophthalmology.	The OR will continue to slow down 25-35% next week	
2		26-Apr-2021	3-May-2021	Dartmouth General Hospital Halifax Infirmary Victoria General Hospital	21-40%	Impacted surgical services may include general surgery, cardiac surgery, orthopedic, urology, neurosurgery, ENT and ophthalmology.		
3		6-May-2021	14-May-2021	Halifax Infirmary	21-40%	25% reduction in surgical service	see dashboard	
4		6-May-2021	14-May-2021	Halifax Infirmary Victoria General Hospital	41-60%	reduce SDA by 60%	see dashboard	
5		2-May-2021	5-May-2021	Cape Breton Regional Hospital		•1 week reduction of surgical admissions at CBRH beginning Monday May 3rd to increase bed capacity for COVID positive patients.	Maintain day surgery procedures unless human resources are needed.	Step 2 to this would be if human resource requirements arise we would temporarily reduce perioperative services at NSGH as there is redundancy in the system and those services are offered at other facilities.
6		2-May-2021	5-May-2021	St. Martha's Regional Hospital		Immediate reduction of surgical same day admissions with exception of high risk patients such as Cancer Care etc., to increase bed capacity for COVID positive patients, reassessing impact in 10-14 days, providing time to understand epi and rate of admission/length of stay of COVID-19.	Maintain day surgery procedures unless human resources are needed.	
7		9-May-2021	18-May-2021	Northside General Hospital	81-100%	Reduce surgery at NSGH for 2 weeks to pull staff to cover CBRH PACU/Day Surgery to release critical care trained staff to staff ICU to allow for preparation for COVID ICU surge	100% service reduction at NSGH however, theses services can be accesed at CBRH or GB for the duration of the reduction	Reduce surgery at NSGH for 2 weeks to pull staff to cover CBRH PACU/Day Surgery to release critical care trained staff to staff ICU to allow for preparation for COVID ICU surge
8		9-May-2021	18-May-2021	Cape Breton Regional Hospital	41-60%	extend additional 2 weeks, reduction of surgical admissions at CBRH beginning may 10, 2021. to ensure bed capacity for COVID + patients. Maintain reduction to 4 same day admissions per day at CBRH to be used for urgent/malignant procedures. Maintain day surgery procedures unless human resources are needed. Reassess situation on Tuesday May 18th, 2021 for admissions for the following week.	60% reduction in admissions/surgeries due to limited bed cpacity at CBRH and community sites. allow for 4 admissions per day to be used for malignant and urgent procedures while all other day surgeries will be maintined unless further reductions are required for Human Resources needs.	•Extend additional 2 weeks, reduction of surgical admissions at CBRH beginning Monday May 10th to ensure bed capacity for COVID positive patients. •Maintain reduction to 4 Same day admissions per day at CBRH to be used for urgent/malignant procedures. •Maintain day surgery procedures unless human resources are needed. •Reassess situation on Tuesday May 18th for admissions the following week
9		24-May-2021	1-Jun-2021	Cape Breton Regional Hospital St. Martha's Regional Hospital Northside General Hospital	21-40%	Two week extension of previously submitted reduction.	CBRH & SMRH reduction of surgical admissions by 30%, all day surgery procedures are going forward. NSGH 100% service reduction of surgery & endoscopy, however these services can be accessed at CBRH or GBH.	To be reassessed on June 1st.
10		7-Jun-2021	9-Jun-2021	Cape Breton Regional Hospital St. Martha's Regional Hospital Northside General Hospital	0-20%	Reintroduction of Perioperative Services in EZ	Cape Breton Regional Hospital: June7th -June 11th: same day admissions increased from 4 to 8 per day (2 per general anesthesia block) Provided COVID cases remain low we will look to increase to full admissions on June 14th St Martha's Regional Hospital: June7th -June 11th: same day admissions will be increased to 1 per day. Northside General Hospital: June7th -June 11th: resumption of service.	
11		26-Apr-2021		Colchester East Hants Health Centre Aberdeen Regional Hospital Cumberland Regional Health Care Centre		Starting April 29, 2021, cancel/reschedule all elective surgeries at CRHCC, CEHHC and ARH requiring inpatient admission (based on risk adjustment, i.e. cancer). This represents approx. 7 to 13 surgeries per day across the Norther Zone.	Day surgeries will continue and be assessed on a case by case to prevent turning to an admission.	
12		3-May-2021	7-May-2021	Colchester East Hants Health Centre Aberdeen Regional Hospital Cumberland Regional Health Care Centre	21-40%	Peri-Op has reduced elective surgery by 25% to maintain a max of 2 admissions per day and close 1 OR per day for Cumberland Regional and Colchester Regional. Aberdeen reducced elective surgery admissions to 4 beds per day but has not fully implemented 25% reduction. Which will impacted 3 clinical staff per site.	Surgeon, Anesthesiologists and surgical assists who are all fee for service	
13		10-May-2021	19-May-2021	Colchester East Hants Health Centre Aberdeen Regional Hospital Cumberland Regional Health Care Centre	61-80%	Beginning Monday, May 10th, only emergent, urgent and cancer surgery cases will proceed, as well as urgent or cancer related endoscopy.	Clears beds for non-covid admissions and allow transfer of patients to allow full Covid unit to open.	

	Zone Group	Start Date	Reassess Date	SiteMerge	Surg % Reduction	Surgery Change Desc	Surg Impact	Comments
14		22-May-2021	25-May-2021	Colchester East Hants Health Centre Aberdeen Regional Hospital Cumberland Regional Health Care Centre	41-60%	Maximum number of scheduled surgery per day requiring admission per site as follows: Truro 1 per day, Cumberland 1 per day, Aberdeen 2 per day. Urgent or emergent or cancer cases will continue.	Client surgery will be postponed.	Cumberland will complete cases that are not urgent, emergent or cancer provided that they remain within the allocated staffing and OR capacity that remains after deployment
15		26-May-2021	31-May-2021	Colchester East Hants Health Centre Aberdeen Regional Hospital Cumberland Regional Health Care Centre	0-20%	Colchester surgerical activity levels remains at 75% normal operations. Aberdeen and Cumberland are working to resume at 100%, expect to reach near 100% may 31.	All sites will closely monitor bed capacity for inpatients and ICU, including the need to quickly repatriate patients from other zones, and support COVID services provincially.	Our process is agile, and we can dial up, or down surgical services as required to match our zone requirements, and the overall needs of NSH.
16		3-May-2021	4-May-2021	South Shore Regional Hospital Valley Regional Hospital Yarmouth Regional Hospital		Up to a 1-week reduction of surgical admissions at all 3 Regional Sites for elective cases commencing Monday May 3, 2021 with reassessments every 2 days. Cases will be cancelled on May 3, 4 & 5th with an re-evaluation occurring on May 4th.	Admissions to be used for urgent/malignant procedures only.	
17		3-May-2021	26-May-2021	Valley Regional Hospital	21-40%	Elective surgeries admissions reduced to urgent or malignant only.	Decreased elective surgery admissions however have increased day surgeries.	
18		5-May-2021	26-May-2021	South Shore Regional Hospital	21-40%	Elective surgeries reduced to malignancies or urgencies only.	Despite decrease in elective surgeries, day surgeries have increased.	
19		5-May-2021	26-May-2021	Yarmouth Regional Hospital	21-40%	Elective surgeries reduced to malignancies or urgencies only.	Despite decrease in elective surgeries, day surgeries have increased.	
20		31-May-2021	3-Jun-2021	Valley Regional Hospital	21-40%	Elective surgeries admissions reduced to urgent or malignant only.	Decreased elective surgery admissions however have increased day surgeries.	
21		31-May-2021	3-Jun-2021	South Shore Regional Hospital	21-40%	Elective surgeries reduced to malignancies or urgencies only.	Despite decrease in elective surgeries, day surgeries have increased.	
22		31-May-2021	3-Jun-2021	Yarmouth Regional Hospital	21-40%	Elective surgeries reduced to malignancies or urgencies only.	Despite decrease in elective surgeries, day surgeries have increased.	
23		7-Jun-2021	9-Jun-2021	South Shore Regional Hospital Valley Regional Hospital Yarmouth Regional Hospital	0-20%	Gradually resuming elective surgery admissions.		Reassessed weekly with next assessment planned for June 9th.

In NSH, since the start of the pandemic (Mar 16, 2020 to Jul 31, 2021), there have been 18,556 surgical cancellations. It is not possible to determine exactly how many of these were directly caused by COVID pandemic, but we do know that 3,563 cancellations were coded with “Pandemic” as the reason for cancellation. However, these cancellation reason codes have been applied inconsistently between sites, at times, so data quality is a concern.

Aside from cancellations, we can look at how many fewer surgeries were performed during the pandemic vs a similar time period before pandemic. This might give a better picture of the decreased surgical activity than the cancellations data.

Since start of pandemic (Mar 16, 2020 to Jul 31, 2021), there were 84,361 completed surgeries in NSH. Comparatively in the pre-pandemic period of Mar 16, 2018 to Jul 31, 2019, there were 99,959 completed surgeries. This amounts to a difference of 15,598 surgeries.

Surgical Services and COVID-19

- Nova Scotia Health's response to COVID-19 required us to make temporary changes to some services, including surgical care.
- We regret having to delay care and the concerns and disruptions this has caused our patients and their families.
- We have continued to encourage patients to follow up with their primary care providers or surgeons if their condition changes while they are awaiting surgery and to seek emergency care if something urgent arises.
- While we recognize the importance of providing timely access to surgeries, this is a critical part of our pandemic response plan as it allows us to build capacity (beds, staffing, other resources) to support COVID-19 related services, including inpatient care and intensive care (ICUs). It also helps us ensure the continuation of other critical, life-saving services, including emergency surgeries and ICUs for non-COVID patients.
- Doing less surgeries allowed us to free-up resources like ventilators and redeploy critical care trained staff from our operating rooms and Post Anesthesia Care Units (recovery units) to deliver intensive care.
- Throughout the pandemic our teams have continued to focus on delivering urgent, emergency and time-sensitive cancer surgeries. They have also worked to minimize reductions, restore services as quickly as possible following disruptions, and to prioritize care based on need.
- We learned valuable lessons in the first wave that allowed us to adjust our approach in subsequent waves and avoid the same level of widescale surgical reductions.
- In fact, despite the higher number of patients being hospitalized/requiring intensive care in wave 3, provincially we have largely been able to keep volumes above 80% since we began reducing surgeries on April 23 (reducing to about 50% of normal volumes the last week of May). In the first wave surgical services were reduced to less than 30% of typical volumes for a prolonged period.
- We have followed a similar strategy for diagnostic imaging services and outpatient clinics, which has allowed us to maintain higher service volumes in these areas as well. For example, in the first wave, diagnostic imaging services were reduced to as low as 25 per cent of our 2019 volumes, however in this third wave we have kept our volumes at nearly 100 per cent, reducing to 78 per cent for only two weeks (peak of Wave 3).

- We have once again begun to increase surgeries at many sites across the province and will continue with this approach, monitoring case numbers and illness in our communities, to determine how best to adjust services in each facility/zone.

- Our recovery plans will involve our teams analyzing at our wait time and utilization data and identifying short- and long-term strategies to increase surgical volumes and the supporting resources required to achieve this.

- To give a sense of the overall impact that COVID-19 has had on surgical volumes, between January 1 and May 26 of 2019, we completed more than 29,600 surgeries, compared to just over 20,100 surgeries for this same timeframe in 2020 and more than 28,000 surgeries for the same timeframe this year. (Note: includes surgical procedures only, excludes endoscopy/bronchoscopy procedures)

- Status of those scheduled cases that were postponed (for any reason – pandemic service reduction or otherwise) in the first or third wave.
    - Wave 1 – 95% of the more than 3300 scheduled cases postponed have been completed or removed from the wait list.
    - Wave 3 – 43% of the 2600 scheduled cases postponed have now been completed (17%), rescheduled (14%), or removed from the wait list (12%).

  (Note: Updated as of June 3, however data can take several days to update in the system. Removals would occur for various reasons – double booking in system completed at another site, patient no longer wishing to proceed with surgery etc.)

How many surgeries have been postponed due to the pandemic?

Wave 1

- In the first wave of COVID-19, based on the concerning situations we were seeing in other jurisdictions, we moved to quickly reduce surgical volumes across the province in advance of an anticipated surge of hospital and ICU admissions. Many clinics and other services were also temporarily halted or scaled back, including surgical consults and orthopedic assessment clinics.

- ***While it was fortunate that our hospitals did not have to respond to a large surge in COVID-19 patients during the first wave, more than 3200* scheduled cases were postponed between the start of the first wave (March 16, 2020) and when we began to gradually reintroduce services (May 25, 2020).*** During this time our overall surgical volumes were down to less than one third of the previous year's volumes.

* This figure represents patients with scheduled surgeries (excludes endoscopies/bronchoscopies) who had their surgery delayed. It does not provide a complete picture of the impact the pandemic had on surgical volumes in Wave 1, as many other patients were not yet scheduled, but would have otherwise proceeded to have surgery during that timeframe.

While most of these cancellations were due to COVID-19 service reductions, this figure reflects all cases cancelled for any reason between March 16-May 25. There would be other reasons for cancellations including patient illness, patients being rescheduled due to emergency/trauma cases, patients changing their mind, equipment issues, etc. We have been working with surgeons and administrative staff to improve and standardize how cancellations are coded to provide better insight into the many reasons for cancellations and how we might improve in certain areas.

Wave 2/Wave 3:

- Recognizing the extent to which surgical patients and providers were impacted in the first wave, our teams took a different approach to planning for future waves.
- Our goal was to ensure we had the capacity and flexibility to respond to emerging COVID-19 demands, while maintaining surgical volumes to the greatest extent possible, for as long as possible, and being prepared to restore services as quickly as possible as pressures subsided.
- Rather than making immediate, largescale reductions to surgical services across the province, our plan for future waves involved us making smaller-scale, more gradual site or zone-based changes as needed and phasing in or staggering further reductions based on the resources that were needed. We also felt it was important for surgical consults/other supporting clinics to continue to the greatest extent possible.
- In the second wave of COVID-19 last fall, hospitalization needs were minimal, and we largely managed to maintain the volume of surgeries completed in 2019/20.
- And when we have needed to minimize admissions, we have worked to increase outpatient procedures to the extent possible, to allow as many surgeries as we could to continue.
- With the most recent wave, we have taken a more staggered and localized approach to scaling back services. Our surge plans include trigger points (e.g. total COVID hospitalizations and ICU admissions) that triggered localized reductions and helped us determine when we needed to extend reductions to other sites to allow for a coordinated provincial response.
- For example, we began gradually reducing surgeries in Central Zone in late April when we saw a jump in new cases and the resulting increased demands for patients requiring both hospitalization and intensive care.
- As the situation progressed, other sites started to reduce surgeries requiring hospital stays and as ICU demands continued to grow in Central Zone, we made further surgical reductions in areas like the Northern Zone. This created capacity to implement our surge plan, which involved, for example, Colchester East Hants Health Centre in Truro accepting patient transfers from the Halifax area when their admissions/ICUs reached certain levels.
- These changes have been regularly reassessed over the past number of weeks and with total new cases, admissions and ICU pressures trending downward, we are beginning to gradually reverse these plans zone by zone and site by site.

- Despite the higher number of patients being hospitalized and requiring intensive care this third wave, our plan has worked as intended. As shown below, since we began scaling back surgeries on April 23, provincially we have largely managed to keep volumes above 80% of 2019/20 volumes, reducing to about 70% when ICU demands peaked in mid-late May and falling to approximately 50% last week (Note: included holiday and data can take several days to update so my underrepresent true volume).

Note: There would be some variations in these reductions by zone, with the Central and Northern Zone experiencing greater reductions than the Western and Eastern Zones due to the high volume of COVID-19 admissions in Central Zone and the Northern Zone's surge plan role as the primary back up to Central Zone facilities. Data reflects all surgical procedures at all sites (excludes endoscopy/bronchoscopy).

- ***Our data currently shows that since April 23 approximately 2600 scheduled surgeries were postponed.*** *(Note: This reflects the number of patients who had a surgery date that was changed.* It does not fully reflect the total number of surgeries that would have otherwise proceeded during this time.)

- To give a sense of the overall impact that COVID-19 has had on surgical volumes, between January 1 and May 26 of 2019, we completed more than 29,600 surgeries, compared to just over 20,100 surgeries for this same timeframe in 2020 and more than 28,000 surgeries for the same timeframe this year.

How long will it take to clear this additional backlog and how much overall time has been added to the existing surgical backlog. Can you provide a breakdown by surgery type?

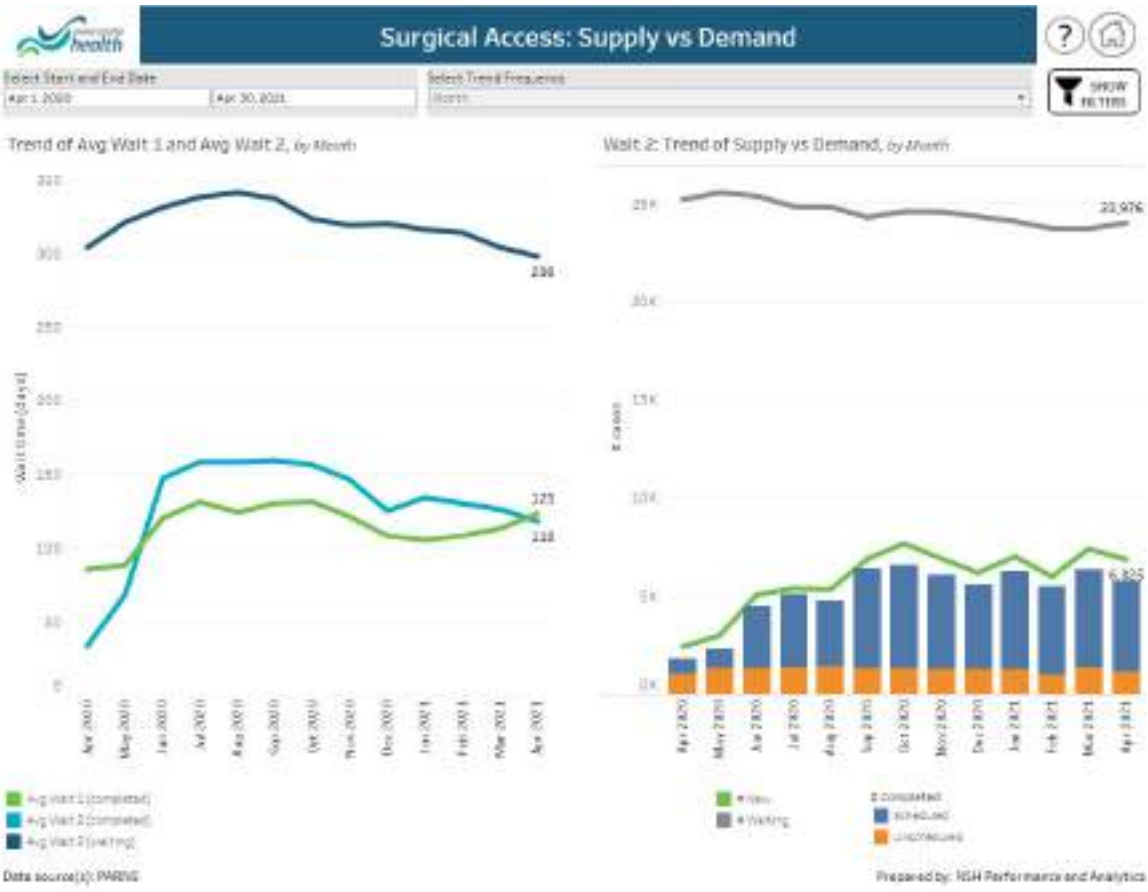
- At this time, it is difficult to quantify the true extent of the backlog and even more difficult to predict how long it would take, and what would be required to make up this backlog. The fact that we have been able the minimize the extent to which services were reduced in this third wave is a positive factor and the quicker we can restore services to our typical activities and volumes, the better.
- We have begun to ramp-up surgical activity across many of our sites this week.
- While we know that our current waitlist (total number of patients waiting) has remained fairly consistent, we don't necessarily have confidence that the current number of patients in the queue for surgery is a true reflection of the demand/need.
- There are a couple of reasons for this, but it is important to note that our PAR-NS surgical wait list only reflects patients who have been determined to require surgery (following surgical consult) and had this information entered in the system by their surgeon.
- We know fewer patients may have seen their primary care provider over the last year to be referred for a surgical consult (wait 1 = time from referral to consult).
- We also know that fewer patients have likely had consults with a surgeon over the past year to determine if they needed surgery (wait 2 waiting = time patient has been waiting for surgery since a decision was made to operate; wait 2 completed = time from decision to operate to completed surgery).
- Some of this can be attributed to the fact that services were scaled back, while patients being concerned about COVID and not seeking care may also be a factor.
- We do have good data on the status of those scheduled cases that were postponed (for any reason) in the first or third wave.
    - Wave 1 – 95% of the more than 3300 scheduled cases postponed have been completed or removed from the wait list.
    - Wave 3 – 43% of the 2600 scheduled cases postponed have now been completed (17%), rescheduled (14%), or removed from the wait list (12%).
      (Note: Updated as of June 3, however data can take several days to update in the system. Removals would occur for various reasons – double booking in system completed at another site, patient no longer wishing to proceed with surgery etc.)
- Our recovery plans will involve our teams looking at both short and long term strategies to help increase the volume of surgeries being completed and the supporting resources required.

- Our plans will focus on:
    - continuing to prioritize patients based on need
    - rebooking/completing surgeries for those patients who had their surgeries cancelled
    - optimizing OR scheduling – making full use of existing OR time/resources across all our sites and expanding OR hours where feasible (e.g. inpatient/ outpatient surgery volumes were increased leading up to Christmas last year, as helping make up some of the lost volumes)
    - continued coordination of resources across the province
    - identifying opportunities to build capacity (e.g. same day joints post first wave, enabling roles)
    - capitalize on/leverage the strategies and lessons learned during COVID-19 to create a new normal
    - continuing data quality efforts to ensure we have clear and accurate data to support decision making, including wait list review and management
    - workforce requirements, including recognition of the impact that the prolonged and intense COVID-19 response has had on our teams

Average wait list comparison over time:

The visual below reflects average (avg) wait times from April 1/19- to April 30/21, including:

- Wait 1 completed = wait from surgical consult to referral. (Note: We do not have accurate wait 1 waiting data, to show how long patients that are still waiting for surgical consults have been waiting.)
- Avg wait 2 completed = wait from decision to operate to surgery
- Avg wait 2 waiting = how long patients have been waiting since decision to operate
- These waits are all higher than pre-COVID but have been generally trending in the right direction since last summer.
- The fact that Wait 1 is going up could reflect the fact that more patients are now seeing their primary care providers once again and being referred for consults. This could also be a result of the fact that patients were being referred, but surgeons were not completing as many office consults at points in time, and have started to catch up, with data better reflecting pent up demand.



Completed cases – year over year comparisons for January 1–May 20 (2019–2021)

Shows change in volumes for seven highest volume surgical sub-specialties

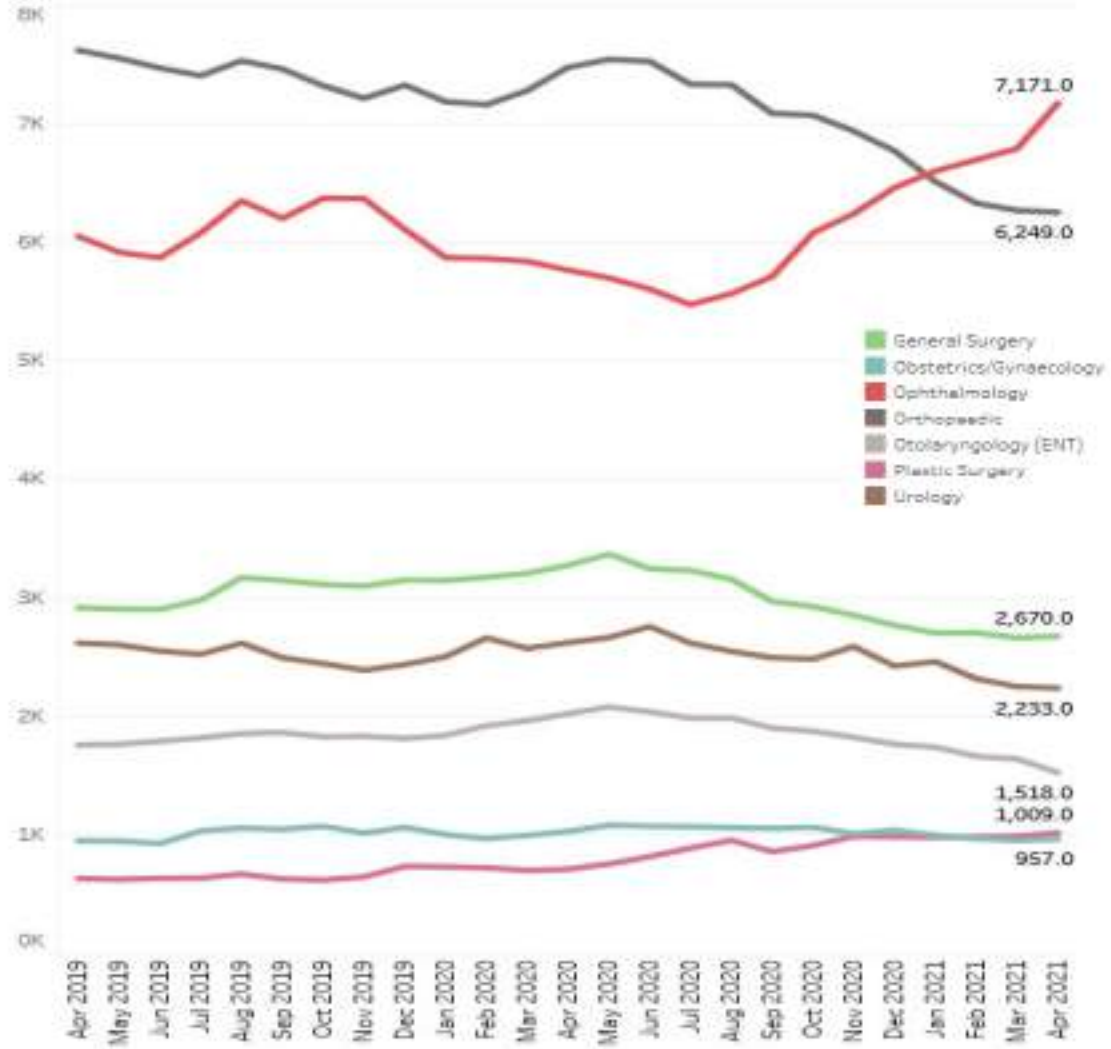
	2019	2020	2021
Grand Total	100.0%	68.0%	93.1%
Ophthalmology	100.0%	53.4%	92.8%
Orthopaedic	100.0%	65.9%	88.8%
General Surgery	100.0%	78.3%	100.1%
Urology	100.0%	77.6%	103.5%
Obstetrics/Gynaecology	100.0%	81.0%	97.5%
Otolaryngology (ENT)	100.0%	57.2%	88.7%
Plastic Surgery	100.0%	62.7%	55.3%

Patients waiting for surgery (Wait 2 waiting)

Shows Wait 2 trends for seven highest volume surgical sub-specialties

Waiting

Trend by Month



From: Wood, Krista
To: Armstrong, Brooke J
Cc: Gillis, John W; Elliott, Brendan; Grant, Krista L
Subject: Surgery Messages
Date: Thursday, June 3, 2021 11:27:00 AM
Attachments: Surgery messages - reductions wave 1 and wave 3 - June 3.docx
image002.png
image003.png
image004.png

Hi Brooke,

Sharing some messaging and background we have compiled for other requests. This has been updated with today's data.
This includes some key messages about impact and where we are with making up cancelled procedures. Also includes some more detailed information about wait time/wait list impacts.

It would be great to emphasize the deliberate efforts made to avoid the same types of impacts we saw in wave 1 and the fact that our surgical volumes are much higher this wave than last spring.

We have also begun the process of restoring services this week, with the goal to get back to 100 per cent of usual service levels faster than we did in the first wave.

This data includes surgical procedures only not endoscopy/bronchoscopy.

Thank you and please call if you have any questions,
Krista

Krista Wood, BPR, CHE
Senior Communications Advisor, Perioperative Services
Public Engagement and Communications
Nova Scotia Health Authority
90 Lovett Lake Court, Suite 201
Halifax, NS B3S 0H6
Cell: 902-890-4354
www.nshealth.ca

I live and work in Mi'kma'ki, the unceded ancestral territory of the Mi'kmaq people.

Pronouns: She/Her/Hers

visit | like | follow | subscribe

Learn more about our efforts to improve access and care for hip and knee joint replacement patients at www.nshealth.ca/hip-and-knee

Privacy Office; Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

June 30, 2021

Sent via regular mail

Re: Full Disclosure – OUR FILE# NSHA-2021-086

On June 25, 2021 Nova Scotia Health (NSH) received your request under the *Freedom of Information and Protection of Privacy Act* (*FOIPOP Act*).

We understand your application to be for a copy of the following:

1. *Re: PCR testing dates, March 1, 2020 to current date. The different test settings for PCR, swab, polymerase chain reaction. To be specific, the "cycle count" aka "cycle threshold" aka "PCR value" aka "number of amplifications" aka "count value" used as well as the time frames and dates for these settings. All of them since the beginning of the swab test for COVID-19 screen to the date this request is received.*
2. *Also re: these swabs, did any kits used by the department contain "sterile EO" on ethylene oxide?*

Please find a copy of the records located in response to your request. We are providing these records to you in their entirety. We are now closing your file.

Should you have any questions, please do not hesitate to contact me.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review.

Sincerely,
Katie Smith
Freedom of Information Officer
Nova Scotia Health Authority
Halifax, Nova Scotia

1. *Re: PCR testing dates, March 1, 2020 to current date. The different test settings for PCR, swab, polymerase chain reaction. To be specific, the "cycle count" aka "cycle threshold" aka "PCR value" aka "number of amplifications" aka "count value" used as well as the time frames and dates for these settings. All of them since the beginning of the swab test for COVID-19 screen to the date this request is received.*

Laboratory	SARS CoV 2 Test	Ct value
QEII	In house assay based on BCCDC primers for RdRp on ABI 7500 fast	Total cycles – 45 RdRp CT <35 = positive RdRp CT 35 -38 = indeterminate
	Hologic Panther Aptima SARS CoV 2 assay	Total cycles – not described by manufacturer Positive based on manufacturer's criteria. Assay does not produce a Ct value
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	Roche 6800 – Cobas SARS CoV 2 assay	Total cycles – not described by manufacturer Ct<38 = positive Ct ≥ 38 = indeterminate
IWK	Biofire Respiratory 2.1 panel	Total cycles – not described by manufacturer Positive based on manufacturer's criteria - Ct value not reported by the instrument and cut off not defined by manufacturer
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
Cape Breton Regional	Hologic Panther Aptima SARS CoV 2 assay	Total cycles – not described by manufacturer Positive based on manufacturer's criteria. Assay does not produce a Ct value
	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
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	Biofire Respiratory 2.1 panel	Positive based on manufacturer's criteria - Ct value not reported by the instrument and cut off not defined by manufacturer
St Martha's Hospital	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
Aberdeen Hospital	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
Colchester Regional	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
Cumberland Regional Health Care Center	Biofire Respiratory 2.1 panel	Positive based on manufacturer's criteria - Ct value not reported by the instrument and cut off not defined by manufacturer
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Valley Regional Hospital	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	Biofire Respiratory 2.1 panel	Positive based on manufacturer's criteria - Ct value not reported by the instrument and cut off not defined by manufacturer
Yarmouth Regional Hospital	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45

		Ct<37 = positive Ct ≥ 37 = indeterminate

2. *Also re: these swabs, did any kits used by the department contain "sterile EO" on ethylene oxide?*

   Nova Scotia Health has procured a number of swab kits from various supplies. Many of these companies sterilize their swabs using Ethylene Oxide, a widely used method of sterilization.

Privacy Office; Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

August 25, 2021

Sent via e-mail

Re: Full Disclosure – OUR FILE# NSHA-2021-087

On June 28, 2021 Nova Scotia Health (NSH) received your request under the *Freedom of Information and Protection of Privacy Act* (*FOIPOP Act*).

We understand your application to be for a copy of the following:
Please provide all information related to, and no less than all queries indicated below:

1. *Use of Nasopharyngeal Swab to conduct RT-PCR test information, studies, research and effectiveness, used to direct decisions made by the Government of Nova Scotia and Nova Scotia Health Authority.*
2. *All information related to RT-PCR testing cycles, what triggers or determines test cycle frequency increase and decrease. The number preferred for RT-PCR test cycles, the decision-making criteria used for test cycles by the Nova Scotia Health Authority and the Government of Nova Scotia.*

Please find a copy of the records located in response to your request. We are providing these records to you in their entirety. We are now closing your file.

Should you have any questions, please do not hesitate to contact me.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review.

Sincerely,
Katie Smith
Freedom of Information Officer
Nova Scotia Health Authority
Halifax, Nova Scotia

FOIPOP 2021-087:

1. *Use of Nasopharyngeal Swab to conduct RT-PCR test information, studies, research and effectiveness, used to direct decisions made by the Government of Nova Scotia and Nova Scotia Health Authority.*

   We follow and help develop guidance on the use of PCR for COVID-19 testing. We have attached the guidance documents and studies that we have done and used to inform the use of RT-PCR testing.

2. *All information related to RT-PCR testing cycles, what triggers or determines test cycle frequency increase and decrease. The number preferred for RT-PCR test cycles, the decision-making criteria used for test cycles by the Nova Scotia Health Authority and the Government of Nova Scotia.*

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Sample	SARS-CoV-2 10-fold dilution	IDNOW	LDT CoV ABI (E gene)	LDT CoV ABI (RdRp)	LDT CoV ABI (Total)	Panther CoV	Biofire	Xpert CoV (E gene)	Xpert CoV (N2)	Xpert CoV (Total)	Xpert CoV/FluA/B/RSV	6800 CoV (Orf1a)	6800 CoV (E gene)	6800 CoV (Total)
2	-2	POS (3/3)	3/3	3/3	POS (3/3)	POS (3/3)	POS (1/1)	1/1	1/1	POS (1/1)	POS (1/1)	3/3	3/3	POS (3/3)
3	-3	POS (3/3)	3/3	3/3	POS (3/3)	POS (3/3)	POS (1/1)	1/1	1/1	POS (1/1)	POS (1/1)	3/3	3/3	POS (3/3)
4	-4	POS (2/3)	3/3	3/3	POS (3/3)	POS (3/3)	POS (3/3)	3/3	3/3	POS (3/3)	POS (3/3)	3/3	3/3	POS (3/3)
5	-5	NEG (0/3)	1/3	2/3	NEG (0/3)	POS (3/3)	POS (3/3)	3/3	3/3	POS (3/3)	POS (3/3)	3/3	3/3	POS (3/3)
6	-6	NEG (0/3)	0/3	0/3	NEG (0/3)	POS (1/3)	POS (2/3)	2*/3	2*/3	IND (2/3)	POS (3/3)	3/3	3/3	POS (3/3)
7	-7	NEG (0/3)	0/3	0/3	NEG (0/3)	NEG (0/3)	NEG (0/3)	1*/3	1*/3	IND (1/3)	NEG (0/3)	1/3	1/3	IND (2/3)
RepA	-2		27.54	28.61		1242		23.7	25.5		23.7	24.78	24.52	
	-3		31.52	32.16		1159		27.3	29.1		27.3	28.18	27.94	
	-4		36.07	37.08		1231		29.1	30.9		30.6	31.58	31.5	
	-5			39.05		842		35	37.2		34.1	30.02	30.26	
	-6					329		40.9	41.5		37.4	36.32	36.12	
	-7					270		43.3	43.1		0		38.08	
RepB	-2		27.19	28.30		1193		30.4	32.7		30.5	25.22	24.89	
	-3		31.29	32.29		1238		32.8	35.7		34.0	27.5	27.37	
	-4		35.22	35.94		1228		0	0		36.9	31.09	30.87	
	-5					1147		0	0		0	33.44	33.79	
	-6					332						35.73	36.85	
	-7					272						37.47		
RepC	-2		26.93	27.34		1199		29	30.8		30.4	24.46	24.1	
	-3		31.27	32.25		1208		32	33.6		32.9	27.72	27.4	
	-4		32.34	33.22		1159		38.9	41.2		36.8	31.06	30.78	
	-5		38.86	38.70		1110		0	0		0	33.79	33.87	
	-6					636						35.44	36.59	
	-7					285								

AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews®

PRACTICAL GUIDANCE FOR CLINICAL MICROBIOLOGY

Practical Guidance for Clinical Microbiology Laboratories: Viruses Causing Acute Respiratory Tract Infections

Carmen L. Charlton,[a,b] Esther Babady,[c,d,e] Christine C. Ginocchio,[f,g] Todd F. Hatchette,[h,i] Robert C. Jerris,[j] Yan Li,[k,l] Mike Loeffelholz,[m] Yvette S. McCarter,[n,o] Melissa B. Miller,[p] Susan Novak-Weekley,[q] Audrey N. Schuetz,[r] Yi-Wei Tang,[d,s] Ray Widen,[t] Steven J. Drews[a,b]

[a]Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, Alberta, Canada
[b]Provincial Laboratory for Public Health, Edmonton, Alberta, Canada
[c]Microbiology Service, Memorial Sloan-Kettering Cancer Center, New York, New York, USA
[d]Department of Laboratory Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York, USA
[e]Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York, USA
[f]Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York, USA
[g]bioMérieux/BioFire Diagnostics, New York, New York, USA
[h]Division of Microbiology, Department of Pathology and Laboratory Medicine, Nova Scotia Health Authority, Halifax, Nova Scotia, Canada
[i]Department of Pathology, Dalhousie University, Halifax, Nova Scotia, Canada
[j]Microbiology, Children's Healthcare of Atlanta, Atlanta, Georgia, USA
[k]Influenza and Respiratory Viruses Section, National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, Manitoba, Canada
[l]Department of Medical Microbiology, University of Manitoba, Winnipeg, Manitoba, Canada
[m]Department of Pathology, Clinical Microbiology Division, University of Texas Medical Branch, Galveston, Texas, USA
[n]Department of Pathology and Laboratory Medicine, University of Florida College of Medicine, Jacksonville, Florida, USA
[o]Clinical Microbiology Laboratory, UF Health-Jacksonville, Jacksonville, Florida, USA
[p]Department of Pathology & Laboratory Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA
[q]Medical Affairs, Qvella Corporation, Carlsbad, California, USA
[r]Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine and Science, Rochester, Minnesota, USA
[s]Department of Pathology and Laboratory Medicine, Weill Medical College of Cornell University, New York, New York, USA
[t]Esoteric Testing/R&D Pathology Department, Tampa General Hospital, Tampa, Florida, USA

Citation Charlton CL, Babady E, Ginocchio CC, Hatchette TF, Jerris RC, Li Y, Loeffelholz M, McCarter YS, Miller MB, Novak-Weekley S, Schuetz AN, Tang Y-W, Widen R, Drews SJ. 2019. Practical guidance for clinical microbiology laboratories: viruses causing acute respiratory tract infections. Clin Microbiol Rev 32:e00042-18. https://doi.org/10.1128/CMR.00042-18.

Address correspondence to Steven J. Drews, drews@ualberta.ca.

Published 12 December 2018

SUMMARY Respiratory viral infections are associated with a wide range of acute syndromes and infectious disease processes in children and adults worldwide. Many viruses are implicated in these infections, and these viruses are spread largely via respiratory means between humans but also occasionally from animals to humans. This article is an American Society for Microbiology (ASM)-sponsored Practical Guidance for Clinical Microbiology (PGCM) document identifying best practices for diagnosis and characterization of viruses that cause acute respiratory infections and replaces the most recent prior version of the ASM-sponsored Cumitech 21 document, *Laboratory Diagnosis of Viral Respiratory Disease*, published in 1986. The scope of the

original document was quite broad, with an emphasis on clinical diagnosis of a wide variety of infectious agents and laboratory focus on antigen detection and viral culture. The new PGCM document is designed to be used by laboratorians in a wide variety of diagnostic and public health microbiology/virology laboratory settings worldwide. The article provides guidance to a rapidly changing field of diagnostics and outlines the epidemiology and clinical impact of acute respiratory viral infections, including preferred methods of specimen collection and current methods for diagnosis and characterization of viral pathogens causing acute respiratory tract infections. Compared to the case in 1986, molecular techniques are now the preferred diagnostic approaches for the detection of acute respiratory viruses, and they allow for automation, high-throughput workflows, and near-patient testing. These changes require quality assurance programs to prevent laboratory contamination as well as strong preanalytical screening approaches to utilize laboratory resources appropriately. Appropriate guidance from laboratorians to stakeholders will allow for appropriate specimen collection, as well as correct test ordering that will quickly identify highly transmissible emerging pathogens.

KEYWORDS clinical, guidance, laboratory, respiratory, virus

INTRODUCTION

Background

The most recent version of the American Society for Microbiology (ASM)-sponsored Cumitech 21 document, *Laboratory Diagnosis of Viral Respiratory Disease*, was published in 1986 (1). The scope of the original document was quite broad, with an emphasis on clinical diagnosis of a wide variety of infectious agents and laboratory focus on antigen detection and viral culture. The date of publication of the most recent Cumitech document was roughly 3 years after Kary Mullis' initial work on PCR technology. Since that time, the practice of clinical microbiology has significantly changed, most notably with the development of molecular approaches that have increasingly replaced traditional methods for diagnosis of respiratory viruses. Specimen collection techniques have likewise improved and have enhanced the predictive values of these new molecular methods. Development of electronic order entry systems, computerized laboratory information systems, and automated reporting has reduced turnaround times (TATs) for laboratory results dramatically even in environments where laboratory centralization has occurred. The continual emergence of new respiratory pathogens requires laboratorians to recognize laboratory testing limitations and understand when and how to refer suspicious cases to public health reference laboratories.

Purpose

This document is an ASM-sponsored Practical Guidance for Clinical Microbiology (PGCM) identifying best practices for diagnosis and characterization of viruses that cause acute respiratory infections (ARIs). The document is designed to be used by laboratorians in a wide variety of diagnostic and public health microbiology/virology laboratory settings, especially by members of the ASM worldwide. As such, this consensus document is structured to cover a wide range of practice settings, and to reflect changes in available technology, clinical practice, and viral pathogens since 1986. The document outlines the epidemiology and clinical impact of acute respiratory viral infections, including preferred methods of specimen collection and current methods for diagnosis and characterization of viral pathogens causing acute respiratory tract infections. Laboratory-developed and commercial diagnostic tools, approaches for diagnosis of emerging pathogens, and detection of antiviral resistance in influenza A virus (FLUA) and influenza A virus (FLUB) infections are also discussed. Specimen handling approaches for specimens from multiple body sites, such as nasopharyngeal swabs (NPS), nasopharyngeal aspirates (NPA), nasal swabs (NS), nasal washes (NW), oropharyngeal and throat swabs (OPS/TS), sputa, bronchoalveolar lavage (BAL) fluids, bronchoalveolar washes (BAW), and other lower respiratory tract specimens, are cov-

ered. Given the changes in turnaround time for these newer technologies and increases in clinical use, the document also addresses appropriate laboratory utilization of diagnostic respiratory viral testing. The scope of the document has shifted since the last version of the Cumitech, which included discussion on clinical overlap of viral pathogens causing acute respiratory tract infections as well as other pathogens that were shown to infect the respiratory tract, such as atypical bacterial pathogens. The current document focuses strictly on viruses that primarily cause acute respiratory infections, related syndromes, or disease processes. Viruses that can infect or shed from the respiratory tract but lead chiefly to other presentations such as rash, vesicles, parotitis, gastroenteritis, or mononucleosis-like syndromes (herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, parvovirus B19, measles virus, rubella virus, mumps virus, bocavirus, and hantavirus) are not discussed in this document.

The primary focus of this document is pathogens with well-documented causal effects for acute respiratory infections, namely influenza A virus (FLUA), influenza B virus (FLUB), respiratory syncytial viruses (RSVs) A and B, respiratory enteroviruses (EVs), rhinoviruses (RVs), respiratory adenoviruses (ADVs), human metapneumovirus (hMPV), parainfluenza viruses (PIVs) 1 to 4, and coronaviruses (CoVs) (NL63, OC43, HKU-1, and 229E). The document also discusses the diagnosis and characterization of emerging respiratory viral pathogens, including CoVs (causing Middle Eastern respiratory syndrome [MERS] and severe acute respiratory syndrome [SARS]) and novel FLU strains arising from swine and avian sources.

EPIDEMIOLOGY AND CLINICAL PRESENTATION OF ACUTE RESPIRATORY VIRAL INFECTIONS

Circulation of Respiratory Viruses: a Global Problem

The increased capacity for molecular diagnostics worldwide has enhanced our understanding of global circulation patterns of respiratory viruses (2). From the clinical laboratory perspective, understanding the circulation patterns of viruses will influence the predictive value of respiratory virus testing and potentially the interpretation of respiratory virus test results based on pretest probability (3). A number of geographic regions now have well-established surveillance systems for FLU and occasionally other respiratory viruses associated with acute illness (4–7). A complicated global viral circulation pattern shows that some viruses maintain consistent seasonality, while others vary extensively. In the Northern Hemisphere, RV and respiratory EVs typically circulate in the late summer and early fall (autumn), while FLUA predictably peaks in December or January (Fig. 1). PIV types, however, have varied circulation patterns with seasonality depending on the subtype, and dominant types can change from year to year (8). Although we can begin to predict patterns of respiratory virus circulation as surveillance and detection capacities improve (9), viruses may be identified outside their normal seasonal infection patterns due to patient activities, such as travel to regions where the virus is currently circulating (10). Knowing the travel history combined with active pathogen surveillance (e.g., identifying a patient who presents during a North American summer with acute respiratory infection after travel to the Southern Hemisphere where FLU or RSV is circulating) can help direct appropriate infection prevention and control measures, as not all respiratory viruses require the same level of patient isolation (11, 12).

Acute respiratory infections. Acute respiratory infections (ARIs) are among the most common infections reported worldwide. In the 2013 global disease burden study sponsored by the World Health Organization, respiratory infections were listed as the leading cause of infectious disease and as being responsible for approximately 120 million disability-adjusted life years (DALYs) (a measure of the disease burden and its impact on quality of life) (13). Lower respiratory tract infections (LRTIs) accounted for greater than 90% of all DALYs, with approximately 35% of cases occurring in children less than 5 years old (13, 14). The impact of respiratory infections on human health is reflected in the large number of hospital and emergency room visits for both adults and children (e.g., in the United States, there are 140,000 to 710,000 FLU-related hospital-

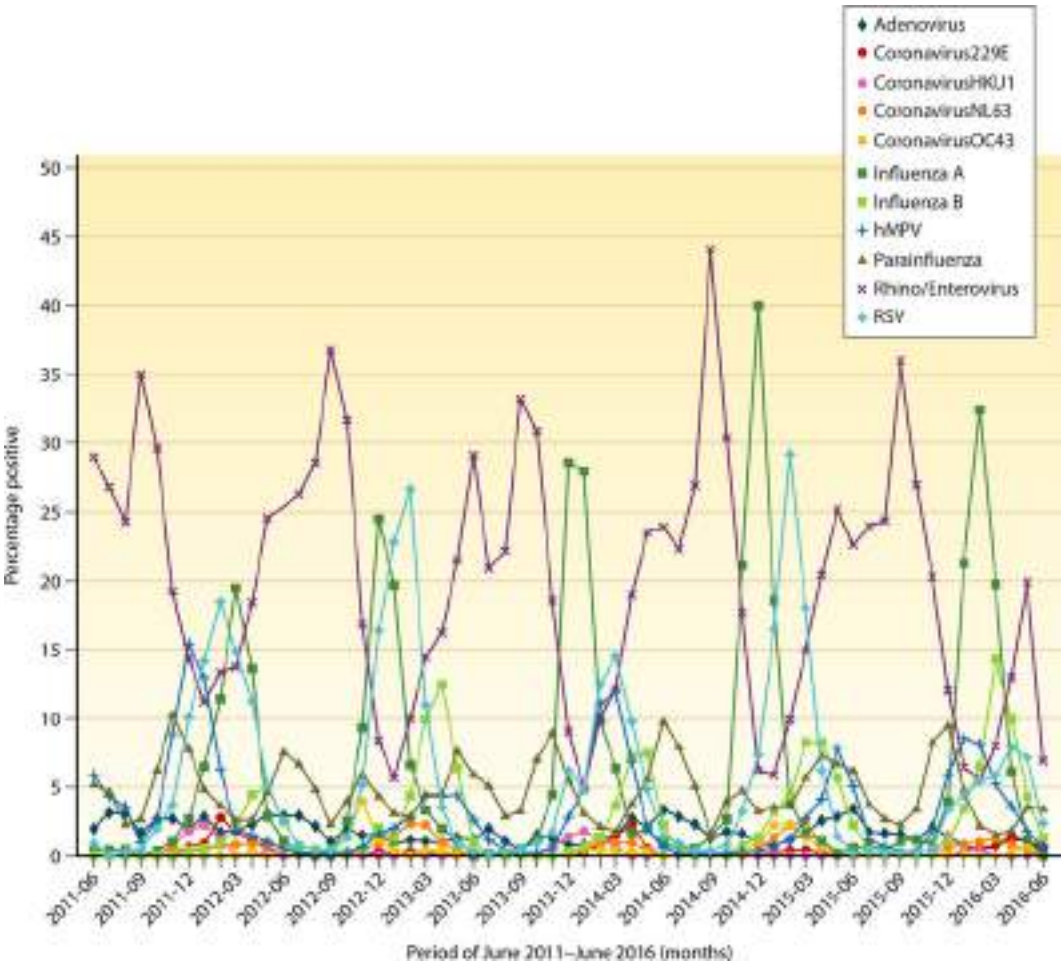

FIG 1 Circulation of common respiratory viruses in a large geographic area within the Northern Hemisphere. The data represent all acute respiratory virus testing for multiple years in a population of 4.1 million patients, using a common testing algorithm. The seasonality of viruses varies. (Generated by S. J. Drews and the ProvLab Alberta Laboratory Surveillance and Informatics Team, 2016.)

izations per year), where respiratory viral infection is the most common reason to seek medical care (15, 16).

Mechanisms of transmission. Respiratory viruses are transmitted primarily through two mechanisms: (i) inhalation of infectious droplets and (ii) contact with contaminated fomites. Aerosol transmission is the most common route of infection. Large (10 to 100 μm in diameter) aerosolized droplets can transmit viruses from the index case to a new host in close proximity ($\leq$0.9 m), while small ($<$10 μm in diameter) aerosolized droplets, produced during coughing or sneezing or through aerosol-generating procedures, can carry viral particles to new hosts several meters away ($\geq$1.8 m). Transmission via fomites from self-inoculation of the respiratory tract mucosa is the second most common route of infection (17) (Table 1). Survivability and infectivity of viruses on surfaces may vary from hours to days and depend on a number of viral and nonviral factors. Nonenveloped viruses are more likely to cause infection via direct contact, as they are more stable in the environment than enveloped viruses and are therefore more likely to survive for extended periods outside the host (18). Animal and climatological model systems suggest that respiratory virus (e.g., FLUA) transmission may also be enhanced under specific environmental conditions, such as low temperature and low humidity (19–21). It is important for laboratorians and clinicians to be aware of likely transmission routes used by respiratory viruses in order to implement adequate infection control practices, select appropriate specimen types, and safely perform laboratory manipulations (Table 1) (22).

TABLE 1 Classification and characterization of common respiratory viruses

Virus group(s)	Family (reference[s])	Nucleic acid	Nucleic acid structure[a]	Enveloped	Large-droplet transmission (reference)	Survival time as fomites (reference[s])[b]	Isolation precautions (reference[s])[c]
Adenoviruses	*Adenoviridae* (333, 334)	Linear, nonsegmented	dsDNA	No	Yes (11)	14–30 days (18)	Contact, droplet (11, 335)
Coronaviruses	*Coronaviridae* (333, 334)	Linear, nonsegmented	(+) ssRNA	Yes	Yes (11)	1 h–28 days (18, 336)	Airborne, contact, droplet, standard[d] (11, 337)
Enteroviruses, rhinoviruses	*Picornaviridae* (333, 334)	Linear, nonsegmented	(+) ssRNA	No	Yes (11)	Limited data	Droplet, standard[e] (11)
Influenza A/B viruses	*Orthomyxoviridae* (333, 334)	Linear, segmented	(−) ssRNA	Yes	Yes (11)	5 min–7 days (18, 338–341)	Droplet, standard,[f] ± airborne[g] (11, 335)
Parainfluenza viruses 1–4	*Paramyxoviridae* (333, 334)	Linear, nonsegmented	(−) ssRNA	Yes	Limited data (333)	4–10 h (18, 342)	Contact, standard (11, 335)
Human metapneumovirus	*Pneumoviridae* (333)	Linear, nonsegmented	(−) ssRNA	Yes	Limited data (333)	Limited data	Contact, standard (11)
Respiratory syncytial viruses A/B	*Pneumoviridae* (333)	Linear, nonsegmented	(−) ssRNA	Yes	Yes (343)	20 min–8 h (18, 344)	Contact, standard (11, 335)

[a]dsDNA, double-stranded DNA; ssRNA, single-stranded RNA.
[b]Survival on dry surfaces or hands. Survival times are impacted by temperature, humidity, and type of surface. Nucleic acid has been detected.
[c]Isolation precautions can be found at: https://www.cdc.gov/infectioncontrol/pdf/guidelines/isolation-guidelines.pdf. Note the caveat regarding the use of droplet precautions when undertaking procedures likely to create splashes or sprays.
[d]Isolation precautions vary by coronavirus type; the listed precautions are specific to SARS-CoV.
[e]Rhinovirus isolation precautions.
[f]Changes in hemagglutinin and neuraminidase may impact transmission of influenza viruses; for up-to-date seasonal recommendations see https://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm.
[g]Airborne transmission may be possible in some cases.

Close contact in living environments such as long-term care facilities facilitate transmission to the elderly, who are often at higher risk for severe outcomes from respiratory virus infections, such as pneumonia, acute-care hospitalization, and death. In addition, illness may also occur in staff members. Challenges may arise because these environments are not thought of as primary health care environments and may not have infection control protocols that are as stringent as those in health care settings (23, 24).

Similarly, pediatric day care settings are another transmission setting for exposure to multiple respiratory viruses. A prospective cohort study from Washington State identified RSV, ADV, and RV as leading pathogens, with hMPV and CoV being less frequent, in children in day care settings (25), and air sampling experiments have identified RSV these settings (26). Children attending day care are at increased risk for respiratory infections (all etiologies), especially at the start of entry into day care (27), and can be a potential source of RSV infection for premature infants, who are at high risk of severe compilations and outcomes (28).

Acute respiratory viral infections. There is significant overlap in clinical symptoms associated with the different viruses causing respiratory illnesses (Table 2). The U.S. Centers for Disease Control and Prevention (CDC) has established influenza-like illness (ILI) criteria used for epidemiological surveillance to identify patients with likely influenza infection (29, 30). These clinical criteria include cough, fever (temperature greater than or equal to 100°F [37.8°C]), and/or sore throat and no identifiable cause other than influenza (31); however, the specificity of these criteria is poor, as many other patients with noninfluenza respiratory viruses can present similarly (32). In many cases, acute respiratory infection (ARI) due to these viruses is indistinguishable from illness due to bacteria on the basis of clinical presentation alone. Table 2 provides examples of diseases and disorders that are caused by respiratory viral infection; however, this table does not exclude the possibility that an unlisted virus may be the causative agent of a disease or disorder.

(i) The host. The host response to viral infections relies on elements of both the innate immunity and the adaptive immunity. Epithelial cells covering the mucosal surface of the airway constitute the first physical barrier encountered by respiratory viruses. Here, tight junctions connect the cells and provide a sealed environment, preventing viral movement outside the respiratory tract. A layer of mucus overlays the epithelial surface, and an upward directional movement of cilia effectively traps and clears virus particles from the airway epithelium (33, 34). Binding and phagocytosis of viruses result in production of several proinflammatory molecules, including interleukins (e.g., interleukin-1β [IL-1β] and IL-18), α/β defensins, collectins, type I interferons alpha/beta, and immunoglobulin A (IgA), and attract natural killer cells. Upregulation of this innate immune response limits local spread of the respiratory viruses (34) and serves as the front-line defense prior to activation of the adaptive immune system.

In infants, the immune system is still developing. The lack of complete immune memory, reduced innate and adaptive immunity, and physiological differences in airways compared to those in adults (35) increase the susceptibility to viral infections and disease severity (36). The immune response to respiratory viral infections may be augmented by protective effects of passive antibodies transmitted *in utero* (37) and other factors, including breastfeeding (38, 39). Reinfections with the same virus are not uncommon, and disease severity as well as patient outcomes is dependent on multiple factors, including viral genetic diversity and intrinsic/extrinsic patient factors (34, 40–42).

Individuals at increased risk for complications due to respiratory virus infections include children, older adults (>65 years old), patients with underlying respiratory conditions, and those with suppressed immune functions (e.g., transplant patients). In patients with underlying respiratory conditions (e.g., chronic bronchitis, chronic obstructive asthma, chronic obstructive pulmonary disease [COPD], or emphysema), a decrease (mucostasis) or increase (mucus hypersecretion) in the mucociliary escalator function may lead to decreased clearance of viral pathogens and increased risk of

TABLE 2 Diseases and disorders associated with respiratory viral pathogens[a]

Virus(es)	Respiratory diseases and disorders	Comments	Key references
ADV	Pharyngitis, common cold, laryngitis, bronchitis, bronchiolitis, pneumonia	Main cause of pharyngitis in infants and children; types 4 and 7 caused pneumonia in military recruits; multiplex NAAT-based assays which include ADV are available; latency and persistent shedding can confound interpretation of qualitative tests	(130, 236, 281, 345–349)
CoVs NL63, OC43, HKU1, 229E, SARS-CoV, and MERS-CoV	Common cold, pharyngitis, laryngitis, bronchitis, bronchiolitis, pneumonia, SARS, MERS	Multiplex NAAT-based assays are available for the detection and differentiation four genotypes of CoV (229E, OC43, NL63, and HKU1); genotypes such as SARS-CoV and MERS-CoV can be detected only by NAAT, often at reference/public health laboratories	(236, 348–356)
EV	Bronchiolitis, bronchitis, common cold, pharyngitis, pleurodynia	EV-D68 is associated with severe respiratory illness outbreaks in the USA (2014); multiplex NAAT-based assays which include EV are available; as described in the text, many panels cannot differentiate between EV and RV or detect all types of EV (e.g., EV D68); LDTs have been utilized for typing	(236, 357, 358)
hMPV	Bronchiolitis, common cold, laryngitis, bronchitis, pneumonia	hMPV infection is associated with a substantial burden of hospitalizations and outpatient visits among children throughout the first 5 years of life, especially during the first year; elderly adults also susceptible; multiplex NAAT-based assays are available for hMPV detection; two groups and four subgroups of hMPV can be detected and identified by molecular assays	(236, 281, 348, 349, 359, 360)
RVs	Bronchiolitis, bronchitis, common cold, pharyngitis, pneumonia	The leading pathogen causing common cold and the most common viral cause (8%) of pneumonia in adults in the USA; multiplex NAAT-based assays are available for RV detection; molecular assays are the only method for detection of RV genotype C; some molecular panels cannot distinguish between RV and EV	(236, 348, 349, 358, 361–363)
FLUA (including subtypes H1, H3, and H5) and FLUB	Bronchitis, bronchiolitis, common cold, influenza, laryngitis, pharyngitis, pneumonia	Common pathogen of pneumonia in adults; multiplex NAAT-based assays are available for FLUA detection; on-demand and point-of-care molecular tests are available; genotyping and subtyping can be done by molecular assays; clinical relevance of viral load determination merits further investigation	(236, 281, 286, 348, 349, 361, 364–366)
PIVs 1–4	Bronchiolitis, bronchitis, common cold, laryngitis, otitis media, pharyngitis, pneumonia	PIV 1 and PIV 3 are the most common types causing bronchitis; PIV 4 has not been confirmed to be a definite pathogen in humans; multiplex NAAT-based assays are available, including detection and differentiation of PIVs 1–4	(236, 281, 349, 354)
RSVA and -B	Bronchiolitis, bronchitis, common cold, otitis media, pneumonia	Leading cause of bronchiolitis and common pathogen of pneumonia in children; disease severity is significantly associated with viral load rather than RSV subgroup; multiplex NAAT-based assays are available for RSV, and some of them provide subgroup information on RSVA and RSVB	(236, 348, 349, 367–369)

[a]Abbreviations: ADV, adenovirus; SARS, severe acute respiratory syndrome; MERS, Middle East respiratory syndrome; CoV, coronavirus; EV, enterovirus; hMPV, human metapneumovirus; RV, human rhinovirus; FLU, influenza virus; PIV, parainfluenza virus; RSV, respiratory syncytial virus; NAAT, nucleic acid amplification test; LDT, laboratory-developed test.

infection (33). In older adults, increased susceptibility to viral infections, age-dependent vaccine effectiveness (43) and more severe disease have been attributed to waning innate and adaptive immunity. Particularly, infection with RSV has been attributed to a decrease in memory $CD8^+$ T-cell function (44, 45). Similarly, immunosuppressed patients with profound and prolonged reduction in T-cell immunity are at increased risk for severe disease from viral infection (particularly ADV, hMPV, PIV, and RSV infections) (46, 47). A few studies have suggested that genetic polymorphisms of innate immune effectors, such as Toll-like receptors (e.g., TLR-4), are associated with increased susceptibility to severe respiratory viral infection (48, 49).

(ii) Environmental factors. Environmental factors may also influence the incidence of disease caused by respiratory viral infection either alone or with other underlying factors such as asthma (50). These factors may include the number of siblings in family, environmental smoking exposure (51), air pollution, climatic conditions, or weather (52, 53).

(iii) Anatomic site of infection. As the name suggests, most acute upper respiratory tract infections (URTIs) affect sites in the upper respiratory tract, including the larynx, nasal cavities, nasopharynx, oropharynx, throat, sinuses, conjunctiva, and inner ear, and commonly manifest as rhinosinusitis or the "common cold" (54), acute sinusitis (55, 56), acute laryngitis (57–59), conjunctivitis (54, 60–65), and otitis media (64, 66, 67). (Table 2).

Viruses in lower respiratory tract infections (LRTIs) affect deeper structures below the larynx, including the trachea, bronchus, and bronchoalveolar site, and manifest as bronchiolitis (68–71), bronchitis (72–76), and acute pneumonia (77–81).

Zoonotic viruses: human-animal health interfaces. The One Health concept is an integrative and collaborative approach that works to improve the health of humans and nonhuman animals while ensuring the protection of the natural environment (82). Clinicians and laboratorians should remain aware of the potential impact of One Health human-animal interfaces to allow for the emergence of new human respiratory viral pathogens (83, 84). Recent examples include human infection with the Middle East respiratory syndrome coronavirus (MERS-CoV) with camel exposure (83), swine variants of FLUA (84), pandemic FLU (pdm09), avian FLUA (e.g., H7N9) (85), and severe acute respiratory syndrome coronavirus (SARS-CoV) associated with bats and civet cats (86, 87). Laboratorians should establish effective communication links with epidemiologists, clinicians, and animal health experts to understand the impact of zoonotic viruses on human illness (88). Identification of at-risk patients early by clinicians can reduce the potential for nosocomial transmission of zoonotic pathogens. From the laboratory perspective, this means following the epidemiology of emerging infections and communicating with clinicians and public health workers to assess risk and determine the testing required based on travel histories and animal exposures (89–91). These approaches not only will identify patients at risk and allow public health practitioners to implement strategies to reduce transmission and limit further exposure in health care facilities and the community but also will ensure that laboratories can work up specimens using appropriate biocontainment approaches to reduce the risk of laboratory transmission of pathogens (92).

Section Summary and Recommendations

Respiratory viruses are a global problem with varied temporal and geographic patterns of circulation. Laboratorians and clinicians should understand that multiple viruses can cause similar signs and symptoms when infecting the upper or lower respiratory tract. Although some viruses may be more likely to be associated with some diseases, it is difficult to use clinical presentations alone to determine the causative agent. Laboratorians should have a firm understanding of viruses that are circulating in their region, as well as emerging infections in other regions of the world, as this information may guide clinicians and laboratorians in developing appropriate algorithms to test for agents causing respiratory illness.

GUIDELINES ADDRESSING THE DIAGNOSIS AND MANAGEMENT OF SYNDROMES ASSOCIATED WITH ACUTE RESPIRATORY INFECTIONS

Laboratorians must consider how laboratory testing impacts the diagnosis and management (including infection control considerations, treatment, and prophylaxis) of patients presenting with ARIs so that they collaborate with their health care providers to develop effective utilization strategies and develop algorithms that prioritize of testing of patients for whom results can influence clinical decision making. The following section summarizes U.S. and international guidelines written in the English language for the diagnosis and management of respiratory virus infections. Although viral diagnosis does not typically affect the patient management of otherwise-healthy adult patients, these guidelines identify scenarios where respiratory virus testing has been identified to influence patient management.

Infectious Diseases Society of America

Community-acquired pneumonia. Together, the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) published consensus guidelines for the management of community-acquired pneumonia in adults in 2007 (note that revisions of the ATS guidelines are in progress) (79). In the guidelines, they outline specific microbiological testing recommendations and discuss how to take an appropriate travel history to support the diagnosis of pneumonia. The document identifies respiratory viruses as an important cause of community-acquired pneumonia (CAP) in outpatients and inpatients and emphasizes the importance of testing for and public health reporting of emerging or novel virus strains. Improvements to diagnostic testing using molecular approaches are encouraged, and drawbacks to rapid antigen testing, including cost and false-negative and false-positive results, are discussed. The document also provides support for use of antivirals (oseltamivir, zanamivir, or peramivir) in the treatment of seasonal and pandemic FLU, and it strongly supports vaccination in the prevention of seasonal influenza disease (79).

More recently (2011), the IDSA and the Pediatric Infectious Diseases Society (PIDS) published combined guidelines for the management of CAP in infants and children older than three months (93, 94). Since viral pathogens cause the majority of CAP in preschool-aged children, antibiotic therapy is not routinely required in this population. Testing for respiratory viral infections with a rapid, highly sensitive, and specific assay is recommended, as it may reduce the use of antibiotics in patients without clinical, laboratory, or radiological findings suggestive of bacterial coinfection. Antiviral therapy should be started as early as possible in children with moderate to severe CAP when FLU is circulating and symptoms are worsening. The group suggested that treatment not be delayed for laboratory confirmation, as negative laboratory tests (especially with rapid antigen testing) may not exclude disease. The American Academy of Pediatrics, in a policy statement by the Committee on Infectious Diseases and Bronchiolitis, did not recommend ribavirin for the treatment of RSV-CAP in infants. However, palivizumab prophylaxis of RSV was recommended by the American Academy of Pediatrics (94). The palivizumab guidelines have since been updated (95) and do not emphasize laboratory testing for RSV. No recommendations were provided for the use of antivirals against PIVs, ADVs, hMPVs, or CoVs in pediatric CAP.

FLU-specific guidance. In 2009, the IDSA released guidelines on the diagnosis, institutional outbreak management, chemoprophylaxis, and treatment of FLU in adults and children (96) (an update for this document is currently in process). Specific demographic criteria were outlined for whom should be tested for FLU, and testing was recommended only if results would influence clinical management. These situations partially include the following: immunocompetent outpatients with acute febrile respiratory symptoms (within 5 days of onset) at high risk for hospitalization or death, immunocompromised outpatients with febrile respiratory symptoms (regardless of onset date), and immunocompetent and immunocompromised hospitalized patients with fever and respiratory symptoms, including CAP patients (regardless of onset date). FLU testing was also recommended for elderly and infant patients with fever of

unknown origin or sepsis (regardless of onset date), children presenting for medical care with fever and respiratory symptoms (regardless of onset date), patients who after admission develop fever and respiratory symptoms (regardless of onset date), and individuals (e.g., health care workers, residents, or visitors) with febrile respiratory symptoms (within 5 days of onset) connected to an institutional FLU outbreak.

Rhinosinusitis. The IDSA "*Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults*" provides guidance on clinical presentations to identify patients with viral and bacterial rhinosinusitis (97). Bacterial rhinosinusitis is defined as any of the following (i) >10 days of symptoms without improvement and with onset of high fever (≥102°F [39°C], (ii) high fever with purulent nasal discharge or facial pain during the first 3 to 4 days of illness, or (iii) worsening symptoms (e.g., fever, headache, or increase in nasal discharge) after apparent resolution of an upper respiratory tract infection. This document emphasized the use of clinical approaches and not laboratory testing to distinguish between bacterial and viral rhinosinusitis due to the self- limiting nature of this illness (97).

Other U.S. and International Guidelines Concerning Specific Populations and Settings

SOT. In 2013, the Infectious Diseases Community of Practice of the American Society of Transplantation, the American Society of Transplantation, and the Canadian Society of Transplantation released guidelines for infectious disease testing on solid organ transplant (SOT) patients (98). The guidelines recommend testing for common respiratory viral infections, including FLU, RSV, PIV, hMPV, RV, and CoV (99) with nasopharyngeal swabs, nasal washes, or aspirates. The use of BAL fluid samples should be considered for patients with negative upper respiratory tract specimens or with clinical or radiological evidence of lower tract disease processes. Multiple approaches may be used for diagnosis (e.g., nucleic acid amplification tests [NAATs], direct fluorescent-antibody [DFA] tests, rapid antigen detection, or culture), but the guidelines emphasize that NAAT is the most sensitive approach, and use of multiplexed NAAT improves the diagnostic capacity by testing for a variety of targets, which should be seriously considered in lung transplant patients. Prophylactic interventions for FLU (vaccination and neuraminidase [NA] inhibitors [NAIs]) and RSV (palivizumab) and the use of therapeutics for influenza (neuraminidase inhibitors) and RSV (ribavirin/intravenous immunoglobulin [IVIG]) are also outlined in the document (99).

The American Society for Transplantation Infectious Diseases guidelines for the diagnosis and management of ADV in solid organ transplant patients were published in 2013 (100). The document describes posttransplantation timelines for risk of ADV infection, where the first three months following SOT represents the highest risk. The guidelines emphasize that pediatric patients had the highest incidence of ADV infection, at 6.25%, which carried an organ-specific risk level (liver > heart > kidney). In adult SOT recipients (liver, heart, kidney, and kidney-pancreas), 10.5% of those with self-limited viremia after transplant later developed ADV-associated respiratory symptoms within the first year. Although ADV subgrouping does not play a role in the clinical laboratory, it may provide a sense of molecular epidemiology. For example, respiratory tract infections were associated with subgroups B1 (serotypes 3, 7, 16, 21, and 50), B2 (serotypes 11, 14, 34, and 35), C (serotypes 1, 2, 5, 6), and E (serotype 4), while disseminated disease (involvement of two or more organs) was associated with subgroups A (serotype 31), B2 (serotypes 11, 34, and 35), C (serotypes 1, 2, and 5), and F (serotype 40). Multiple diagnostic approaches can be used for suspected ADV infection, including NAAT, culture, DFA testing, and histopathology (considered the gold standard by the guidelines group for invasive ADV infection), but due to long-term shedding in respiratory specimens (as well as urine and stool), detection of ADV is not necessarily indicative of a disease process cause by ADV. Clinical symptoms, detection of the virus in multiple sites, and histopathology may strengthen the association of ADV detection with disease; however, the American Society for Transplantation Infectious Diseases guidelines do not offer predictive algorithms to link detection of ADV in

multiple sites with disease. The lack of clear clinical cutoffs in qualitative and quantitative NAATs adds to the confusion of whether positive results represent a current active infection. Issues with false-negative ADV results with some NAAT panels are also described later in this review. The American Society for Transplantation Infectious Diseases guidelines indicate that NAAT on a blood sample may be used successfully to monitor therapy, particularly if a baseline quantitative value is determined. ADV infections can be treated with cidofovir; however ribavirin should not be routinely used to treat ADV infections even though some subtype C viruses may respond to ribavirin treatment (100).

HSC recipients. International guidelines (combined recommendations of the Center for International Blood and Marrow Transplant Research [CIBMTR], the National Marrow Donor Program [NMDP], the European Blood and Marrow Transplant Group [EBMT], the American Society of Blood and Marrow Transplantation [ASBMT], the Canadian Blood and Marrow Transplant Group [CBMTG], the IDSA, the Society for Healthcare Epidemiology of America [SHEA], the Association of Medical Microbiology and Infectious Diseases Canada [AMMI], and the [CDC]) for preventing infectious complications in hematopoietic cell transplant recipients were released in 2009 (101). Patients are at risk from respiratory virus infection (FLU, RSV, hMPV, and PIVs) at all transplant stages from preengraftment to late phase. Prolonged shedding times after viral infections were identified in hematopoietic stem cell (HSC) recipients, with the following potential shedding times for the following viruses: ADV, $\geq$2 years; FLU, $\geq$4 months; and RSV, $\geq$22 days. Preventative measures for FLU include vaccination of close contacts and antiviral prophylaxis (for close contacts and patients). No recommendations were made for the use of ribavirin as a preemptive therapy for RSV. Evidence supporting the efficacy of palivizumab prophylaxis for RSV prevention in HSC recipients $<$4 years of age was thought to be insufficient to recommend for or against use. No recommendations were made for prophylaxis of PIV or hMPV infections. Testing for RSV and FLU in HSC recipients with signs and symptoms of respiratory infection during periods of circulation was recommended; however, routine surveillance of asymptomatic patients for these respiratory viruses was not endorsed (101).

Recently, guidelines from the Fourth European Conference on Infections in Leukemia addressed the diagnosis and treatment of RSV, PIVs, hMPV, RVs, and CoVs in patients with leukemia and those undergoing HSC transplants (102). The group had several recommendations regarding diagnosis of upper and lower tract community-acquired respiratory viruses, including (i) testing to guide infection prevention and control, treatment, and decisions for deferral of chemotherapy or HSC transplant, (ii) evidence for collecting specimens from the site of involvement (e.g., pooled swabs for the upper respiratory tract and BAL fluid [or tracheal swab if BAL fluid not available] for the lower tract), (iii) evidence to support the use of first-line or routine diagnostic tests for FLU, RSV, and PIV, (iv) evidence to test for other community-associated respiratory viruses based on assessment of risk of exposure and local epidemiology, and (v) evidence to consider collection of BAL fluid or biopsy samples for broader respiratory viral pathogen testing in patients with lower tract disease. Treatment with ribavirin and IVIG was recommended for RSV infection, while ribavirin alone was recommended for patients with PIV infection (102).

In 2016, the Infectious Diseases Working Party of the German Society for Hematology and Medical Oncology released guidelines for the diagnosis and management of community-acquired respiratory viruses (103). The risk of infection with FLU, RSV, PIVs, hMPV, and ADV in cancer patients is significant, and infection is associated with high rates of pneumonia and mortality. The document highly recommends NAAT for RSV, FLU, PIV, and other circulating/prevalent viruses in symptomatic patients. NAAT is recommended over antigen detection or culture as the test of choice for identifying these viruses. For patients with lower tract infection or critical illness, expanded testing for hMPV and ADV (and potentially other rare causes of lower tract disease [e.g., RVs and CoVs]) is suggested. Moderate support for recommendations for causal treatment of FLU (oseltamivir, zanamivir, and peramivir), RSV (ribavirin and IVIG), and ADV

(cidofovir) was given. Marginal support for recommendations for causal treatments of PIVs (ribavirin) was given (103).

Patients in the ED setting. In 2016, the American Academy of Emergency Medicine approved a clinical practice paper for the vaccination, diagnosis, and treatment of FLU. For seasonal FLU in the emergency department (ED), providers should (104) (i) perform testing only if results will change clinical management, (ii) understand the limited sensitivity and false-negative rates of rapid antigen detection tests (RADTs), (iii) consider NAAT if clinical suspicion is moderate to high, and (iv) if rapid antigen detection tests are negative but clinical suspicion is high, consider empirical antiviral therapy. Additionally, FLU antivirals are recommended for patients who are (i) hospitalized, (ii) at higher risk for complications, and (iii) have progressive illness (104).

Patients requiring isolation precautions in a health care setting. The Health Care Infection Control Practices Advisory Committee (HICPAC) document "*Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings*" discusses key functions of the clinical laboratory (11). The document recommends that microbiologists help guide the limited application of rapid testing to clinical situations where this testing influences patient management decisions and that they oversee nonlaboratory workers who perform this testing. The document also recommends the application of rapid tests to support treatment decisions, bed management, and implementation of infection prevention and control measures (e.g., barrier precautions, chemoprophylaxis, and vaccination); however, the authors of this PGCM document emphasize that the test characteristics (e.g., sensitivity, specificity, and predictive values) of an assay should be taken into account when making this decision. Surveillance of FLUA and RSV was emphasized for case finding or cluster analysis, particularly when infection precautions may be implemented. Removing a patient from isolation is virus specific (see Table 1 regarding isolation precautions); however, of note, RSV antigen tests are considered inadequate to remove patients from contact precautions, as false-negative results are frequent.

Outbreak investigations. The U.S. CDC guidelines "*Unexplained Respiratory Disease Outbreaks (URDO)*" outline the steps taken to define and investigate a respiratory outbreak of unknown origin (105). Detection and characterization of the pathogen are key steps allowing for effective clinical management, infection prevention and control practices, and defining the time period of the outbreak. The document identifies a variety of testing, including NAAT, culture, serology, and antigen detection, that may be used to investigate the etiology of an outbreak (105).

Emerging pathogens. In the last few years a number of emerging viruses have been identified globally, including FLU subtypes (H5N1, H5N6, and H7N9 [106–108]) and CoV strains (MERS-CoV [109]\and SARS-CoV [110]). A number of guidelines have been published to help in the diagnosis and management of these emerging pathogens (111–113). Optimal timing of collection differs. Although the ideal specimen collection time for influenza virus is as soon as possible after symptom onset, NAAT for MERS-CoV can be performed 14 days postonset due to improved sensitivity of the assays. From the laboratory perspective, NAAT is the recommended method of detection. A wide variety of respiratory specimens may also be collected. If upper tract swabs are negative, then lower tract specimen collection should be pursued. Although the cultivation of these pathogens requires a higher level of biocontainment, the majority of activities for identification via NAAT can be done in biosafety level 2 (BSL-2) facility in a biosafety cabinet (BSC) using enhanced precautions. As new pathogens emerge (e.g., H7N4), laboratorians should confer with reference centers (e.g., the U.S. CDC) on the most appropriate testing approaches to detect and characterize these viruses.

(i) MERS-CoV. In June 2015, the most recent version of the MERS-CoV biosafety guideline was released as "*Interim Laboratory Biosafety Guidelines for Handling and Processing Specimens Associated with Middle East Respiratory Syndrome Coronavirus (MERS-CoV)—Version 2*" (113). Activities appropriate for BSL-2 facilities using standard BSL-2 practices included molecular testing of extracted nucleic acid and final packing of specimens for transport to diagnostic laboratories for additional testing. Activities to

be undertaken in a class II BSC included aliquoting specimens, diluting specimens, performing diagnostic tests not involving propagation of potentially infected specimens, and nucleic acid extraction from potentially infectious specimens. Cell culture propagation and the characterization of propagated material should be undertaken in a BSL-3 facility using BSL-3 practices (113).

In June 2015, "Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens from Patients Under Investigation (PUIs) for Middle East Respiratory Syndrome Coronavirus (MERS-CoV)—Version 2.1" was released by the CDC (114). The guidelines recommended, when possible, the collection of upper respiratory tract, lower respiratory tract, and serum specimens for the diagnosis of MERS-CoV. Potential lower respiratory tract specimens included BAL fluid, tracheal aspirate, pleural fluid, and sputum. Appropriate upper respiratory tract specimens included NPS and OPS (which could be combined in the same transport container if the test is validated for this type of combined collection) and nasopharyngeal aspirates. Upper and lower respiratory tract specimens should be collected within 7 days of symptom onset; however, NAAT can be performed 14 days postonset due to improved sensitivity of the assays (112).

(ii) Novel and emerging FLU strains. In January 2014, guidelines for possible infection with avian FLUA (H7N9) virus were released by the CDC (111), and these were later updated for novel FLU strains (116). These guidelines outline appropriate testing for emerging FLU strains such as A(H7N9) and A(H5N1), and they describe exposure risk and clinical symptoms specific for each virus. Specimens should be collected as early as possible after symptom onset (ideally within 7 days) (116). Sample collection after this point is still relevant in children, immunocompromised patients, and critically ill patients with lower tract disease, as virus can be shed for longer periods in these patient populations. As new strains emerge (e.g., H7N4), laboratorians should confer with reference centers (e.g., the U S. CDC) on the most appropriate testing approaches to detect and characterize these viruses (117).

Acute Respiratory Viral Infection following Travel

The book *CDC Health Information for International Travel* (also known as the "Yellow Book") (118) is a reference for health professionals who care for international travelers. The "Yellow Book" identifies viral pathogens as the most common cause of respiratory infections in travelers. Etiologies can vary widely, including infection with RV, RSV, FLU, PIVs, hMPVs, ADV, or CoV (118); however, in the absence of severe illness or pneumonia, laboratory diagnosis is not always clinically necessary (118). Depending on the travel history, novel causes of respiratory illness (e.g., MERS-CoV and avian FLU strains) should be considered for symptomatic patients.

It should be noted that the positive predictive value (30 to 88%) for laboratory-confirmed influenza in returning travelers can vary widely depending on the seasonality of infection and method of detection (119). While the negative predictive value of FLU NAAT in returning travelers can be used to rule out FLU infection, earlier-generation antigen detection test methods should not be used to rule out influenza virus infection, particularly when emerging strains are suspected. Patients who should be tested for FLU infection include (i) symptomatic hospitalized patients, (ii) cases where diagnosis of FLU will affect patient management, and (iii) cases where FLU testing would affect infection prevention and control or management of close contacts (119).

Section Summary and Recommendations

Multiple guideline groups have addressed the role of laboratory diagnosis of viruses in specific patient populations. Laboratorians should be aware that many guidelines are greater than 5 years of age and may not have taken into account the changes that have occurred in the types of tests available for the diagnosis of respiratory viruses. Although some of these documents are now aging, it is clear that testing may play a more important role in the management of severely ill patients and the immunocompromised and less of a role in the management of immunocompetent and relatively healthy adults and children. Laboratory testing may assist in supporting public health

investigations (e.g., emerging pathogen investigations and outbreak investigations), epidemiological investigations, and infection control functions. Most simply, laboratory testing may be considered when it positively impacts clinical decision making and supports patient management.

SPECIMEN COLLECTION FOR LABORATORY DETECTION OF ACUTE RESPIRATORY VIRUSES

Risk Assessment for Emerging Pathogens Prior to Specimen Collection

During clinical assessment, clinicians should ask about travel history and animal exposure that could be consistent with acquisition of (or exposure to) an emerging pathogen (e.g., MERS-CoV or avian FLU). Prompt consideration of an emerging pathogen based on epidemiological risks with engagement of public health and the implementation of appropriate of infection prevention and control measures are essential to prevent nosocomial spread of these infections. In the MERS-CoV outbreak in South Korea (May to July 2015), the lack of prompt identification of risk factors in patients presenting to the ED allowed spread between patients and staff at several hospitals (120). Early identification and upfront screening procedures could have isolated the index patient and reduced the number of contacts, thus limiting the spread of infection (121). This is consistent with mathematical modeling showing that rapid identification of index cases is the most important factor in reducing spread of infection and that patient isolation and quarantine have the strongest correlation with transmission prevention (122). As soon as an emerging pathogen is suspected, the laboratory should be notified to provide advice on appropriate specimen collection and testing to ensure identification and to ensure that the specimens are handled with the appropriate biocontainment considerations for the novel pathogen.

Appropriate Specimen Collection Is Critical for Virus Detection in the Laboratory

When to collect a specimen. Clinicians should collect specimens from symptomatic individuals with acute respiratory illness within 5 days of symptom onset (preferably within 48 h). Specimen collection later than 5 days after onset is recommended only when symptoms persist or worsen, in young children, or in the immunocompromised (96, 123).

Virus-specific shedding estimates can further direct best collection guidelines for respiratory specimens; however, it should be noted that estimates are typically performed on select patient populations, and differences may be due to differences in study designs, differences in specimen types, and differences in detection technologies between studies (124–126). NAAT is the most sensitive method of detection, and sampling as soon as possible after the onset of symptoms is considered ideal for healthy individuals; most viral targets can be effectively identified in the first 2 days after symptom onset, and multiple studies indicate that viral loads in respiratory specimens will generally decrease over time. Furthermore, a delay in specimen collection following onset of respiratory symptoms will negatively impact the sensitivity of laboratory tests to detect a pathogen.

In RV infection, NAAT identified peak shedding within 2 days of symptom onset, with decreasing viral loads up to 7 days after onset (127). When virus culture and NAAT were both used to test specimens, 57% of human hMPV isolates were detected within the first 2 days of symptom onset, while only 19% were detected greater than 4 days after onset (128). Only 27% of hMPV NAAT-positive specimens collected after day four were positive by culture (128). In children tested for RSV by DFA testing, viral shedding (measured in upper respiratory tract specimens [e.g., nasal, throat, and NPS specimens]) peaked 2 days after onset of illness, and the median shedding duration was 4.5 days. Similar shedding patterns were identified for FLU infection. In community patients with acute respiratory illness, FLUA viral loads measured by NAAT peaked at day one following symptom onset and were detected until day eight, while in patients who had one symptom (but did not meet the case definition for acute respiratory illness), loads peaked on day one with detection until day six (129). In contrast, FLUB viral loads were

found to be highest on the day of symptom onset and to persist until day six to eight (129).

It should be noted that there are no standard "case definitions" on how long positive respiratory virus results detected by NAAT should be considered part of the same infection event. Some preliminary studies propose a 30-day period for ADV infection in children and for RV infection in infants as a definition of a single case (130, 131); however, the temporal definition of a new viral infection should be assessed in the clinical context, as the presence of comorbidities can significantly alter viral shedding times. The duration of shedding can be influenced by multiple factors. Although prior infection may not completely prevent reinfection, it may alter the duration of shedding. Older individuals (suggested to have prior exposure) and children with prior RSV infection generally shed for shorter periods of time (125, 132). The strain of virus or subtype or coinfection with different viruses (133, 134) can also influence shedding patterns. RSVA was detected 5.8 days longer than RSVB (135). Similarly, when children with acute expiratory wheezing were found to be coinfected with EV and RV, shedding of RV persisted for 2 to 3 weeks, whereas EV shedding persisted for 5 to 6 weeks (136).

Other factors may increase shedding time and still allow for productive specimen sampling and detection of viral pathogens. Some studies suggest that viral shedding may also be extended in patients with more severe disease (125, 137). Shedding can also be prolonged in immunosuppressed patients. Although the number of patients with detectable virus (FLU, PIV, or RSV) was highest in the first 2 weeks following symptom onset, long-term virus detection ($>$30 days) with NAAT on upper and lower respiratory tract specimens has been described for FLU, PIV, and RSV in patients with hematological disorders (138). Testing these patients for "test of cure" is not recommended or appropriate for viral upper respiratory tract infections, as viral shedding often does not represent active infection (139).

Biosafety considerations and PPE required for collection. Respiratory viruses such as FLU can be efficiently transmitted through the air (140, 141); however, the direct risk to health care workers who are collecting upper and lower respiratory tract specimens by different aerosol-generating procedural methods (e.g., bronchoscopy, sputum induction, endotracheal intubation, positive pressure ventilation, nebulizer treatment, airway suction, tracheostomy, chest physiotherapy, and high-frequency oscillatory ventilation) is currently unknown (142). Analysis of historical data is confounded by growing evidence that infection prevention and control practices for respiratory viruses may not be uniformly followed (143). A recent analysis of practices in multiple U.S. states found low practice adherence, with many health care workers unsure of when appropriate personal protective equipment (PPE) should be worn (143). Droplet precautions for patients with confirmed or suspected infection with FLU should be practiced to prevent transmission during collections. The need for N95 masks can be controversial, and local infection prevention and control procedures should be followed to minimize aerosolization and risk of health care worker infection (144–146). Even if more "effective" respirators are used when clinicians are in contact with patients, their benefit may be negated if generally poor infection prevention and control practices are utilized (145). The laboratorian with expertise in respiratory virus transmission and viral characteristics can be a valuable member of local teams when creating respiratory protection program protocols.

Sampling from upper respiratory tract sites: which specimen to use? For an upper respiratory tract infection, a variety of specimens can be used to diagnose respiratory infections (NPA, NPS, NW, NS, OPS/TS, and sputum) (Table 3), and the U.S. CDC offers collection guidance for each; however, laboratories should use manufacturers' recommended specimen types in U.S. Food and Drug Administration (FDA)-cleared or validated/verified laboratory tests (147, 148). Selection of specimen type is dependent on a variety of factors: patient age, patient willingness to undergo a specific procedure, clinical presentation, the nature of the potential pathogen, and the appropriateness of the specimen type for verified laboratory diagnostic approaches. Although a combination of different specimen types can improve the sensitivity of NAATs (149–155), this

TABLE 3 Sensitivity of respiratory viral detection from different specimen types[a]

Specimen type	Sensitivity of detection[b] of:						
	FLUA/B[c]	RSV	RV/EV	ADV	hMPV	PIVs	CoVs[c]
NPS	++	++	++	++	++	+++	++
NPA	+++	+++	+++	+++	+++	+++	+++
OPS	++(+)[d]	++	+	++	+	+	+
TS	++	++	+	++	+	++	++
Sputum[f]	+++	+++	+++	+++	++	+(+)	++(+)[e]
BAL fluid	+++	+++	++	++	++	+(+)	++
Lung biopsy specimen	++	++	+	+	+	o	+++

[a]For specimen collection, it is important that appropriate infection control practices are followed, as collection can be aerosol generating. FDA clearance and laboratory-based validation/verification of the specimen source for assay need to be considered. Appropriate collection methods should consider downstream testing to ensure that specimens are handled, stored, and shipped properly prior to testing. Preanalytical specimen storage information provided by the laboratory should indicate storage temperature, retention time, and stability of the specimens (123, 178, 179, 370). Combinations of different specimen types can significantly increase the yield for viral detection. Results for nasal specimens are not included in this table because the literature describing their efficacy in detection is variable (372–374).

[b]+++, specimen type has high detection rates for the indicated virus; ++, specimen type is acceptable for viral detection, but sensitivity may be reduced due to the sampling or testing method used for detection; +, specimen type has reduced sensitivity for indicated virus; ++(+), minor reduction; +(+), moderate reduction; o, limited utility.

[c]For emerging avian influenza virus strains or for CoVs such as SARS-CoV or MERS-CoV, lower respiratory samples are additionally recommended for enhanced detection.

[d]NPS were more sensitive for detection of FLUB, while OPS were more sensitive for FLUA strains (153).

[e]Sputum sensitivity varies between CoV strains (180).

[f]Sensitivity of sputum results can vary widely depending on the quality of the specimen received. Sputa received for viral testing are not screened for specimen adequacy as for those received for bacterial workup (371).

must be balanced in such a way to maintain high detection rates yet still maintain a cost-effective approach. For emerging pathogens (e.g., novel FLUA H5/H7/H9 or emerging CoV), a collection of multiple different types (OPS, NS, NPS, BAL fluid, etc.) may be necessary to identify specimens that most reliably result in detection of the pathogen. Depending on the pathogen (e.g., emerging CoV or novel FLUA), other, atypical specimens such as blood or stool for direct virus detection may also be suggested for collection (156–158).

Traditionally, NPA were used as the gold standard for detection of respiratory viruses (159). Previous publications suggest that NPS is equivalent to NPA for the detection of multiple viruses in children (160). Although NPS/NPA are generally more sensitive than throat swabs for detection of most viruses (152, 154, 161, 162), NS are easier to obtain, are less painful (163–165), and can be self-collected with yields equivalent to those collected by a clinician (166). Reduced diagnostic sensitivity using NS samples is often considered an acceptable trade-off for increased compliance, particularly when the prevalence of disease is high (159, 167). In addition, there are increasing data suggesting that the combination of both an NS and an OPS in adults and children has a yield equivalent to that of NPS/NPA (10, 151, 155). Use of a flocked swab with a liquid viral transport medium may additionally improve viral detection (161, 168, 169). Easier midturbinate collection with flocked swabs may provide an alternative to proper nasopharyngeal specimens, albeit with potentially a lowered sensitivity (170, 171). Finally, when using commercially available rapid antigen detection tests (RADTs), laboratories should use the kit-recommended swab unless the performance of the test with a different specimen type has been verified (172).

Approaches to specimen collection from the lower respiratory tract. Lower respiratory tract specimens such as sputum, bronchoalveolar lavage/wash, and lung tissue may be considered in cases where the patient may be infected with an emerging pathogen (173, 174) or is under intensive/critical care for pneumonia (175), in cases involving autopsy (176), or where molecular detection requires pathological evidence of invasive disease (e.g., ADV infection in lung specimens of lung transplant patients) (177). In severe illness due to influenza and emerging pathogens, upper respiratory

tract sampling may yield false-negative results (112). Accurate diagnosis in these cases often will require a variety of specimens from the upper and lower respiratory tracts. Selection of lower respiratory tract specimens should be dependent on the disease course (e.g., anatomic location of the diseases process, stability of the patient/risk in sampling, and ability to access the anatomic site) (176, 178–180). Given these issues, specimen collection and therefore determination of the lower respiratory tract infection may not be possible.

Lower respiratory tract specimen types vary in their ability to be used to detect specific viral etiologies (Table 3). Sputum may be considered an appropriate specimen for sampling the lower respiratory tract in some patients (178–180). However, data are limited. Specimen viscosity and higher rates of PCR inhibition make sputum a more difficult specimen type to use in the laboratory (174), and most FDA-cleared assays for respiratory viruses are not validated by the manufacturer for sputum or other lower respiratory tract samples (e.g., BAL fluid). Bronchial washes and lavage fluids can be useful specimen types, provided that they are collected appropriately in sterile containers, as the viral load for lower respiratory tract infections can be higher in these specimen types. Lung tissue collected during bronchoscopy, open surgical procedure, or autopsy should be placed in a sterile container with a small amount of sterile saline to keep it moist (176). Specimens should not be put into formalin, as it reduces the sensitivity of NAAT, and formalin-preserved samples are not commonly verified sample types for most laboratory test systems. Procedural variability for specimen collection (e.g., volumes collected and dilution factors) makes comparison of the performances of these off-label specimens difficult.

Transport medium and transport considerations. Viral transport medium or universal transport medium facilitates viral culture, direct fluorescent-antibody (DFA) testing (181), rapid antigen detection tests (RADTs) (182), and molecular testing (181, 183, 184). Stability guidelines outlined in the package insert (storage at room temperature, refrigeration, or freezing) should be used as per the manufacturer's instructions. Other transport devices may be considered (e.g., dry swabs [185, 186] or alcohol-based transport medium [185]) but are not widely used. Transport should be in accordance with regulators' guidelines in each jurisdiction.

Section Summary and Recommendations

Always ensure that clinicians are aware of processes for safe specimen collection from patients who are suspected of being infected with routine and emerging respiratory viruses. For the detection of routine seasonal respiratory viruses, samples should be collected as early as possible from patients following onset of illness. Shedding studies of multiple viruses indicate that viral titers drop daily following the onset of illness. Thus, sampling from patients at later time points is expected to negatively impact the sensitivity of diagnostic assays. Sample collection from the upper respiratory tract may be easiest, but upper tract sampling may not detect viruses causing lower tract disease. Following specimen collection, ensure that appropriate transport and storage conditions are used for specimens.

LABORATORY DETECTION OF ACUTE RESPIRATORY VIRUSES

The Role of Cell Culture is Limited

Cell culture was long considered the gold standard for virus isolation and identification prior to the availability of molecular assays (187, 188). Modification of cell lines (including primary lines, immortalized lines, mixed cell lines, and transfected lines) has improved the ability to detect respiratory viral pathogens (189). For laboratories offering cell culture analyses, detailed procedures can be found in the Clinical and Laboratory Standards Institute document "*M41: Viral Culture*." (190).

There are a variety of drawbacks to using cell culture compared to molecular methods, and many virology laboratories have opted to discontinue viral culture in the laboratory for these reasons. It is well established that cell culture has a lower sensitivity than molecular techniques (191, 192), the turnaround time and hands-on time required

to perform cell culture compared to molecular testing are increased, and the technical expertise for performing cell culture is often not available. Traditional tube cultures are slow and can take up to 10 days for detection of respiratory infections (36). A study in pediatric patients indicated that positive viral culture results would not impact the management of healthy children hospitalized for illness attributed to community-acquired respiratory viral infection due to the delay in time to culture positivity (193). Shell vial assays can decrease the time to detection; however, 1 to 2 days is still required for growth and identification of the virus. Care must be taken when selecting cell lines for viral growth, as not all cell lines will allow for propagation of all viruses, and cell lines may be viral strain specific (194). Yields from cell culture are often decreased following freezing, due to reduced numbers of viable virus particles; therefore, samples that are frozen prior to culturing may be falsely negative (139, 195). As a safety note, culture approaches may inadvertently propagate emerging pathogens and compromise laboratory biosafety (195); however, maintaining cell culture capabilities in public health laboratories remains important for identification of unknown or emerging pathogens, particularly when specific molecular amplification processes are not available, and can provide an understanding of the virus viability within a clinical specimen (196).

Direct Fluorescent-Antibody and Immunofluorescent-Antibody Assays for Respiratory Viruses

Direct fluorescent-antibody (DFA) and immunofluorescent-antibody (IFA) assays have been used to detect a variety of respiratory viruses from primary specimens (chromatographic immunoassays for the detection of respiratory viruses are discussed in the following section). Commercial and standardized clinical reagents are available for select respiratory pathogens (e.g., FLUA/B, PIVs 1 to 3, ADV, hMPV, and RSV) (197). Like that of traditional cell culture techniques, the quality of DFA/IFA assays is impacted by specimen quality and collection method (171). Unlike the case for traditional cell culture, DFA and IFA assays do not require viable viruses and the turnaround times are short ($<$4 h) and on a single-specimen basis can be shorter than those for older laboratory-developed molecular approaches (which have, e.g., separate extraction steps, greater numbers of manual steps, and manual interpretation and data entry in laboratory information systems) or batched-based testing; however, DFA/IFA technologies are labor-intensive, require a skilled technologist to read and interpret results, require a fluorescence microscope, and are subject to reader error. Furthermore, the hands-on time required per test is not structured for high-throughput result reporting. Compared to molecular detection methods, DFA and IFA assays have significantly reduced sensitivity and specificity (197). Some argue that the lower sensitivity can identify "clinically relevant infections" in some patient populations (e.g., hospitalized pediatric patients) (198) in contrast to detection of free nucleic acid as in molecular detection. Additionally, microscopic examination of samples for DFA testing can directly determine specimen quality (199) by allowing for observation of the number of epithelial cells present in the sample.

Rapid Antigen Detection Tests for the Detection of Respiratory Viruses

Clinical Laboratory Improvement Amendments (CLIA)-waived tests are intended for use in "professional" settings (e.g., physicians' offices, mobile clinics, and pharmacies) and/or by untrained operators with no laboratory expertise (200). A summary of rapid antigen detection test (RADT) technologies that may be used as near-patient or point-of-care (POC) tests is given in Table 4. Technologies for these guidelines are discussed in general here; specific products are not discussed, and company names are not mentioned.

Earlier RADT assays detected antigens of FLUA, FLUB, and RSV. Use was often restricted to specific specimen types (e.g., NPS or NS), the sensitivities of these assays in pediatric and adult populations varied but were considered to be poor, and the assays could not be used to rule out infection (201, 202). Performance characteristics of these assays were typically determined during normal respiratory virus seasons, with

TABLE 4 Respiratory viral testing approaches with CLIA waivers[a]

Patient population(s)	Virus(es)	Viral targets	Technologies	Sensitivity (%) vs real-time PCR assays	Specificity (%) vs real-time PCR assays	Specimen type(s)	General TAT	References
Clinically ill, no age restrictions	FLUA, FLUB	Antigens	Immunochromatographic (first generation)	FLUA, 15–56; FLUB, 24–56; combined, 23–69	FLUA, 99–100; FLUB, 99–100; combined, 96–97	NPS, NS, NW/ nasal aspirate	Minutes	207, 375–378
Clinically ill, neonatal and pediatric, age varies	RSV	Antigens	Immunochromatographic (first generation)	58–80	91–100	NPS, NPA, NW/ nasopharyngeal wash	Minutes	212, 375, 379–381
Clinically ill, no age restriction	FLUA, FLUB	Antigen	Assisted/automated reading of immunoassay (second generation)	FLUA, 67–81; FLUB, 33–92	FLUA, 98–100; FLUB, 90–100	NPS, NS, NW/ nasal aspirate	Minutes	211, 288, 376, 381, 382
Clinically ill, pediatric patients, age varies	RSV	Antigen	Assisted/automated reading of immunoassay (second generation)	78–82	97–99	NPS, NW/nasal aspirate	Minutes	214, 383
Clinically ill, no age restriction	FLUA, FLUB	Nucleic acid	Isothermal amplification and molecular beacon probe detection	FLUA, 73– 94; FLUB, 75–97	FLUA, 63–100; FLUB, 54–100	Direct NS or NPS	≤1 h	286–288, 384
Clinically ill	FLUA, FLUB	Nucleic acid	Automated sample preparation, amplification, detection, and result interpretation, real-time multiplex RT-PCR	FLUA, 98–99; FLUB, 99–100	FLU, 99–100; FLUB, 99–100	NPS	≤1 h	289, 385
Clinically ill	FLUA, FLUB, RSV	Nucleic acid	Automated sample preparation, amplification, detection, and result interpretation, real-time multiplex RT-PCR	FLUA, 95; FLUB, 100; RSV, 99	FLUA, 98; FLUB, 99; RSV, 99	NPS	≤1 h	386, 387
Clinically ill adult and pediatric patients	FLUA H3 subtype and 2009 H1 subtype, FLUB, ADV, CoV, hMPV, PIV 1–3, RSV, RV, EV	Nucleic acid	Single-instrument configuration, real-time multiplex NAAT	96.8% positive agreement vs other FDA-cleared molecular comparative method	99.5% negative agreement vs other FDA-cleared molecular comparative method	NPS	Approx 1 h	388, 389

[a]Abbreviations: FLU, influenza virus; RSV, respiratory syncytial virus; ADV, adenovirus; CoV, coronavirus; hMPV, human metapneumovirus; PIV, parainfluenza virus; RV, rhinovirus; EV, enterovirus; NAAT, nucleic acid amplification test; RT-PCR, reverse transcription-PCR; NPS, nasopharyngeal swab; NPA, nasopharyngeal aspirate; NW, nasal wash.

acceptable specificity for RSV and FLU (203, 204); however, the performance characteristics are significantly reduced when assays are used out of season (205–207). Many believe that the clinical utility of employing FLU and RSV POC assays, given the high numbers of both false-positive and false-negative results, is questionable (205–207), and the future long-term availability of rapid antigen detection kits is in doubt. On 23 February 2017, the U S. Food and Drug Administration (FDA) reclassified rapid antigen influenza virus test kits from class I to class II medical devices (208). This was meant to address growing concern about the variable performance of these assays as well as poor sensitivity compared to other methods such as NAATs and culture. Existing kits could be purchased until 12 January 2018 and used until the kit expiry date. Following that point in time, manufacturers were expected to monitor kit reliability and provide updates to users. Additionally, some assays are unable to differentiate between FLUA and FLUB, which may impact epidemiological investigations (209), and they have particularly poor sensitivity to detect avian influenza virus and other emerging subtypes (210). However, RADT may still have a place in management of outbreaks or in locations with limited access to molecular diagnostics (209), but consideration of the assay performance and the seasonality should be taken into account when using these assays.

A second generation of viral antigen POC tests improved the sensitivity for FLUA/B and RSV detection compared to that of earlier technologies (211, 212); however, the performance characteristics were still reduced compared to those of routine molecular testing (Table 4). Similar to the case for earlier generations, respiratory viral infection could not be ruled out with the newer POC tests, and sensitivities and specificities varied depending on the FLU target and the comparator molecular method used (Table 4). For RSV, sensitivity and specificity were reduced compared to those with molecular methods (Table 4). The sensitivity of these tests is highest during the RSV season when the positive predictive value is high (213–215). If clinicians feel there is a need for RSV antigen-based POC testing for pediatric patients (e.g., when there is no nearby laboratory access or in resource-poor environments), laboratorians need to inform clinicians of the newer test technologies, provide information on the current prevalence of these pathogens, and assist in generating algorithms that reduce the risks of these technologies.

Molecular Detection Approaches as the New Reference Standard

Extraction considerations. The first step in NAAT requires extraction, purification, and preservation of target organism nucleic acids. Extraction technologies should be able to cleanly isolate both high-quality viral RNA and DNA and, depending on the assay, to additionally sample human nucleic acids to allow the detection of human genes (e.g., that for glyceraldehyde 3-phosphate dehydrogenase [GAPDH] or β_2-microglobulin [β2M]) as control targets. The ubiquitous presence of RNase enzymes in most human samples makes isolation of RNA nucleic acid targets (e.g., FLU, RSV, and CoV) (Table 1) more difficult than isolation of DNA (e.g., adenovirus) (Table 1) and often requires additional steps for processing. Multiple extraction methods may be employed for respiratory virus detection. Heat-mediated lysis is an approach where target organisms are lysed or homogenized to release target nucleic acids (216). This approach is used in some commercial NAATs. Manual extraction using phase separation, capture via magnetic beads, or immobilized silica spin or vacuum wash columns may also be used. Automated extraction systems may be employed and generally use magnetic silica or other particles designed to capture RNA, DNA, or both. In fully automated instrument systems, all steps from extraction through to amplification are incorporated into a single cartridge or pouch.

Commercially available respiratory virus NAAT kits for detection of respiratory viral targets generally have a specific extraction method that is qualified for sample processing as part of the FDA clearance. Often, the FDA-cleared NAATs will have claims for specific specimen types (NPS, NS, etc.) but may or may not specify the type of transport medium. If the laboratory chooses to use specimen types besides those that are FDA

cleared, the laboratory should perform a verification study to document recovery of the target nucleic acids and acceptable performance of the NAAT (217). A validation plan should consider a variety of factors, including the frequency of specimen type being tested and the risk that specimen types may not be compatible with the assay. Similarly, if the testing laboratory chooses to use a different extraction protocol, verification for comparable performance is required. The requirement for verification of additional specimen types is outlined in the College of American Pathologists' *Microbiology Checklist, Molecular Microbiology, MIC.64810* (sections titled "Test performance—manufacturer's instructions" and "Laboratory-developed or modified FDA-cleared/approved tests") (217). Many in-depth documents and reviews discussing the requirements of molecular assay validation have previously been published (218, 219); therefore, a detailed discussion will not be included in this article.

Assay control considerations. All NAATs, whether laboratory-developed tests (LDTs) or FDA-cleared assays, should include a set of controls, including external positive and negative controls for respiratory viral targets that are tested by all steps in the assay. An internal amplification control should be added to all specimens except in assays where inhibition rates of the NAAT have been shown to be below acceptable limits (often defined by the laboratorian) (220, 221). These controls ensure that target nucleic acid is recovered and any potential NAAT inhibitors are removed during the sample processing stage. While commercial NAAT kits are designed to flag invalid results (when internal controls fail), LDTs require manual checks and result review to detect invalid specimens. The number of external controls and their frequency of use should be established by the laboratory based on regulatory requirements and its individualized quality control plan (IQCP), with a focus on risk assessment. Rules for review and result-based actions items should be addressed in the laboratory IQCP (222, 223).

Contamination. Molecular target amplification assays are susceptible to false-positive results caused by contamination, and false-positive results may occur at any step in sample collection and processing. Preanalytical contamination may occur when specimen integrity is breached during the collection process or when integrity is breached during early handling processes in the laboratory (221). Even when using a biosafety cabinet, steps should be taken to limit the production of aerosols and to process specimens in a manner that prevents cross contamination (224). Given that respiratory viruses can be identified in health care environments, it is possible that inappropriately handled swabs or other specimens could be contaminated with these viruses (225). It is also possible that a laboratory worker infected with a respiratory virus may act as a contaminating vector in the laboratory. The greatest risk of contamination is from amplicons created (and possibly aerosolized) during previous molecular runs. Most commercial assays using either real-time reporters or array-based detection are designed to minimize risks of amplicon contamination unless the laboratorian fails to correctly handle the reaction vessels (221).

Assays that incorporate manual postamplification processing present the highest risk of contamination to the laboratory. Multiple amplicon sterilization processes have been established to decrease the chance of amplicon carryover in molecular assays. These include the use of UV light to create thymidine dimers (cross-linking contaminating DNA), altered amplification chemistry using modified nucleotides, addition of uracil DNA glycosylase (UNG), and the use of hydroxylamine to prevent cytosine and guanine base pairings in subsequent reactions; however, numerous chemical approaches may be used (226–228).

Good laboratory practices can also be used to control contamination or carryover of amplicons (Table 5). These are particularly relevant when multiple processes such as reagent preparation, nucleic acid extraction, amplification, and postamplification processing are utilized. Open systems (where extraction, amplification, and/or detection stages are exposed to the environment) and closed systems (where extraction, amplification, and detection are completed within a single compartment not exposed to the environment) have different contamination control requirements (Table 4). Staff training protocols and laboratory standard operating procedures (SOPs) should emphasize

TABLE 5 Good laboratory practices for molecular assays

Laboratory practice to decrease contamination events	Recommendation for type of molecular system[a]	
	Open	Closed
Unidirectional flow (clean to dirty)	Recommended	Not required
Physical separation of pre- and postwork areas	Recommended	Not required
Regular decontamination of work areas	Recommended	Recommended
Use of aerosol-resistant pipette tips	Recommended	Recommended
Change of PPE between processing steps	Recommended	Not required
Restricting worker movements postamplification	Recommended	Not required
Centrifuging reagents	Recommended	Recommended
Ensuring that only one specimen is uncapped at a time	Recommended	Recommended
Process to monitor contamination events	Recommended	Recommended
Dedicated equipment for pre- and postamplification areas	Recommended	Not required
Monitoring environment for contamination (e.g., by environmental swipe tests)	Recommended	Recommended

[a]Based on the type of molecular system, laboratory practices to decrease contamination are either recommended or not required (217, 221–223, 228).

the organization of workflow process (such as unidirectional flow, separate areas for pre- and postamplification processing, regular decontamination of work areas with bleach, strict adherence to use of aerosol resistant pipette tips, mandating changing of gloves and lab coats between processing steps, and restricting work on new samples after handling postamplification reaction mixtures [228]) and technical practices (such as aliquoting of reagents, centrifuging of reagents, and care in capping and uncapping tubes, which may also prevent cross contamination). Physical separation of workspaces dedicated to different assay steps (e.g., pre-PCR and post-PCR) can also decrease the risk of contamination (221) and is recommended for open systems, but it is not necessary for closed systems.

Additionally, laboratorians should develop processes to monitor contamination events. Sentinel systems, such as running negative or no-template controls in each amplification assay, can be used for detecting large-scale contamination (221), while low-level contamination events may be identified by laboratorians as an excessive or unusual amount of low-level positive specimens (e.g., positive results near the cutoff). Care should be taken when interpreting results for higher numbers of low-level positive results outside the normal respiratory virus season, as many low-level positive results may represent contamination. Care should be taken when interpreting specimens that are positive for multiple targets, and laboratorians should have a sense of the coinfection rates within their settings. Coinfection rates may vary widely between adult and pediatric patient populations and may account for over 10% of all specimens in some pediatric populations (229–231). Environmental swipe tests should be considered to monitor workspaces for contamination from current or recently circulating viruses as well as control materials, and they can be used to detect widespread amplicon contamination events (232); however, sporadic contamination events may be missed due to sampling bias. Some FDA-cleared assays have specific recommendations for environmental monitoring and outline routine decontamination measures. For other tests, it is up to the laboratory to define intervals as part of their quality assurance program or IQCP (217, 221–223).

Positive predictive value and false-positive tests. In general, molecular tests for respiratory viruses have high sensitivity and excellent negative predictive values, which can reliably rule out infection when assay results are negative. Most molecular assays for respiratory viruses also have excellent positive predictive values, in the range of 90% or higher. Because molecular amplification assays for these pathogens are generally more sensitive than culture-based methods (233), it is often difficult to determine if a molecular result is a false positive when the reference culture method is negative. In some instances, a second molecular assay using a different gene target may be used to resolve discrepant results; however, it should have analytical sensitivity equal to (or better than) that of the first assay (220). Additionally, when the respiratory viral pathogen is present at a level close to the assay's limit of detection, discrepant results

due to Gaussian distribution effects can be observed (234). Finally, sampling error can affect the results of comparative studies if two separate swabs or collection protocols are utilized.

Labor and cost of molecular assays. The use of molecular approaches has traditionally been accompanied by higher supply costs than for antigen- or culture-based methods (235); however, modern molecular technologies provide improved performance characteristics compared to culture and/or DFA/IFA (197). Automation and integrated molecular test platforms can provide labor savings to the laboratory to offset increased reagent and platform costs (236) and may also decrease downstream costs for the health care system by providing more rapid and accurate results. Incorporation of molecular assays has resulted in variable patient management outcomes depending on studies, with some studies showing positive effects and other studies showing no effect, as identified in a recent review by one of the authors of this article (237). Negative effects on patient management have not been identified. Positive effects on patient management include decreased patient isolation times (238), length of stay (LOS) (239), administration of antibiotics and oseltamivir (240), and duration of antibiotic therapy (241).

Understanding Applications of Molecular Detection Approaches

Limited role of viral loads in predicting patient outcomes. A growing body of evidence shows a correlation of respiratory viral load and patient outcome. In one study of immunocompetent adult patients, age and hospitalization time were associated with earlier reverse transcriptase PCR (RT-PCR) cycle threshold (C_T) values for FLUA/B of $\leq$20 than later C_T values (242). Association of viral load and outcome can also vary by genotype, as RV-A viral loads were higher in patients with severe disease than in patients without severe disease, while no difference in viral load was observed for patient groups infected with RV-C (243). Furthermore, increased fatalities in adult CAP patients were associated with sustained viremia and high viral loads of ADVs in sputum and tracheal aspirates (244).

However, current laboratory practices generally report qualitative results for a respiratory virus NAAT, rather than determining a true viral load. The currently available laboratory-developed viral load assays have multiple problems, including the lack of an international standard, lack of standardized technology, and lack of consensus on specimen types (245). Additionally, the timing of specimen collection can influence viral load results. In fact, viral load samples taken on day 3 postonset may have a stronger association with clinical outcome than samples taken on day 0, 1, or 2 (246). Given the viral load data described in this section, the viral shedding data (described above), and the impact of age, immune status, and/or coinfection with other respiratory viruses (134), additional studies are needed to determine when viral loads are appropriate in different patient populations and how to appropriately interpret the results. Due to sampling errors, time of collection, patient age, etc., viral loads may not be comparable from one patient to another. In the future, possible roles for these viral load assays may include monitoring an individual patient over time to assess for viral clearance or response to antiviral therapy.

Molecular panel testing for respiratory viruses. (i) Defining multiplex assays. Multiplexing of molecular assays was traditionally restricted by the number of targets that could be efficiently amplified within a single reaction vessel (247–249). The earliest approaches were often batch-based assays that relied on a single nucleic acid extraction followed by one or more molecular assays. Often, panels of multiple individual targets or small multiplexes with 1 to 3 targets could overcome some of the inefficacies of massively multiplexed reactions (250); however, development of new technologies with improved multiplexing capabilities has allowed detection of multiple virus targets from a single sample (251–253).

(ii) Recommendations for patient populations in which multiplexed respiratory viral panel testing may be appropriate. Testing requirements may vary depending on the patient setting and resources, as the costs of the multiplex assays are high. The

most appropriate patients to test may vary depending on the health care setting, as some studies show questionable utility in testing adult outpatients for viruses other than FLU (254), Instead, for FLU patients who meet ILI criteria and are at high risk for complications, a highly accurate rapid test may have the greatest utility. Others have shown that multiplexed viral panels can directly influence antibiotic utilization practices (241).

Hematology and oncology patients may be appropriate patient populations for testing. The Infectious Diseases Working Party of the German Society for Haematology and Medical Oncology identified community-acquired respiratory virus infection as a significant cause of morbidity and mortality in oncology patients (103). Infectious viral etiologies were widely varied and included both single and mixed infections. For example, RSV infection has a high likelihood of progressing to a lower respiratory tract infection (30%) and a high chance of mortality (27%) in oncology patients. Therefore, testing for FLU, RSV, PIV, and other prevalent community-circulating viruses in all oncology patients presenting with symptoms (103) is suggested.

Transplant patients may also be an appropriate patient population for multiplex testing. Given the poor predictive value of the U.S. CDC's ILI criteria not only in adult transplant patients but in general, some authors have suggested an increased role for the use of multiplex respiratory NAAT assays in adult transplant patients with suspected respiratory virus infection (32). In lung transplant patients, identification of mixed viral infections using a multiplex panel could be used as a predictor of poor outcome (e.g., biopsy-proven rejection or sustained decline in forced expiratory volume [FEV1]) (255). In lung transplant patients, the detection of one or more viruses using a respiratory virus panel in a BAL fluid sample during the first year after transplant has also been associated with significantly faster development of bronchiolitis obliterans syndrome (BOS) (256).

Intensive care unit (ICU) patients may be another appropriate patient population for respiratory viral multiplex panel testing. In a recent review, respiratory viruses such as FLU, RSV, and RVs were suggested to cause immunosuppression in ICU patients (257). Given the clinical severity of illness in patients in the ICU, they are good candidates for respiratory virus panel testing. Appropriate identification of the severity of patient illness as well as the patient location (including the ICU) within the health care facility can often be challenging for the laboratory. Therefore, identification of critically ill patients with suspected pneumonia has previously been used as a selection criterion in the absence of accurate hospital location data (258).

Pediatric patients with an underlying illness may also be an appropriate patient population for respiratory viral panel testing. Panel testing may allow for identification of pathogens associated with specific risks in pediatric patients. This may include increased risks for asthma and wheezing in critically ill patients (259) or a lack of FEV1 improvement in pediatric cystic fibrosis patients (260).

(iii) To multiplex or not to multiplex? A variety of commercial and FDA-cleared *in vitro* diagnostic tools are currently available. Incorporation of these highly multiplexed assays into the laboratory significantly decreases turnaround time compared to that when performing all assays individually (252). Additionally, ease of use is improved with many assays giving "sample-to-answer" detection of respiratory viruses. Multiplex assays often have excellent performance characteristics, allowing clinicians to be confident with test results and make informed clinical decisions with concrete patient and health system benefits. Compared to complex algorithms involving multiple ordering of tests for small numbers of viral targets (e.g., FLU, FLU/RSV, EV, and RV alone), multiplex panels used as a routine test ordering choice can remove some of the confusion or indecision described by clinicians when ordering tests for smaller numbers of viral targets individually (261, 262). However, given that these panels are expensive, demonstration that the results impact patient care help justify the increased cost to the laboratory. A variety of studies have looked at indirect benefits of multiplexed panel testing; however, the identified outcomes are not consistent between studies. In patients 3 months to 21 years old, panel use has been associated with decreased length

of stay (LOS) in emergency departments and inpatient wards (241). Identification of a viral etiology has also shown improvements in hospital isolation resource use, which can be removed as appropriate and targeted only to patients who require isolation. Compared to other methods, multiplex panels can decrease the amount of antibiotic and antiviral use, and they may be used to appropriately triage patients in acute care settings (239, 263, 264). A significant decrease in the duration of antibiotic use and the number of chest radiographs was observed in an adult tertiary care center when rapid multiplexed panels were used compared to traditional antigen detection and older molecular methods (239). Adult outpatient outcomes were assessed at a Connecticut VA Center that used an on-demand respiratory panel. Outpatients were divided into those with FLU detected, those with a non-FLU virus detected, and those with no pathogen detected. Antibacterial prescription rates did not vary between groups; however, there was a statistically significant difference between antiviral prescription rates: the FLU-positive group was more likely to be treated with an antiviral agent (80/105 [81%] treated) than were patients in the non-influenza virus pathogen group (6/109 [5.5%]) and the no-pathogen-detected group (2/81 [2.5%]) ($P < 0.001$) (254). Respiratory panel use allows for more comprehensive characterization of viruses for general epidemiology/surveillance (15, 265) and outbreak investigation. Other, less tangible but important, benefits to respiratory viral panel use may also include improved patient and physician satisfaction with an improved test turnaround time.

Multiplexed respiratory virus panels may have significant costs for implementation, and some may have significant costs to operate. Health care administrators need to be made aware of the indirect and direct benefits of panels and how cost savings may be generated through improved workflow practices and lower labor costs (266, 267). Laboratorians and clinicians may need to reassess how clinical utility studies are undertaken and consider group efforts to undertake well-controlled and standardized studies (264).

(a) Multiplexing and the utility of identifying mixed infections. Multiplexing of molecular assays can facilitate identification of mixed viral infections (268–270). Coinfections are defined as the detection of more than one virus in a patient specimen. The rate of coinfection will depend on the particular virus, the methodology used for detection, the patient population demographics, and the geographic location of the study (271). However, understanding the impact of coinfections on patient outcomes is challenging, particularly when molecular tools are used for diagnostics. Nonviable virus from a remote infection or virus not associated with the current infection may be detected by molecular methods. Important considerations include (i) whether identification of mixed infections leads to a better understanding of patient prognosis, (ii) whether identification of mixed infections leads to changes in patient management, (iii) whether identification of mixed infections leads to changes in infection prevention and control practices, and (iv) whether the increased identification of viruses not routinely identified in nonmultiplex panels allow for placing patients in cohorts based on etiology during isolation.

In some cases, coinfections may make up a significant proportion of total viral cases within a population. In one recent study, coinfections with bacteria and viruses were identified in 40% of viral respiratory tract infections requiring hospitalization (272). For example, in Japan, a recent study found that 43.8% of patients who were diagnosed with a CoV infection were also infected with an additional virus (273). In another study, coinfections of two or more viruses were identified in approximately 18% of infants with an acute respiratory illness; RV was the most common coinfecting virus, but other viruses, such ADV, hMPV, and PIVs, were also codetected (270). Thus, the impact of mixed infection on patient outcomes is still under debate. Some studies show no difference in patient outcomes when coinfections are compared to single virus-infections, even in highly immunocompromised patient populations (268). Additionally, studies in immunocompetent children with lower respiratory tract infection found that RSV coinfection with any other respiratory virus was not associated with more severe disease than RSV infection alone (274). Conversely, other studies show that coinfection

with RSV and a second virus in infants with lower respiratory tract infections is associated with increased length of stay (LOS) (275). In another study, an increased risk of life-threatening disease (e.g., intensive care unit [ICU] admission, need for mechanical ventilation, or death) was identified in patients with ADV-RSV coinfections compared to RSV single-virus infections. In a secondary outcome analysis, FLU-RSV coinfections had an increase in LOS compared to RSV single-virus infections (274), while ADV coinfections were more likely to be associated with the need to treat with supplemental oxygen than were ADV single-virus infections (276). Furthermore, in cases of community-acquired pneumonia, viral-bacterial infection has been associated with a more complicated course (e.g., hospital death or mechanical ventilation for >7 days) than infections with bacteria alone, viruses alone, or no identified etiology (277).

(b) Commercially available molecular test panels may not fulfill all testing needs. A major drawback of multiplexed panels is the inability to differentiate closely related viruses or to detect all targets with equivalent sensitivity, and some targets on commercial multiplex panels continue to be detected more efficiently by singleplex assays (278) (also see comments on emerging pathogens below). In one study, detection of RSVA and FLUA had decreased sensitivity in panel tests compared to that with singleplex NAAT (279). Likewise, detection of ADV in multiplex panels often has decreased sensitivity compared to that with in-house NAAT assays (280), particularly for ADV group E (279). Of note, only respiratory species of ADV (B, C, and E) will be detected in multiplex panels, while nonrespiratory ADV species (A, D, and F) will be missed. In commercial panels, the proprietary nature of primers and probes does not allow investigation for detection of emerging viral pathogens, which may be missed by commercial assays (281).

Another limitation in some available assays is the inability to distinguish EVs from RVs. This can lead to secondary laboratory differentiation algorithms to characterize infection (282), and this is compounded by the limited ability to detect emerging EV strains (278). For example, enterovirus D68 may require altered patient management compared to seasonal EV strains, as it is associated with extrapulmonary syndromes such as acute flaccid paralysis (282). Additionally, detection of nonrespiratory ADV in the respiratory tract can precede systemic infection in immunocompromised children (283). Unfortunately, there is currently no practical gold standard to determine whether ADV detection in the respiratory tract is causal or incidental (284).

(iv) Near-patient or POC tests. As highlighted above, CLIA-waived tests are intended for use in "professional" settings (e.g., physicians' offices, mobile clinics, and pharmacies) and/or by untrained operators with no laboratory expertise (200). A summary of NAAT assays that can be used as point-of-care (POC) or near-point-of-care tests is in Table 4. Technologies for these guidelines are discussed in general here; specific products are not discussed, and company names are not mentioned.

The availability of newly developed CLIA-waived NAAT assays which detect FLUA/B or both FLUA/B and RSV is increasing. Multiple assays are now emerging in the marketplace and may have similar test characteristics (285); users should consult up-to-date resources for a list of waived products. Users should note that in general, reverse transcriptase PCR technologies may have higher sensitivities than isothermal assays (286–289).

Benefits of near-patient NAAT assays include ease of use and reduced process steps compared to those with older molecular assays, software that allows for easier result interpretation, and closed systems to reduce contamination (286–289). Drawbacks of near-patient NAAT assays include the potential to cause unforeseen strain on the laboratory (e.g., for confirmatory testing and quality assurance program support), the impact on resource utilization outside central laboratories, and the limited scope of specimen types that can be used (290–292).

A recent review of POC testing, including NAAT, identifies several barriers to understanding the benefits of point-of-care testing for respiratory viruses (237). Implementation of rapid nucleic acid testing could be associated with decreases in number of hospital admissions, length of stay, emergency department length of stay, duration

of antimicrobial use, droplet contact days, total isolation days, and receipt of antibiotics (238–241).

Appropriate Test Utilization in the Era of Molecular Testing

Respiratory virus testing algorithms vary between health care institutions. Resources, types of laboratory facilities, and different patient populations (to name a few) may all play a role in the testing algorithm chosen. Choosing Wisely is a campaign started in 2012 that focuses on initiating discussions with both the patient and physicians about unnecessary procedures, treatments, and tests (293). This section focuses on Choosing Wisely and discusses (i) which testing options might be suitable to perform depending on needs, (ii) what laboratories can do when resources are limited, (iii) how the importance of preanalytics plays into the testing decision being made, and (iv) what additional considerations need to be discussed up front before any test or piece of equipment is adopted by the laboratory or health care environment. The following sections describe key steps in ensuring that health care workers choose respiratory tests appropriately.

Stakeholder engagement. To provide high-quality, cost-effective laboratory services, it is imperative to understand the clinical needs of the end users when considering solutions for detection of respiratory viruses (294). Depending on the health care system, the laboratory may be asked to offer testing within the main laboratory or to play a role in determining the best test for near-patient testing. Because diagnostic needs vary, it is important to identify the right stakeholders at the beginning in order to determine appropriate process development and assay deployment.

Stakeholder discussion should include the needs of primary care providers, characteristics of the patient population, clinical practice settings, required test turnaround time, availability and expertise of nonlaboratory staff to perform POC testing, the volume of testing, and potential outcomes of a new assay/process. Physician groups utilizing testing are broad and may include the emergency department, inpatient/ICU, infection prevention and control groups, and pediatric and adult outpatient services such as urgent care or family practice. The laboratory, along with infectious diseases physicians, should engage these providers to completely understand the provider/patient need.

In order to choose wisely for respiratory virus testing, one must have a fundamental understanding of the needs of the organization. Early engagement with the provider and operational stakeholders (departmental administrators or managers overseeing specimen collection and/or testing) is paramount to successful test implementation. It is crucial for an institution to consider and understand the potential clinical and financial impact of a diagnostic test. Some decisions may be made based on outcome data in the literature or data that are internally generated (263, 295–304). Outcomes can include (but are not limited to) cost, TAT, infection prevention and control decisions, antibiotic administration, antiviral administration, inpatient LOS, rates of admission to the hospital, referrals, and ancillary testing (chest radiography or other laboratory testing) (299, 302). A positive or defined outcome not only demonstrates the utility of a specific test but can also be presented to administrators to support the proposal. Many institutions today are implementing test algorithm changes in part due to evidence-based medicine and outcome data.

A PubMed search for the terms "respiratory," "virus," "testing," "utilization," and "compliance" found no articles related to utilization and compliance for respiratory virus testing; however, we have identified a need for monitoring usage after implementing algorithms to ensure compliance and appropriate utilization of tests by the ordering health care workers.

Choosing the right test. As evidenced by the diversity of institutional provider groups discussed above, a single solution might not work for all patient populations or specialties of care. In choosing wisely, regardless of the test or the ability to be reimbursed, the emphasis should be on what the provider will do with the result and how implementation will impact the clinical outcome, the quality of care given

to the patient (e.g., reduction in unnecessary antibiotic use or duration) or the institution (e.g., reduced length of stay [LOS] in the hospital). Because many laboratories are being asked to do more with less, it is incumbent on not just the laboratory personnel, but all health care professionals, to spend money wisely and show the impact of testing that is implemented. Quality of care is also improved when physicians understand how to best use a result from a laboratory test. In many electronic medical records (EMR), decision trees can be adopted to aid in appropriate test selection, and tests can be restricted by patient location (e.g., inpatient versus outpatient) to promote effective ordering habits. As fee-for-service models are replaced with integrated care delivery systems, test reimbursement becomes less of a driver for best practices for respiratory virus testing. For example, laboratorians should consider the importance of providing influenza A virus subtype data when using/considering molecular assays, as some FDA-cleared tests do not provide the subtype. In some settings, clinicians may not voice concerns about lacking subtype information. An argument against subtyping is that subtyping matters only when circulating subtypes have different patterns of resistance to antiflu drugs. In other settings, clinicians may use subtyping data to place patients in cohorts in health care settings with low bed-to-patient ratios.

As described above, many providers have historically relied on RADTs, culture, or direct fluorescent-antibody (DFA) testing for the detection of respiratory viruses. RADTs have still maintained their popularity because of their rapidity even though they are suboptimal in regard to sensitivity (209, 305). Over the last decade, the use of NAATs with relatively faster sample-to-answer times has replaced that of more traditional methods (306). Sample-to-answer methods with TATs of ~1 h may be acceptable for hospitalized patients, or perhaps patients in the ED, but TATs exceed those required in outpatient setting. More recently, FDA-cleared and CLIA-waived NAATs with sensitivities and specificities comparable to those of FDA-cleared laboratory-based molecular tests have become available (307).

Complex multiplex PCR assays are often restricted to hospital settings and reserved for the most ill patients with associated comorbidities. Diagnosis of respiratory illness in this setting is deemed important to the physician even though treatment might not be available for a specific pathogen. The infection prevention and control needs of a health care institution may warrant the implementation of multiplexed testing to appropriately place patients with similar infections in cohorts when bed space is restricted. These multiplex assays can be further divided into random-access and batched testing platforms (306). Both routine and unplanned-for laboratory needs may require the laboratorian to consider utilizing both batched testing and random-access test systems. Random-access platforms are suggested for daily use in laboratories with low to medium specimen volumes, with the benefit of a rapid turnaround time and simplified workflow. As test volumes increase, the laboratorian may reconsider test algorithms and utilize a batched testing platform (308). Some algorithms may improve cost-effectiveness by offering a less-expensive upfront singleplex assay for FLU or duplexed or triplexed assays, including FLU and RSV, and using multiplex panels only if the sample is negative for FLU; however, algorithms will vary by institution, time of year, and prevalence of influenza. Furthermore, algorithms should be chosen based on stakeholder engagement and the individual testing needs of the patient population.

So, how is this made operational? We have provided a risk assessment flow chart in Fig. 2. We realize that a single approach will not be applicable to all laboratories. Therefore, laboratorians should work with their clinical partners and manufacturers to establish risk-based algorithms which can be used to determine the appropriateness of testing. Test ordering systems, clinical information, and patient location, as well as demographic identifiers, can be used to streamline the placing of specimens into appropriate test algorithms (e.g., no testing, testing for limited targets, or broad panel testing). Laboratorians should offer clinicians the opportunity to discuss cases that do

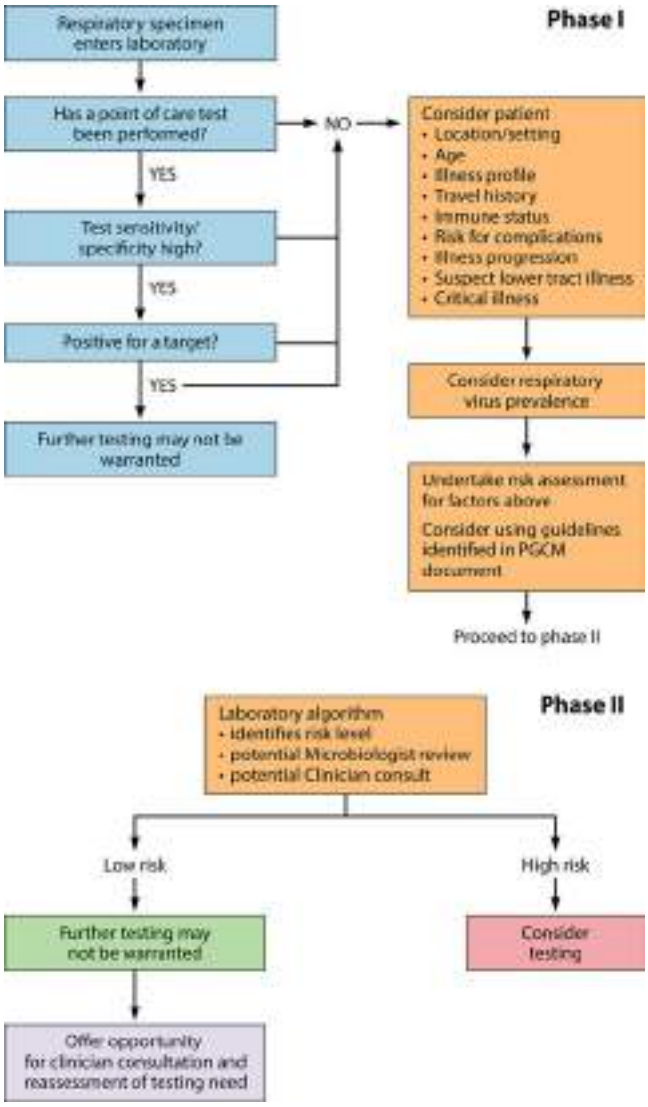

FIG 2 A risk assessment approach to determine populations most effectively served by acute respiratory virus testing. The decision-making model can be used to identify the level of test complexity for patient populations.

not fit into general risk groups (e.g., low versus high), where patients may benefit from specific laboratory tests.

Recent Issues Surrounding LDTs for the Diagnosis of Acute Respiratory Viral Infections

LDTs may find a role in the clinical laboratory under the following scenarios: where commercial assays are not available, when performance issues emerge with commercial respiratory virus assays, or when a new assay is required immediately (e.g., in the event of an emerging respiratory pathogen) (309). LDTs are defined as assays developed and performed by high-complexity laboratories (e.g., "home brew" or "in-house" assays) that are "intended for clinical use" (310). Draft guidance documents surrounding LDT use were released in 2014 by the FDA, which provide guidance for clinical laboratories, industry, and drug administration staff (310). As of 2016 to 2017, the FDA proposed a "risk-based, phased-in approach, in combination with continued exercise of enforcement discretion for certain regulatory requirement and certain types of LDTs"; however, it is up to the individual laboratory to calculate the risk associated with the use of LDTs (311). These issues are not specific to the United States (312). This proposed framework

would place each LDT into a specific risk class (305), and laboratories in other countries may benefit from comparing how they and their U.S. colleagues perform risk assessments (313).

Section Summary and Recommendations

Older methods such as rapid antigen detection techniques, DFA tests, and viral culture have essentially been replaced by more rapid and sensitive NAAT assays, which have improved the characteristics of laboratory tests for the diagnosis of acute respiratory viral infections. However, the highly sensitive nature of these tests as well as the possibility for molecular contamination means that laboratorians need to develop processes and practices to prevent molecular contamination. Laboratorians should understand the risks and benefits of using LDTs and potential regulations restricting their use. Rapid POC NAATs are allowing for the rapid detection of multiple respiratory pathogens compared to routine laboratory NAATs. Multiplexed NAATs, including POC tests, now allow for rapid detection with faster turnaround times (TATs) and sensitivity and specificity equivalent to those of laboratory-based NAATs. Apart from patient management for FLU, the patient and system benefits of multiplexed NAATs require further study, and current study outcomes may be confounded by multiple factors. Laboratorians should consider strong utilization approaches when initiating supporting NAAT POC test and multiplexed NAAT implementation. Laboratory utilization discussions should take into account the clinical utility of testing in specific patient populations. Finally, although NAATs are the primary method of detection, laboratorians should coordinate testing in a reference laboratory that undertakes viral culture techniques to allow for phenotypic influenza virus characterization and/or antiviral susceptibility testing as part of ongoing public health surveillance.

ANTIVIRAL AND PROPHYLACTIC AGENTS: IMPACT ON THE CLINICAL LABORATORY

RSV Prophylaxis and Antiviral Agents

The use of palivizumab (314) has been described above. Laboratory diagnosis of RSV has no direct impact on the decision-making on when to initiate palivizumab prophylaxis, but general laboratory testing trends may help in the determination of when the RSV season starts and ends in some locations (95).

Although the use of multiple agents to treat respiratory viral infections has been described, the number of antiviral agents with FDA approval is limited. For treatment of RSV infection, the only approved agent is ribavirin (in aerosolized form). The use of aerosolized ribavirin can pose health hazards to health care workers and is not easy to deliver to patients, making it a less-than-ideal treatment choice. The 2012 *Report of the Committee on Infectious Diseases* (*Red Book*) focuses on pediatric infections and indicates that primary treatment for RSV is supportive. The *Red Book* does not recommend the routine use of ribavirin but does indicate that use may be considered in "selected patients with documented, potentially life-threatening RSV infections" (315). Research-focused approaches regarding RSV mutations is not described further here; however, potential mutations driving resistance against palivizumab and issues with ribavirin are described in a recent review (215). A comprehensive review of the effectiveness of antivirals for these viruses is beyond the scope of this guidance document, but there are emerging data supporting the use of oral ribavirin in treatment of URTI and LRTI in stem cell transplant patients (102, 103, 316–318). As new antiviral agents for RSV (and other viruses) become approved, laboratorians may need to develop processes for systematic antiviral resistance testing and surveillance.

Treatment and Prevention of Influenza

FLU is the only respiratory virus discussed in these guidelines that currently has a vaccine available for prevention (315). Clinical laboratories should work with their public health laboratories to ensure that appropriate FLU characterization by culture and molecular methods occurs. Culture may still be required for phenotypic strain

typing as well as antiviral susceptibility testing as part of studies or national surveillance systems. These data may also help support decision-making regarding FLU vaccine effectiveness (41).

Currently licensed antivirals for influenza include the adamantanes, which block the activity of the M2 protein (active only against FLUA), and neuraminidase (NA) inhibitors (NAIs), which block the activity of the NAs of influenza A and B viruses. At the time of this publication, NAIs are the only drugs that are effective for the prevention or treatment for influenza. Adamantanes, which do not have activity against FLUBs, are no longer effective against seasonal FLUA (319). Two NA inhibitors, oral oseltamivir and inhaled zanamivir, are licensed in many countries. In addition, intravenous peramivir is licensed in Japan, China, South Korea, Canada, and the United States. A fourth drug of this class, long-acting inhaled laninamivir, is licensed in Japan. Similar to the case for M2 blocker-resistant viruses, viruses resistant to an NA inhibitor(s) may gain an evolutionary advantage and spread beyond countries employing NA inhibitor therapy. In 2007 to 2009, oseltamivir-resistant A(H1N1) seasonal prepandemic viruses rapidly emerged and spread globally (320, 321). In contrast, influenza A H1N1 (pdm09) virus strains are almost universally susceptibility to oseltamivir and zanamivir (322). Continuous antiviral susceptibility testing of seasonal FLU viruses is imperative to identify and track the emergence and spread of viruses resistant to NA inhibitors and M2 blockers.

Relevance of FLU Antiviral Resistance Testing

Guidelines from the Community Network of Reference Laboratories for Human Influenza in Europe suggest that testing for antiviral resistance is typically indicated in the following instances: (i) in patients lacking virological improvement (persistent virus shedding after 5 days of treatment using ab NAAT that "delivers semi-quantitative information" [e.g., a real-time PCR with a C_T value]), (ii) in patients treated with antivirals with severe FLU who do not clinically improve (time frame not given), (iii) in fatal cases where an understanding of resistance may influence prophylaxis of contacts, (iv) in cases of FLU developed during or after antiviral prophylaxis, and (v) in contacts of antiviral-treated FLU patients who developed respiratory symptoms or in contacts of FLU patients for whom the presence of resistant virus had been confirmed (323). One group that may benefit from antiviral testing is patients who shed virus for long periods of time and who do not improve after treatment (e.g., highly immunocompromised patients) (324, 325).

As molecular markers of resistance are not well established and vary depending on virus type/subtype and NA inhibitor, determination of antiviral resistance should be carried out in a reference laboratory with experience in these techniques (326). Documents created by the WHO's Global Influenza Surveillance and Response System (GISRS) and the WHO Influenza Antiviral Working Group (WHO-AVWG) can assist in the interpretation of these results (327, 328). Other documents may be available from other committees which provide guidance on the use of influenza antivirals (329).

Section Summary and Recommendations

Laboratorians should identify a reference laboratory for the characterization of influenza and antiviral susceptibility testing. Antiviral testing is not a routine test, and the time required to undertake such testing limits the clinical relevance of this testing in most patient populations. Antiviral testing may be required for epidemiological studies as well as cases of failure in prophylaxis. One patient population that may benefit from this testing is patients who are highly immunocompromised who do not clinically improve following antiviral treatment and who may shed virus for an extended period of time.

CODING AND REIMBURSEMENT

This section was introduced into the guidance document following presentation of these guidelines in the draft from at an ASM general meeting. Current procedural

terminology (CPT) is a set of guidelines, codes, and descriptions used to elucidate and standardize services by health care professionals, including testing in the clinical laboratory. The CPT codes for microbiology and virology are established through the Pathology Coding Caucus (PCC) of the American Medical Association (AMA). CPT codes in microbiology and virology have a 5-digit identifier with a description of the target and procedure (e.g., 87,633, CPT code in the category "infectious agent detection by nucleic acid [DNA or RNA]"). New codes are published yearly. Inclusion of a code in the CPT manual does not imply endorsement of the test, nor does it cover insurance or reimbursement policies.

In general, when a new test that needs a code is available, a proposal for coding is presented to the PCC. Among the criteria used by the PCC to review the request are test methodology definition, the volume of test utilization, the medical necessity, and scientific publications detailing performance and outcomes studies for the new test. After each caucus meeting, a document entitled "CPT Editorial Summary of Panel Actions" is prepared, which summarizes the actions that were taken by the panel on each of the code applications.

Pricing/fee setting for a CPT code is the purview of the Centers for Medicare and Medicaid Services (CMS). Annually, the CMS holds the Clinical Laboratory Fee Schedule (CLFS) meeting at its headquarters in Baltimore, MD. Stakeholders present the code(s) (as established by the PCC) and a proposed reimbursement amount (based on an existing rate or as a recommend new rate based on a comprehensive cost analysis). The CMS Advisory Panel on Clinical Laboratory Diagnostic Tests functions to establish payment rates based on crosswalking or gapfilling and establishes factors used for determining coverage and payment processes (330).

Per the CMS (331), crosswalking occurs when a new test (or substantially revised test) is determined to be similar to multiple existing test codes, portions of an existing test code, or an existing test code. Gapfilling occurs when there is no existing comparable test available (331).

As of 2017, reimbursement compliance is a system in place to ensure that the testing being performed is medically relevant for the clinical situation. Here, appropriate testing for specific clinical conditions and clinical outcomes is critical. The issue of medical relevance has been raised in virology recently in regard to multiplex respiratory virus and gastrointestinal panels. In brief, CPT code 87,633, defined as respiratory virus (e.g., ADV, FLU, CoV, hMPV, PIV, or RV), includes multiple NAAT reactions, and multiplex NAAT panels with target numbers (including types or subtypes) ranging from 12 to 25 targets. The medical necessity and reimbursement for these multiplex assays have been challenged, and Medicare and Medicare administrative contractor (MACs) alerted providers that a "broad-net" or "one-size-fits-all" panel contributes to test overutilization and increased health care costs without specific benefit to a given patient. They assert that testing should be limited to organisms with the greatest likelihood of occurrence in a given patient population and, if results are negative, to provide reflexive testing to more "exotic" organisms.

A consortium of clinical organizations whose members represent testing laboratories has submitted comments directly to MACs, recommending a thorough review of this issue. At the time of this writing, only a partial resolution has occurred (as per verbal communication by one of the authors).

Payment rates continue to be under scrutiny and have been discussed during implementation of the Protecting Access to Medicare Act (PAMA). This statute calls for a market-based fee schedule based on a weighted median of individual private payor test reimbursements reported by "applicable laboratories," which by specific requirements excluded hospital laboratories. Applicable laboratories included 45% of all commercial laboratories and 5% of physician office laboratories. As such, the data for reimbursement are heavily weighted by discounted pricing by large commercial entities to major payors (MACs). Beginning in January 2018, the intention was for price reductions to be implemented at 10% in each of the next 3 years, followed by a 15% reduction for the following 3 years, until the established

weighted median price is hit. These new fees were to be applied to all who are paid using the CLFS. Of note, concerned organizations and individuals have contacted CMS about the detrimental effect of the act and the predicted closure of many laboratories and the impact on patient care. The status of these new fees was in question as of January 2018 (332).

Section Summary and Recommendations

Laboratorians should be aware of reimbursements for existing and new diagnostics for respiratory in their locations.

CONCLUSIONS

This is the most recent update of ASM practice guidelines for clinical microbiology, addressing changes to acute respiratory viral infection diagnostics since the previous document, which was published in 1986. Since that time, laboratory practices as well as clinical practices have changed extensively. The guidelines were developed for the laboratory diagnosis of viruses causing acute respiratory illness, with technologies ranging from low- to high-complexity testing. Respiratory virus testing may be considered if a diagnosis has impact on patient management, especially when FLU treatment decisions are based on test results or in immunocompromised patients. In general, testing immunocompetent patients will not impact patient management. However, testing may be undertaken for surveillance in sentinel labs, to guide infection control decisions/practices, or when highly pathogenic emerging pathogens are suspected.

The landscape of respiratory virus testing has significantly changed in the last 30 years. The decreased use of older technologies such as viral culture and direct antigen detection represents a significant programmatic change in the diagnosis of respiratory viruses. Many front-line clinical laboratories have completely phased out viral culture, and testing such as strain typing and antiviral resistance testing is generally limited to reference laboratories. Molecular techniques are now the preferred diagnostic approaches for the detection of acute respiratory viruses and are more amenable to automation and high-throughput workflows. Good molecular laboratory practices and quality assurance programs are keys to preventing laboratory contamination. The decreasing complexity of platforms used for molecular testing has expanded the geographic capacity of these assays, which can now be placed closer to patients as POC tests, while newer technologies have made multitarget panels widely available. For novel and emerging respiratory viruses, laboratory-developed tests will still be required to compensate for testing gaps that often need to be filled quickly. With all the advances in technology, however, effective communication between clinicians and the laboratory is still essential to quickly identify highly transmissible emerging pathogens and reduce health care worker exposure. Laboratorians should work closely within their teams as well as with other clinicians and public health practitioners to ensure that health systems are prepared for the inevitable emergence of new respiratory viral pathogens.

Implementation of clinically relevant testing algorithms can ensure optimized patient care and improve laboratory resource management. Particularly, strong preanalytical screening approaches can facilitate appropriate specimen collection and direct providers to correctly order diagnostic tests as needed. Laboratorians should ensure that they continue to work with their public health reference laboratory colleagues to align processes to enable continued virus characterization and antiviral resistance testing.

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Carmen L. Charlton, Ph.D., M(ASCP)CM, F.C.C.M., D(ABMM), is a clinical microbiologist at the Provincial Laboratory for Public Health (ProvLab) and Assistant Professor of Laboratory Medicine and Pathology at the University of Alberta. Her current research focuses on vaccine-preventable diseases, with emphasis on infections passed from mother to infant during pregnancy. She obtained her Ph.D. in biochemistry and biomedical sciences from McMaster University in 2010 and completed her clinical microbiology training at the University of California, Los Angeles (UCLA), in 2013. Dr. Charlton is the Virology Program Leader for HIV, Hepatitis, Prenatal and Immunity Screening, and Human Papillomavirus at ProvLab. She is incoming President of the Canadian Association for Clinical Microbiology and Infectious Disease (CACMID), served on the American Society for Microbiology's (ASM's) Practical Guidance for Clinical Microbiology Committee, and is a current member of the Clinical and Public Health Microbiology planning committee for the ASM Microbe meeting.

Esther Babady, Ph.D., D(ABMM), is the Director of Clinical Operations for the Microbiology Laboratory Service, Director of the CPEP Clinical Microbiology Fellowship program, and an associate attending microbiologist in the Department of Laboratory Medicine at Memorial Sloan-Kettering Cancer (MSKCC) in New York, NY. She received her Ph.D. in biochemistry and molecular biology and completed a postdoctoral CPEP fellowship in clinical microbiology, both at the Mayo Clinic in Rochester, MN, before joining MSKCC. She is board certified by the American Board of Medical Microbiology and serves on the editorial boards of the *Journal of Clinical Microbiology* and *Journal of Molecular Diagnostics*. Her research interests include rapid diagnosis of infections in immunocompromised hosts and the development and evaluation of the clinical utility of molecular microbiology assays.

Christine C. Ginocchio, Ph.D., MT(ASCP), is Vice President, Medical Affairs, bioMérieux, Vice President, Scientific and Medical Affairs, BioFire Diagnostics, and Professor of Medicine, Northwell School of Medicine, New York. She has 40 years of experience in all phases of laboratory management and clinical diagnostics. She has been the principal investigator for more than 60 diagnostic industry and pharmaceutical clinical trials, including 23 studies of *in vitro* diagnostic devices for U.S. FDA clearance. Her areas of extramural funded research included HIV, cytomegalovirus, respiratory viruses, human papillomavirus, antibiotic resistance, and molecular diagnostics for infectious diseases. Her awards include the President's Award and Irving Abrahams Award for outstanding basic science research, the PASCV 2012 award in diagnostic virology, and an ASM 2013 BD award for research in clinical microbiology. She is co-editor-in-chief for the *Journal of Clinical Virology*, a section editor for the 10th, 11th, and 12th editions of the *Manual of Clinical Microbiology*, and on the editorial board for *Clinical Microbiology Reviews*.

Todd F. Hatchette, M.D., F.R.C.P.C., completed his M.D. and internal medicine residency at Memorial University of Newfoundland. After completing residency training in infectious diseases and medical microbiology at Dalhousie University, Dr. Hatchette completed postdoctoral research training in virology at St. Jude Children's Research Hospital in Memphis, TN. Dr. Hatchette is the Chief of Service for the Division of Microbiology, Department of Pathology and Laboratory Medicine, in the Nova Scotia Health Authority's Central Zone and a Professor in the Department of Pathology with cross-appointments in the Departments of Immunology and Microbiology and Medicine, where he is a consultant in infectious diseases. Dr. Hatchette has expertise in the clinical and laboratory diagnosis of viral infections and serves as an advisor on a number of local, provincial, and national committees. He is the President of the Association of Medical Microbiology and Infectious Disease, Canada.

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Robert C. Jerris, Ph.D., D(ABMM), is Medical Director, Microbiology, at Children's Healthcare of Atlanta and Adjunct Professor at Emory University School of Medicine. He completed his Ph.D. in experimental pathology at Emory University in 1981 and a postdoctoral fellowship at the Centers for Disease Control and Prevention. He has concentrated his research career in rapid methods (molecular and matrix-assisted laser desorption ionization–time of flight [MALDI-TOF]) for microbial identification and antimicrobial resistance. Dr. Jerris is the founding father of the South Eastern Association for Clinical Microbiology, has served for over 30 years in numerous positions with the American Society for Microbiology, and currently is the Chair of the ASM Committee on Professional Affairs.

Yan Li joined the National Microbiology Laboratory (NML) of the Public Health Agency of Canada in September 1998. He is the Chief of the Influenza and Respiratory Viruses Section of NML. He received his Ph.D. from the University of Ottawa in 1992. As the head of the WHO National Influenza Center in Canada, Dr. Li takes a leadership role in planning, developing, and maintaining a comprehensive national surveillance programs for influenza virus and other respiratory pathogens. He provides ongoing scientific advice and technical expertise to stakeholders in influenza surveillance and diagnostics. He has 187 peer-reviewed publications.

Mike Loeffelholz earned a Ph.D. in microbiology from Ohio University in 1987 and completed a postdoctoral fellowship in medical and public health microbiology at the University of Rochester in 1990. Dr. Loeffelholz is currently a Professor in the Department of Pathology and Director of the Clinical Microbiology Laboratory and the American Society for Microbiology CPEP-accredited Medical Microbiology Fellowship program at the University of Texas Medical Branch at Galveston. Dr. Loeffelholz has over 80 peer-reviewed publications and book chapters. He is editor-in-chief of the *Clinical Virology Manual*, 5th edition, and an editor of the *Journal of Clinical Microbiology*. Dr. Loeffelholz has served on a number of committees at the national level, including the ASM Committee on Professional Affairs, the CDC Board of Scientific Counselors/Office of Infectious Diseases, and the Association of Public Health Laboratories board of directors. He is a diplomate of the American Board of Medical Microbiology (ABMM).

Yvette S. McCarter, Ph.D., D(ABMM), is a Professor of Pathology and Laboratory Medicine at the University of Florida College of Medicine-Jacksonville and Director of the Clinical Microbiology Laboratory at UF Health Jacksonville. Dr. McCarter received her Ph.D. in pathology from the Medical College of Virginia and completed a postdoctoral fellowship in medical and public health microbiology at Hartford Hospital under the mentorship of Dr. Raymond C. Bartlett and Dr. Ann Robinson. She is a diplomate of the American Board of Medical Microbiology. Dr. McCarter recently completed a term as Chair of the American Board of Medical Microbiology. She is the microbiology associate editor for *Lab Medicine* and currently serves on the American Society for Clinical Pathology LabQ editorial board and Workshops and On-Demand Webcasts Committee. Her research interests include utilization controls in the clinical microbiology laboratory, cost-effective laboratory medicine, and evaluation of new diagnostic tests.

Melissa B. Miller, Ph.D., D(ABMM), F(AAM), is a Professor of Pathology and Laboratory Medicine at the University of North Carolina at Chapel Hill School of Medicine. She has been the Director of the Clinical Mycobacteriology, Mycology, and Molecular Microbiology Laboratories and Associate Director of the Clinical Microbiology-Immunology Laboratory at UNC Medical Center since 2004. Dr. Miller received her Ph.D. in molecular biology from Princeton University and completed the Medical and Public Health Microbiology Fellowship at UNC. She has a long-standing interest is respiratory viral diagnosis, including assessing new technologies, determining appropriate testing algorithms, and assessing impact on patient outcomes. As a past member and chair of the ASM Committee on Laboratory Practices and current chair of the ASM Professional Practice Committee, Dr. Miller has a keen interest in establishing best practices and advocating for standardization and dissemination of these practices.

Susan Novak-Weekley, Ph.D., S(M)A.S.C.P., D(ABMM), is the Vice President of Medical Affairs at Qvella. Dr. Novak-Weekley received her B.S. in microbiology at Colorado State University and her Ph.D. in microbiology at the University of Arizona. She completed a postdoctoral fellowship in clinical microbiology at the University of California, Los Angeles, Medical Center and Wadsworth VA Medical Center in Los Angeles, CA. Dr. Novak-Weekley is currently a member of the American Society for Microbiology (ASM) *Journal of Clinical Microbiology* editorial board. Dr. Novak-Weekley is currently the Councilor for the Southern California American Society for Microbiology (SCASM), in addition to serving as annual meeting and fundraising cochair. Additionally, she is a member of the Committee on Microbial Sciences (COMS) for ASM and also serves on the Nominating Committee for ASM and the New Technologist Mentoring Committee (CMMC).

Audrey N. Schuetz, M.D., M.P.H., D(ABMM), is an Associate Professor of Laboratory Medicine and Pathology at the Mayo Clinic School of Medicine and Science in Rochester, MN. She received her M.D. and completed a pathology residency and medical microbiology fellowship at Emory University School of Medicine. She is board certified in clinical pathology, anatomic pathology, and medical microbiology through the American Board of Pathology and is board certified by the American Board of Medical Microbiology. Dr. Schuetz is Director of Initial Processing and Media Laboratories and Co-Director of Bacteriology in the Division of Clinical Microbiology at Mayo. She is a member of the Expert Panel of Microbiology of the Clinical and Laboratory Standards Institute. Her interests include infectious diseases pathology and evaluation of rapid diagnostic techniques to improve antimicrobial stewardship.

Yi-Wei Tang is currently the Chief of the Clinical Microbiology Service at the Memorial Sloan-Kettering Cancer Center and a Professor of Pathology and Laboratory Medicine at the Weill Medical College of Cornell University in New York, NY, USA. He obtained his medical training from Fudan University Shanghai School of Medicine and Ph.D. in microbiology and immunology from Vanderbilt University. He has been engaged in medical and molecular microbiology translational research, aimed at developing and evaluating new and advanced microbiological diagnostic testing procedures. Dr. Tang is a Fellow of the American Academy for Microbiology and of the Infectious Disease Society of America. Dr. Tang has been recognized for his extraordinary expertise in molecular microbiology, diagnosis, and monitoring and has over 200 peer-reviewed articles and book chapters in this field.

Ray Widen is the Scientific Director, Esoteric Testing and Research, Tampa General Hospital. He has more than 34 years of clinical microbiology experience, 28 years of flow cytometry research experience, and over 24 years of molecular diagnostics assay development and validation expertise. Dr. Widen has an extensive background in applications in leukemia/lymphoma diagnostics as well as infectious disease diagnostics for viral, bacterial, and fungal targets.

Steven J. Drews, Ph.D., F.C.C.M., D(ABMM), is a clinical virologist at the Provincial Laboratory for Public Health (ProvLab), Alberta, Canada. He completed his Ph.D. in experimental medicine (infectious diseases) in 2003 at the University of British Columbia. He then completed his clinical microbiology fellowship at the University of Toronto. Since then, he has focused on both the clinical microbiology and research aspects of respiratory infections and has been involved in respiratory virus surveillance and preparedness planning at a national level in Canada. Dr. Drews currently heads the province-wide influenza and acute respiratory viral diagnostics program at ProvLab, Alberta. Dr. Drews has held faculty positions at both the University of Toronto and the University of Calgary. He is currently an Associate Professor in Laboratory Medicine and Pathology at the University of Alberta, Edmonton, Canada, and the outgoing President of the Canadian College of Microbiologists.

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REVIEW

Tools and Techniques for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)/COVID-19 Detection

Seyed Hamid Safiabadi Tali,[a,b] Jason J. LeBlanc,[c,d,e,f] Zubi Sadiq,[a] Oyejide Damilola Oyewunmi,[a] Carolina Camargo,[g] Bahareh Nikpour,[h] Narges Armanfard,[h,i] Selena M. Sagan,[g,j] Sana Jahanshahi-Anbuhi[a]

[a]Department of Chemical and Materials Engineering, Gina Cody School of Engineering, Concordia University, Montréal, Québec, Canada
[b]Department of Mechanical, Industrial, and Aerospace Engineering, Gina Cody School of Engineering, Concordia University, Montréal, Québec, Canada
[c]Department of Pathology, Dalhousie University, Halifax, Nova Scotia, Canada
[d]Department of Microbiology and Immunology, Dalhousie University, Halifax, Nova Scotia, Canada
[e]Department of Medicine (Infectious Diseases), Dalhousie University, Halifax, Nova Scotia, Canada
[f]Division of Microbiology, Department of Pathology and Laboratory Medicine, Nova Scotia Health, Halifax, Nova Scotia, Canada
[g]Department of Microbiology and Immunology, McGill University, Montréal, Québec, Canada
[h]Department of Electrical and Computer Engineering, McGill University, Montréal, Québec, Canada
[i]Mila Quebec AI Institute, Montréal, Québec, Canada
[j]Department of Biochemistry, McGill University, Montréal, Québec, Canada

Seyed Hamid Safiabadi Tali and Jason J. LeBlanc contributed equally to this work. Author order was determined in order of increasing seniority.

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Address correspondence to Jason J. LeBlanc, jason.leblanc@nshealth.ca, or Sana Jahanshahi-Anbuhi, sana.anbuhi@concordia.ca.

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SUMMARY The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory disease coronavirus 2 (SARS-CoV-2), has led to millions of confirmed cases and deaths worldwide. Efficient diagnostic tools are in high demand, as rapid and large-scale testing plays a pivotal role in patient management and decelerating disease spread. This paper reviews current technologies used to detect SARS-CoV-2 in clinical laboratories as well as advances made for molecular, antigen-based, and immunological point-of-care testing, including recent developments in sensor and biosensor devices. The importance of the timing and type of specimen collection is discussed, along with factors such as disease prevalence, setting, and methods. Details of the mechanisms of action of the various methodologies are presented, along with their application span and known performance characteristics. Diagnostic imaging techniques and biomarkers are also covered, with an emphasis on their use for assessing COVID-19 or monitoring disease severity or complications. While the SARS-CoV-2 literature is rapidly evolving, this review highlights topics of interest that have occurred during the pandemic and the lessons learned throughout. Exploring a broad armamentarium of techniques for detecting SARS-CoV-2 will ensure continued diagnostic support for clinicians, public health, and infection prevention and control for this pandemic and provide advice for future pandemic preparedness.

KEYWORDS COVID-19, SARS-CoV-2, 2019-nCoV, NAAT, PCR, serology, antigen, coronavirus, biomarkers, next-generation sequencing

INTRODUCTION

While coronavirus disease 2019 (COVID-19) is not the first pandemic of the 21st century (1), it has generated unprecedented global concern and responses. COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is thought to have emerged from a zoonotic source (2) and spread rapidly in humans through respiratory droplets and contact. There is some concern for airborne transmission, but the role of this transmission route outside the potential aerosolizing procedures in health care settings is unclear (3–5). With an estimated reproductive number, *R* naught (R_0), of between 1.4 and 5.6, SARS-CoV-2 rapidly spread worldwide (6–9). Since the first cases reported in December 2019 (10–12), there have been over 106 million confirmed cases and 2.3 million deaths reported worldwide (as of 9 February 2021) (13).

From a disease manifestation perspective, SARS-CoV-2 infection can be asymptomatic (14), and COVID-19 spans from a mild influenza-like illness (ILI) to life-threatening complications (15, 16). SARS-CoV-2 not only affects the respiratory tract, resulting in pneumonia, but also can affect gastrointestinal (GI), neurological, or cardiovascular systems. Atypical presentations of COVID-19 include cutaneous manifestations such as a Kawasaki-like disease in children and ophthalmic/gustatory dysfunction (i.e., anosmia and ageusia, which are the loss of smell and taste, respectively), which may have been underestimated in initial reports (17–20).

Despite numerous therapeutic options being explored (e.g., convalescent-phase plasma), no large-scale treatments are available. Public health interventions have evolved over time to limit viral spread (Fig. 1) and have included the use of personal protective equipment (PPE) like masks, handwashing, and containment measures such as city lockdowns, travel restrictions, and physical distancing (21–30). Although these strategies have been essential to reduce the virus's spread, they have had significant adverse socioeconomic impacts, and adherence to these prevention strategies is challenging to sustain (22). Currently, cases of COVID-19 have declined following a first pandemic wave in some areas, whereas other areas are experiencing subsequent waves of activity. Fortunately, many vaccine candidates are under development and undergoing regulatory approval processes (31–35). Recently, COVID-19 mRNA vaccines have been the first licensed for use and are rapidly being administered as supplies are provided (28, 36). However, given the time required for adequate immunization coverage in the population at large, subsequent pandemic waves are anticipated (31, 37–39). Therefore, detection

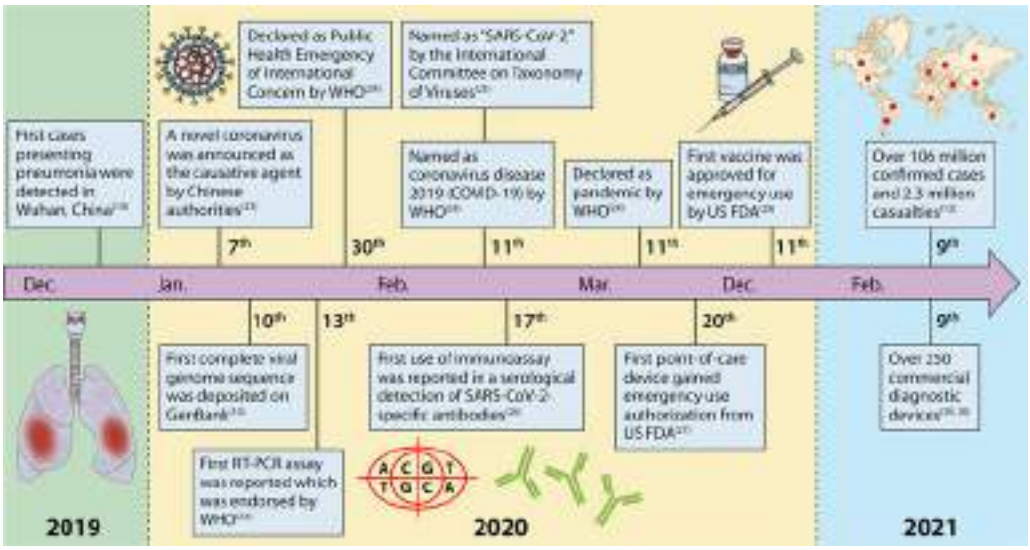

FIG 1 Timeline of COVID 19 spread and the global response to it (10, 13, 23 30). Of note, while SARS CoV 2 was initially thought to have emerged from China in December 2020, there are data to suggest that it may have circulated more broadly earlier than initially recorded in other countries, and further studies are under way to investigate this possibility in other areas (571 574).

methods for SARS-CoV-2 remain a crucial part of containment and mitigation strategies, and lessons learned from this pandemic may help prepare against future pandemics.

In terms of testing, real-time reverse transcription-PCR (RT-PCR) remains the most common method used to identify SARS-CoV-2 (40). While common in diagnostic laboratories worldwide, many laboratories remain faced with supply chain shortages for real-time RT-PCR reagents and consumables, all while being asked to increase testing capacity. As such, delays were common for test results, prompting the exploration of alternative testing options such as specimen pooling or laboratory testing using methods other than RT-PCR. Methods that could enhance testing capacity, streamline testing (i.e., automation), or provide more rapid results in easy-to-use formats that are amenable to point-of-care (POC) applications without complex instrumentation (e.g., isothermal technologies) were all desired (41–47). Rigorous research escalated quickly from the academic to industry partners, and this research is ongoing to develop testing alternatives or complements to existing technologies.

While recent reviews have been published on the management of SARS-CoV-2 (41, 47–55), recent advancements in novel diagnostic methods justify the need for a more comprehensive synthesis of the current literature. In this review, first, the biological characteristics of SARS-CoV-2 are described in order to fully understand the molecular and immunological methods for its detection. Following a brief discussion on the COVID-19 manifestations, compatible signs and symptoms, and disease biomarkers, diagnostic imaging techniques are described in relation to COVID-19 lower respiratory tract involvement, including applications such as monitoring disease severity, the progression of the illness, or complications. Next, a comprehensive review of current and recent advances in molecular, antigen (Ag), and serological immunodiagnostic methods is covered, including rapid diagnostic tests (RDTs) used in the laboratory setting and POC applications. Overall, this review expands our knowledge of current and exploratory avenues for detecting SARS-CoV-2 and COVID-19.

It should be noted that some of the references used in this review were preprints that have not been peer reviewed, and recognizing that data on the detection of SARS-CoV-2 or COVID-19 are rapidly evolving, some details on testing options and guidelines may no longer be recent and should thus be reviewed in the context of recent findings and recommendations. Nonetheless, this review provides a comprehensive

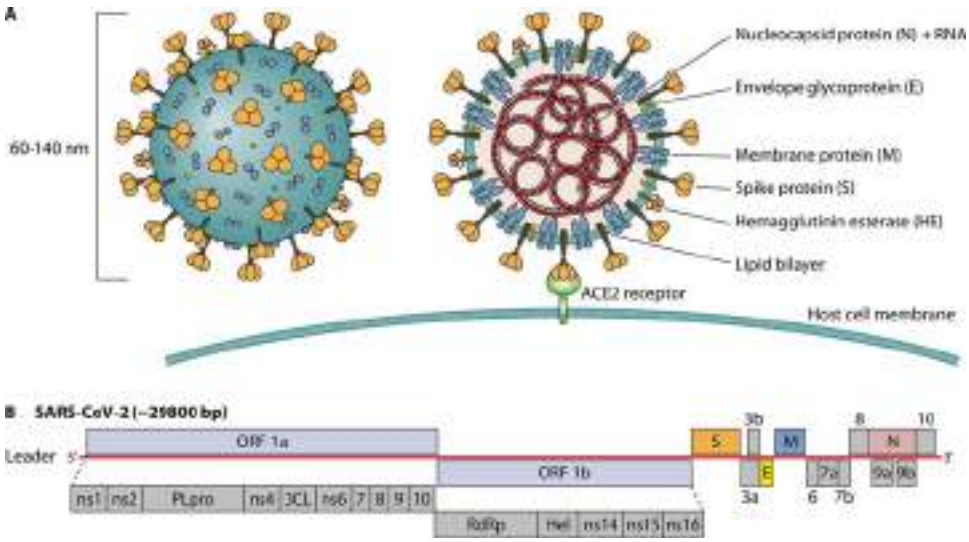

FIG 2 Physical and genome structure of SARS CoV 2. (A) Diagram of the SARS CoV 2 virion. (B) Genome organization and proteins with known or unknown functions.

synthesis of the most current data available to date, along with current recommendations for the detection of SARS-CoV-2 or the diagnosis of COVID-19.

SARS-CoV-2 GENOME AND STRUCTURE

Understanding the genetic and structural properties of SARS-CoV-2 is a prerequisite to developing effective diagnostic tools. SARS-CoV-2 was first isolated and sequenced in China in January 2020 (10–12). Transmission electron microscopy revealed that SARS-CoV-2 has a diameter in the range of 60 to 140 nm, and its morphology was consistent with those of other members of the *Coronaviridae* family (Fig. 2A) (12, 25). SARS-CoV-2 is an enveloped, positive-strand RNA virus, and on the genetic level, it shares 96%, 80%, and 50% sequence identities with bat coronavirus (RaTG13), SARS-CoV-1, and Middle East respiratory syndrome coronavirus (MERS-CoV), respectively (11, 56). Based on these analyses, the International Committee on Taxonomy of Viruses named the virus SARS-CoV-2, which was formerly referred to as the 2019 novel coronavirus (2019-nCoV) or human coronavirus 2019 (hCoV-19) (25).

Our understanding of SARS-CoV-2 structure and function has been largely derived from research on SARS-CoV-1, MERS-CoV, and seasonal coronaviruses. SARS-CoV-2 has a single-stranded positive-sense RNA genome of between 26 and 35 kb, encoding approximately 27 proteins with similarity to proteins of known functions, while others are unclear/unknown or putative (Fig. 2B) (21, 37, 53, 57, 58). The first open reading frame (ORF1a/b) on the 5′ end of the viral genome occupies ~71% of the entire genome and produces two polyproteins (pp's), pp1a and pp1ab. These two polyproteins are processed by the viral proteases into 15 nonstructural proteins (nsp's), and these proteins are collectively involved in polyprotein processing, viral RNA replication, and mRNA synthesis (53, 57). The remaining proteins, including the structural and accessory proteins, are expressed from several nested subgenomic mRNAs produced through a process known as discontinuous transcription by the viral RNA-dependent RNA polymerase (RdRp).

The structural proteins include the small envelope (E) protein, membrane (M) protein (also known as the matrix protein), nucleocapsid (N) protein, hemagglutinin-esterase (HE) protein, and spike (S) glycoprotein (Fig. 2A) (57, 59). The E and M proteins are primarily involved in viral assembly, budding, and virion morphogenesis (60–62), while the N protein complexes with the viral genomic RNA to generate the nucleocapsid (63). The S protein is the major surface glycoprotein on SARS-CoV-2, forming

approximately 40 trimers that play an important role in both receptor binding and membrane fusion through the two functional subunits S1 and S2 (37, 64). The S protein trimers contain a stable stalk separated from the globular heads by three flexible hinges, allowing for orientation freedom to interact with host cell receptors (65). The S1 subunit contains the receptor-binding domain (RBD) that directly interacts with the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell surface, whereas the S2 subunit contains a structural loop responsible for fusion events between the viral and host cell membranes, resulting in the release of the viral genomic RNA into the cytoplasm (66, 67). Of note, along with engaging the ACE2 host cell receptor, the cellular serine protease TMPRSS2 is engaged for S protein priming, and this cofactor has been investigated as a possible antiviral target using viral entry inhibitors (68, 69).

Overall, having knowledge of SARS-CoV-2 pathogenesis can help in understanding disease manifestations and help guide the development of molecular and immunological tools for the identification of this virus.

CLINICAL MANIFESTATIONS OF COVID-19

The spectrum of SARS-CoV-2 infection can vary from asymptomatic infection to life-threatening complications of COVID-19 (37). Using modeling, it was estimated that over 59% of transmissions arise from asymptomatic individuals, with 35% from individuals in presymptomatic stages of infection and 24% from individuals who never develop symptoms (70). These estimates are concerning but emphasize the need for the wide use of vaccines and maintaining key public health interventions like mask wearing, hand hygiene, and social distancing.

In most symptomatic cases, COVID-19 presents as a mild to moderate upper respiratory illness, with signs and symptoms compatible with those of other respiratory viruses (71). As such, the diagnostic accuracy of any individual sign or symptom is very poor, and neither the presence nor the absence of any sign or symptom can be used to rule in or out COVID-19 (71). With the possibility of other pathogens that could present like SARS-CoV-2 infection, case definitions based on clinical presentation are not sufficiently specific but can help support the investigation of suspect COVID-19 cases. On the other hand, given that the list of possible presentations and atypical manifestations of COVID-19 could mirror those of other diseases, identifying the etiology of illness as SARS-CoV-2 requires laboratory testing.

In a recent Cochrane review, a summary of 16 studies (7,706 patients) was presented (71). Only six of the possible signs and symptoms of COVID-19 had sensitivities of $>$50%, and results were highly variable between studies and settings. The most common signs and symptoms (and their performances) are summarized as follows: cough (with sensitivity and specificity from 43 to 71% and 14 to 54%, respectively), sore throat (5 to 71% and 55 to 80%), fever (7 to 91% and 16% to 94%), musculoskeletal symptoms (e.g., arthralgias or myalgias) (19 to 86% and 45 to 91%), fatigue (10 to 57% and 60 to 94%), and headache (3 to 71% and 78 to 98%) (71). It was noted that possible confounders were present, and the high heterogeneity between data suggested that signs and symptoms are variable between individuals (71). Other less common clinical presentations have been documented, including alterations in smell or taste (i.e., anosmia or dysgeusia) as well as neurological or cutaneous manifestations (17–19, 72–76). It is noteworthy that in the early stages of the pandemic, some of these symptoms may have been missed or underreported, but knowledge on possible clinical presentations of COVID-19 have evolved over time.

In some cases of COVID-19, progression to lower respiratory tract illness (e.g., pneumonia) can occur and may require hospitalization, intensive care unit (ICU) support, and mechanical ventilation, and complications can arise, which include acute respiratory distress, multiorgan dysfunction, and death (71, 77–85). In general, adverse outcomes and deaths are more common with increasing age or in individuals with underlying medical comorbidities such as respiratory system disease, cardiovascular disease, and diabetes (78–80). Fatality rates vary among studies and countries but are generally

high in the hospital setting (e.g., 4 to 11%) compared to the overall case fatality rates (e.g., 2 to 3%) in the general population (80, 82, 85, 86). In terms of recovery, the median duration of hospital stay is 10 to 14 days, and resolution generally occurs within 2 to 3 weeks (85). There is a lack of evidence on whether some symptoms can persist after recovery. In one study, patients were monitored up to 60 days after recovery, with 87.4% reporting at least one symptom (86). The most common symptoms were fatigue (53.1%), dyspnea (43.4%), joint pain (27.3%), and chest pain (21.7%).

Overall, while some signs or symptoms may be compatible with COVID-19, none are specific, and laboratory testing is required to confirm the diagnosis. Further studies are required to help identify the frequency of atypical clinical presentations, and additional studies looking at known clinical presentations of COVID-19 should consider possible confounders such as the possibility of other etiologies, host factors (e.g., comorbidities), disease severity, and the times from infection and symptom onset.

BIOMARKERS FOR COVID-19 AND ROUTINE LABORATORY INVESTIGATIONS

Apart from laboratory tests specific for detecting SARS-CoV-2 discussed throughout this review, routine laboratory testing spanning hematological, biochemical, and chemical markers is used to assess a patient's health or identify possible clues to a disease state (87–90). Such routine laboratory workup of individuals is used to refine a medical differential diagnosis, thereby supporting or refuting potential causes of the clinical presentation based on typical outcomes of these investigations for a defined disease. Many of these investigations can evolve through the clinical course of illness, and additional testing can be ordered by physicians based on the clinical presentation. These can include tests such as white blood cell (WBC) counts, markers for inflammatory conditions (C-reactive protein [CRP], procalcitonin [PCT], or interleukin 6 [IL-6]), tests for anticoagulation, and indicators of tissue damage (alanine aminotransferase [ALT], aspartate aminotransferase [AST], lactate dehydrogenase [LDH], and creatine kinase [CK]). While biomarkers for COVID-19 have been the subject of much investigation during the current pandemic, none of these tests are sensitive or specific for COVID-19. In a Cochrane review analyzing 67 laboratory tests from 21 studies encompassing 14,126 COVID-19 cases and 56,585 non-COVID-19 cases, only three markers showed sensitivity and specificity values of $>$50%: a decrease in the lymphocyte count and increases in the inflammatory markers CRP and IL-6 (90). Overall, no individual biomarker can be used reliably to rule COVID-19 in or out, and laboratory testing should be performed. However, it should be noted that some laboratory markers have value for patient management as they can help assess the severity of the disease or progression of the illness or even act as risk factors for death. In the most recent Centers for Disease Control and Prevention (CDC) guidance documents for clinicians caring for patients with COVID-19, a summary of important laboratory tests is described, with lymphopenia being the most common laboratory finding in patients hospitalized with COVID-19 (87). Laboratory markers associated with increased illness severity include lymphopenia, neutropenia, and elevated serum ALT, AST, LDH, CRP, and ferritin (87, 88). Patients with critical illness have high plasma levels of inflammatory makers, and elevated levels of d-dimer and lymphopenia have been associated with an increased risk of death.

Of note, this section is not intended to be a comprehensive review of all biomarkers used in routine or exploratory investigations for COVID-19. We recognize the availability of guidelines for clinicians caring for patients with suspected or confirmed infection with SARS-CoV-2 (87, 88) as well as the expertise of medical staff in ordering laboratory tests to help guide evolving differential diagnoses throughout the clinical course of illness. However, this section also recognizes the ongoing efforts of researchers who are dedicated to understanding the role of existing or novel biomarkers. Overall, no laboratory marker to date is diagnostic for COVID-19, but they have value in patient management over time, regardless of SARS-CoV-2 infection status. Biomarkers for COVID-19 severity or prognosis remain an active area of research that may not only lead to new

diagnostic approaches but also help us understand disease progression and host responses to COVID-19 (91–94).

DIAGNOSTIC IMAGING FOR COVID-19

While testing of specimens collected from the upper respiratory tract is common for diagnosing SARS-CoV-2 infection, the progression of the disease may involve the lower respiratory tract (e.g., pneumonia), with or without detectable SARS-CoV-2 in the upper respiratory tract (55, 95–103). Testing of specimens from the lower respiratory tract (e.g., bronchoalveolar lavage [BAL] fluid) is possible using nucleic acid amplification tests (NAATs) like RT-PCR, but obtaining lower respiratory tract specimens is not always possible (104–107). Along with laboratory testing, diagnostic imaging can complement investigations of COVID-19 to assess the involvement of disease in the lower respiratory tract or other anatomical sites. Diagnostic imaging techniques include chest radiography (or chest X ray [CXR]), computed tomography (CT) scan, ultrasound, magnetic resonance imaging (MRI), and positron emission tomography-CT (PET/CT) (108–116). Among these, CT scans are the most frequently used methods for diagnosis of lower tract involvement or follow-up of COVID-19 cases (110–112). CT scans produce cross-sectional images at different angles, thereby providing a three-dimensional (3D) look at the targeted anatomy. Chest CT scan images can be assembled and assessed by radiologists to check for possible abnormalities suggestive of lower tract disease such as viral pneumonia (53, 112, 117). Typical features of a chest CT image in COVID-19 are ground-glass or reticular opacities (GGOs) with or without consolidations that present bilaterally, peripherally, or in posterior distributions (113).

The utility of diagnostic imaging for routine screening for COVID-19 has been a subject of debate and has not been recommended by most radiology societies (113, 114, 118–121). On the other hand, due to the shortage of RT-PCR supplies during the early days of the pandemic and the possibility of false-negative RT-PCR results from sampling the upper respiratory tract, some hospitals in the Hubei province of China included CT scans in the diagnosis of SARS-CoV-2 infection (53, 117, 122, 123). While diagnostic imaging techniques like CT have merits to help assess lower respiratory tract disease involvement, to monitor disease progression, or to investigate other complications of COVID-19, it should be noted that diagnostic imaging methods are less sensitive than sampling the lower respiratory tract and testing using molecular methods, and specificity is low, given that typical features of COVID-19 are common to other respiratory viruses or illnesses (113–116, 124–128). Initial reports of the utility of CT scans in the diagnosis of COVID-19 suggested an increased sensitivity of CT over real-time RT-PCR, but others have suggested explanations for the disparities between RT-PCR results and diagnostic imaging assessments, including poor sampling techniques, differences in the performances of testing methods, the anatomical site of RT-PCR testing (upper versus lower tract), and disease prevalence (111, 124, 126, 129–134). High sensitivities (i.e., $>$90%) have been reported for CT scans in high-prevalence populations, while low sensitivities ($<$60%) were reported in studies with low-prevalence populations (112–114, 118–121, 123). In a Cochrane review for confirmed cases of COVID-19, the pooled sensitivities were 93.1% (95% confidence interval [CI], 90.2% to 95.0%) for chest CT and 82.1% (95% CI, 62.5% to 92.7%) for CXR, but heterogeneity between studies was considerable (121). Specificity for diagnostic imaging is low, at 18.1% (95% CI, 3.7 to 55.8%) (121). In other words, approximately 80% of individuals would have received a diagnosis of COVID-19 in the absence of disease. As such, the use of diagnostic imaging techniques should be accompanied by careful consideration of factors such as disease prevalence in the study population, severity of the illness, performance and context of the methods used, differences in radiologist opinions, and possible confounding diagnoses (112–114, 118–121, 123, 126, 132–135). On the other hand, it is also important to recognize that diagnostic imaging is a useful tool for patient management with or without a confirmed etiology through laboratory testing, as it can be

used to monitor the severity of illness and disease progression and assess possible complications (136–141).

Understanding the benefits and limitations of diagnostic imaging for COVID-19 is an active area of research, along with applications of artificial intelligence (AI) (also known as machine learning) (142–144). AI-based methods can be used in diagnostic imaging to help recognize abnormal features in images and classify them into defined categories, thus increasing accuracy, standardization, and speed of analyses by radiologists (50, 109, 142–146). AI approaches can be categorized into three main groups: approaches that analyze CT scan images, methods based on X ray, and those that realize diagnosis through jointly analyzing CT scan and X-ray images (147–151). While AI-based applications have shown benefits for diagnostic imaging methodologies (50, 109, 145, 146), more clinical investigations are needed to evaluate their possible incorporation into routine procedures for investigations of suspected cases of COVID-19, and laboratory testing is required to confirm the disease etiology. Furthermore, acquiring a reliable AI-based system requires access to a comprehensive training data set that includes all variations of COVID-19 as well as other lung diseases; providing such an all-inclusive data set is difficult and labor-intensive.

LABORATORY METHODS FOR THE DETECTION OF SARS-CoV-2

Diagnosis of COVID-19 can be performed using molecular detection of SARS-CoV-2 RNA, which is now widely available. Immunodiagnostic methods for identifying viral antigens and serology to recognize an immune response to the virus are also available. The following sections describe the commonly used and potential methods for the laboratory detection of SARS-CoV-2, with important consideration for factors like specimen type and timing of specimen collection.

Specimen Types

Prior to describing methods for SARS-CoV-2 detection, it should be recognized that accurate detection of any infectious disease requires adequate specimen collection at the anatomical site of infection, at a time when the pathogen of interest should be present (152–154). While the virus has been detected in a variety of specimen types using molecular methods (26, 96, 155–161), few have been widely adopted due to unreliable detection or a lack of sensitivity. The use of blood, serum, or plasma for SARS-CoV-2-specific serology and other immunodiagnostic tests is discussed in later sections of this review.

For respiratory viruses like SARS-CoV-2, specimens collected from the upper respiratory tract using a flocked nasopharyngeal (NP) swab that is placed in universal or viral transport medium (UTM or VTM, respectively) are the gold standards (162–164). In contrast to other swabs (e.g., cotton swabs on wooden sticks), specimen collection using flocked NP swabs that are coated with multilength fibers allows for enhanced recovery of respiratory viruses and bacteria, and the UTM or VTM allows a stable medium for transport to the laboratory (133). Other than NP swab specimens, alternative specimens and collection methods have been validated and gained interest, including the use of nasal midturbinate swabs, sampling of the anterior nares (Na), oropharyngeal (OP) swabs, or washes/aspirates from the nasopharynx, nose, or throat (96, 97, 154, 165–172). Specimen combinations can also be used. For example, paired collection using an OP swab along with sampling of the anterior nares was shown to be equivalent to NP swab collection for the detection of SARS-CoV-2, and different options are available for OP/Na collection (133, 154, 167, 168, 173). It is worth mentioning that during the COVID-19 pandemic, procurement of NP swabs and UTM (or VTM) was challenged by global supply chain shortages. Several groups have developed and validated the possibility of using 3D-printed swabs as alternatives to commercial NP or nasal swabs, but while some have been clinically validated for detecting SARS-CoV-2 RNA, further investigations are required for their applicability in SARS-CoV-2 antigen detection (174–178). For media used for swab transport to laboratories, other than the typical UTM or VTM, alternatives have been investigated for use for SARS-CoV-2 testing,

including Amies transport medium, sterile normal saline, phosphate-buffered saline (PBS), M4 medium, and minimal essential medium (MEM), and stability analyses have assessed ideal transport and storage conditions (168, 169, 179).

While NP swabs are considered the gold standard for respiratory virus sampling of the upper respiratory tract, hospitalized adults with progression of COVID-19 to lower tract disease may require additional specimen types (170). When lower tract infection is suspected through clinical presentation or with the aid of diagnostic imaging, specimens such as BAL fluid, endotracheal secretions, or sputum should be considered (55, 95–102, 180).

Recently, the use of noninvasive collection methods like saliva and throat gargles has gained much interest, as these samples are amenable to self-collection and have the potential for large-scale population-based surveillance (181–186). While some studies have demonstrated that the performance of saliva for the detection of SARS-CoV-2 was comparable to that of NP or nasal swab collections (183, 184, 187–190), others challenged the performance of saliva for SARS-CoV-2 detection (191). The variability in saliva collection or differences in the patient populations tested might explain these inconsistencies, but further analyses are required (191, 192). Also, although not used routinely in many laboratories, detecting SARS-CoV-2 RNA from stool is possible in the presence or absence of gastrointestinal symptoms (193). The possibility of culturing SARS-CoV-2 from stool opens discussions regarding the possibility of fecal-oral transmission and human health or ecological risks (194, 195) and also opens the opportunity for research into community-based surveillance in low-prevalence settings using wastewater (193, 196).

In postmortem examinations, the extent of investigations will be dependent on several factors, but NP swabs, swabs from the lungs, and tissue samples can be used for diagnostic testing for SARS-CoV-2 (197–200). Specimens in 10% buffered neutral saline or formalin-fixed paraffin-embedded (FFPE) specimens commonly used for histopathological examinations can also be used, but these pose challenges for NAATs like real-time RT-PCR as RNA can be degraded by formalin, and sensitivity for the detection of SARS-CoV-2 RNA by real-time RT-PCR could be compromised (201). The CDC recommends that these media be used in limited settings (197). Immunohistochemical (IHC) and *in situ* hybridization (ISH) assays for the detection of SARS-CoV-2 have now been developed, but limited data are available on their performance (202).

Timing of Specimen Collection

SARS-CoV-2 has been identified in various clinical specimen types (26, 96, 154–161), but the timing of detection differs between methods and the specimen types collected for testing. SARS-CoV-2 RNA can be detected early in the presymptomatic stage of the disease and later on, even after recovery. However, the timing of specimen collection is critical, as testing too early or too late following exposure can potentially lead to false-negative results (203). It was shown that real-time RT-PCR false-negative rates could be minimized by testing 2 to 3 days after symptom onset, with an average time of symptom onset of 5 days postexposure (204–210). Repeat testing can be considered for individuals with an initial negative test result but for whom there is a high level of clinical suspicion (134). Of note, viral shedding studies are often performed using RNA detection alone and less often in combination with virus culture; however, the absence of cultivable virus does not preclude the potential for SARS-CoV-2 transmission, and laboratory detection of SARS-CoV-2 using molecular methods does not imply infectious virus (208, 211–217). For the purpose of this section, viral shedding is described in the context of RNA detection without implying the potential for viral transmission. A discussion regarding the association of SARS-CoV-2 RNA detection with potential infectivity is covered later in this section as well as in the real-time RT-PCR section below.

The magnitude of the viral load and duration of shedding depend on the specimen type, the anatomical site of illness, the severity of illness, and, likely, the host immune response to infection (170, 208, 218–220). The average duration of SARS-CoV-2 RNA detection in the upper respiratory tract of patients with mild disease ranged from 7.9

to 20 days after symptom onset and from 6 to 30.8 days in cases with moderate to severe illness. The detection of SARS-CoV-2 in the lower respiratory tract ranged from 8 to 38.4 days for mild cases of COVID-19 and spanned between 6 and 26.9 days for moderate to severe illness (221). In a systematic review and meta-analysis, the pooled estimates of the mean duration of SARS-CoV-2 RNA detection from symptom onset in mild adult cases were 12.1 days (95% CI, 10.1 to 14.1 days) in the upper respiratory tract and 24.1 days (95% CI, 10.0 to 38.2 days) in the lower respiratory tract. For moderate to severe cases, the pooled estimates for the duration of SARS-CoV-2 RNA positivity in the upper respiratory tract were 15.8 days (95% CI, 11.1 to 20.6 days) and 23.2 days (95% CI, 21.5 to 25.0 days) in the lower respiratory tract (221). In a systematic review and meta-analysis, the temporal dynamics of SARS-CoV-2 viral loads were stratified by COVID-19 severity and sampling site. In cases of mild adult disease, SARS-CoV-2 RNA in the upper respiratory tract was maximal on day 4, at approximately 6.6×10^8 copies/ml, whereas lower tract viral loads peaked at approximately 2.7×10^8 copies/ml on day 6 after symptom onset (221). In cases of moderate to severe adult disease, maximal SARS-CoV-2 RNA detected in the upper respiratory tract occurred on day 8, at 4.6×10^9 copies/ml, and on day 11, at approximately 3.5×10^8 copies/ml, in the lower respiratory tract (221). Regarding the differences in viral loads and durations of shedding between symptomatic and asymptomatic patients, the literature is inconsistent. Some publications observed little to no difference in viral loads between the two groups (222–226), while others suggested significantly higher viral loads in symptomatic patients (224). Whether these differences are attributed to differences in disease severity, variations in the performances of methods used, or host factors remains to be determined.

As highlighted above, the median duration of viral shedding is variable between individuals and likely dependent on disease severity and several host factors such as age, immunocompromising conditions, or medical comorbidities (208, 212–217, 227–229). While most individuals with mild disease clear the virus within 10 to 20 days, in some cases with severe COVID-19, the duration of shedding can be prolonged (217, 230). The longest durations of viral RNA shedding reported to date were 83 and 111 days after symptom onset (231, 232); however, the persistence of RNA suggestive of low viral loads may be of little clinical significance, as the detection of SARS-CoV-2 RNA does not necessarily imply infectivity (170, 208, 212–220, 227–229). Moreover, many factors can affect the detection of SARS-CoV-2 RNA, such as the quality of sample collection, transport, and variables in laboratory processing; RNA positivity can be intermittent and inaccurate at the later stages of illness (233). Therefore, the CDC recommends that the discontinuation of transmission-based precautions for patients with confirmed SARS-CoV-2 infection should be based on the resolution of symptoms and not based on testing (230). While some countries have similar recommendations for discharge from quarantine, there is some heterogeneity in approaches, and these often vary based on the severity of illness and the presence or absence of symptoms (234).

While not used routinely in many laboratories, detecting SARS-CoV-2 RNA from stool is possible in the presence or absence of gastrointestinal (GI) symptoms (193, 235). However, only 1% of patients had detectable RNA in their stool in the absence of positive respiratory specimens (193, 235). For some patients, viral shedding in stool can occur for a longer period than in the respiratory samples and could help diagnose infection if upper and lower respiratory tract specimens are negative but there is a high suspicion of disease (156–160, 193, 236). Of individuals who test positive with GI specimens, the median duration of RNA shedding in the GI tract is 12.5 days following negative respiratory tract specimens (193, 235). Less frequently, shedding in stool can be prolonged and has been documented up to 70 days after symptom onset or 33 days following clearance from the respiratory tract (236, 237). As for respiratory tract specimens, RNA detection does not necessarily imply that infectious virions are produced, but SARS-CoV-2 has been cultured from stool specimens in some studies (236, 237).

Like molecular methods, antigen testing can be used to detect SARS-CoV-2 proteins in the acute stages of the disease following the incubation period in upper respiratory

tract specimens such as NP swabs, nasal swabs, and possibly saliva. Antigen detection using immunoassays like lateral flow rapid diagnostic tests (RDTs) is often less sensitive than molecular methods (203, 238), but these tests can detect SARS-CoV-2 antigen reliably when the viral load is high in the clinical specimens (i.e., typically from 1 to 3 days before the onset of symptoms to 5 to 7 days after symptom onset), whereas the likelihood of SARS-CoV-2 detection decreases in the second week after symptom onset (238).

In contrast to RNA and antigen detection, immunological responses take longer to appear, with antibodies typically beginning to appear 6 days after symptom onset, as viral RNA levels begin to decline (207). Typically, the first detectible antibody in human blood is immunoglobulin M (IgM), followed by immunoglobulin G (IgG). However, concomitant increases of the IgM and IgG immunoglobulin classes as well as IgG first seroconversion have also been observed (239). Few data are also available for immunoglobulin A (IgA) detection, a marker of mucosal immune responses, but it is evident that both IgA and IgM decline rapidly over the course of infection (240). The median seroconversion times for total antibody, IgM, and IgG were 9, 10, and 12 days after symptom onset (or 15, 18, and 20 days after exposure), respectively (240). It is unclear how long IgG responses last or whether they confer protection against subsequent SARS-CoV-2 reinfection (241). The longest study on the antibody dynamics tracked IgG up to 115 days after symptom onset in sera and saliva (242). Immune responses may vary depending on disease severity and host factors such as immunocompromising conditions or other medical comorbidities, and the value of immune responses will be dependent on the ability to provide neutralizing antibodies (nAbs) or cellular immunity capable of viral clearance. The applications and limitations of serology and other immunodiagnostics are discussed in more detail in later sections of this paper.

Specimen Preprocessing Requirements

While detection of SARS-CoV-2 from respiratory specimens can be performed using RNA or antigen detection, they sometimes require a preprocessing step like heat lysis or inactivation using guanidinium salts before nucleic acid extraction and amplification or testing, to ensure safe handling conditions, depending on local biosafety risk assessments (133, 154, 173, 180). Specimen types such as sputum may require mucolytic agents such as dithiothreitol (DTT), *N*-acetyl-L-cysteine (NALC), or proteinase K (PK) to reduce specimen viscosity prior to testing (243). Other preprocessing steps would include centrifugation for specimens like stool (236), PK digests for tissues (e.g., lung biopsy specimens), and specimen aliquoting into compatible tubes for testing (if testing from primary specimen containers is not possible). With any manipulation of the primary specimen (i.e., preprocessing steps), careful consideration should be undertaken to ensure that there are no potential impacts on downstream testing (e.g., RNA or antigen stability). Of note, some preprocessing steps, like specimen lysis, can be done in conjunction with nucleic acid extraction using automated instrumentation (discussed below in the real-time RT-PCR section of this review).

Overall, the choice of the specimen and timing of collection are crucial for the accurate detection of SARS-CoV-2, as are factors such as the severity of illness. Given that the performance characteristics of diagnostic methods depend on numerous variables as well as the method(s) used as a comparator and disease prevalence, a comprehensive synthesis of all method performances falls outside the scope of this review. However, general concepts for performance characteristics, important considerations, and a description of the technologies used for SARS-CoV-2 detection in the clinical setting or in development are presented in the following sections.

Molecular Methods for Viral RNA Detection

While no true reference standard exists for detecting SARS-CoV-2, nucleic acid amplification tests (NAATs) such as real-time RT-PCR are the methods of choice for SARS-CoV-2 diagnostic testing (40, 41, 48, 53, 54, 244). Following sequencing of its genome (10), laboratory-developed tests (LDTs) for the detection of SARS-CoV-2 were quickly developed, and protocols were circulated broadly by health care regulatory

bodies such as the World Health Organization (WHO) and the U.S. Centers for Disease Control and Prevention (CDC) (23, 40, 245–247). Many commercial kits have since become available and were authorized for use through emergency use authorization (EUA) by entities such as the Food and Drug Administration (FDA) and Health Canada. Lists of authorized medical devices related to COVID-19 in Canada and the United States are regularly updated online (29, 30), and examples of them are summarized in Table 1.

Real-time RT-PCR. Among NAATs, real-time RT-PCR is the most widely used method for the detection of SARS-CoV-2. As shown in Fig. 3A, the sample workflow for SARS-CoV-2 real-time RT-PCR includes specimen collection, transportation of the samples to the laboratory, specimen lysis, purification of viral RNA through nucleic acid extraction, and real-time RT-PCR amplification, detection, and analysis. Prior to real-time RT-PCR amplification, specimens are lysed to provide access to the SARS-CoV-2 RNA, and nucleic acid extraction is performed to remove potential inhibitors that could impede the amplification of the target. Both lysis/extraction and RT-PCR amplification can be performed sequentially through manual processing on individual instruments, or the entire process can be automated.

(i) Specimen lysis and RNA purification. To release viral RNA from host cells and virions, specimen lysis can be performed using physical (e.g., heat, sonication, or homogenization), chemical (e.g., organic solvents, detergents, chelating agents, or chaotropic agents), or enzymatic (e.g., proteases) methods (54, 243, 248, 249). Lysis steps based on enzymatic digestion (e.g., proteinase K digestion) are common for nucleic acid extraction in clinical laboratories. Following specimen lysis, extraction of viral RNA is performed to remove cellular debris and contaminants that could potentially inhibit the RT-PCR and purify the nucleic acids (250–252). In many automated instruments, silica-coated magnetic microbeads are used to capture nucleic acids, which can be sequentially transferred into different wash solutions by a robotic pipetting instrument with a magnetic head (248–252). The efficiencies of several extraction methods have been compared for detecting SARS-CoV-2, and the results favor commercial kits over manual methods like organic extractions containing guanidinium thiocyanate-phenol-chloroform (253).

It should be noted that while nucleic acid extraction is essential to achieve optimal sensitivity in molecular assays, recent studies have described extraction-free protocols for molecular testing for SARS-CoV-2 to circumvent the potential bottleneck of extraction if the supply of extraction reagents or consumables is limited (or to provide options for low-income environments) (254–262). However, without a nucleic acid extraction step to remove PCR inhibitors in clinical specimens, there is a notable reduction in sensitivity, but the extent is dependent on the method and target used for SARS-CoV-2 detection, the type and duration of the lysis/inactivation method (heat or chemical), the input volume, the specimen type, the transport media, and the viral load in the specimen (253, 257, 263–265). For example, the sensitivity of a 60-min heat inactivation alone reached 100% for specimens with moderate to high viral loads (threshold cycle [C_T] values of between 20 and 30) but declined to 54% in specimens with C_T values of $>$30 (264).

(ii) Target amplification and detection. Amplification in real-time RT-PCR involves two main steps. First, an enzyme called reverse transcriptase creates a cDNA from the viral RNA. The cDNA is then used as a template in a real-time PCR amplification step where fluorescence is produced as DNA amplification occurs (41, 266). The PCR portion of real-time RT-PCR contains a fluorescent probe or dye to generate fluorescence (e.g., dually labeled hydrolysis probe or intercalating dyes that bind to double-stranded DNA [dsDNA], like SYBR green) (267–272). Figure 3B illustrates the principle of a typical real-time RT-PCR using a dually labeled hydrolysis probe. Overall, if amplification of the target genes occurs during cycling through the denaturation, annealing, and extension stages, a fluorescent signal is produced that can be captured by the real-time thermocycler (23, 41, 273). If the fluorescence crosses a defined threshold, the cycle in which it

TABLE 1 Examp es of the NAATs approved for emergency use by the U.S. FDA for detect on of SARS-CoV-2 RNA[a]

Device/assay (manufacturer)	Method	Target gene(s)	Specimen type(s)	Authorized setting(s)	Time/throughput	LoD[b]	Reference
cobas 6800/cobas SARS-CoV-2 (Roche Mo ecu ar Systems, USA)	RT-PCR	ORF1ab + E	NS, NPS, OPS	H, M, H-poo ing	3 h for the first-run resu ts but 90 min per run in continuous mode/864 samp es per 8 h	46 copies/m	575
Abbott m2000/Rea Time SARS-CoV-2 (Abbott Diagnostics, USA)	RT-PCR	RdRp + N	NS, NPS, OPS, BAL fluid	H	7 h per run/470 samp es per 24 h	100 copies/m	576
NeuMoDx 288/NeuMoDx SARS-CoV-2 (NeuMoDx Mo ecu ar, USA)	RT-PCR	Nsp2 + N	NS, NPS, OPS, BAL fluid, sa iva	H, M	1.3 h per run/288 samp es per 8 h	150 copies/m	577
Panther Fusion/Aptima SARS-CoV-2 (Ho ogic, USA)	TMA	ORF1ab	NS, NPS, OPS, MTS, NPW, NPA, NA	H, poo ing	2.4 h per run/500 samp es per 8 h	0.026 TC D_{50}/m	578
Liaison MDX/Simp exa COV D-19 Direct (DiaSorin Mo ecu ar, ta y)	RT-PCR	ORF1ab + S	NS, NPS, NW, NA, BAL fluid	H, M	1 h per run/8 samp es per run	500 copies/m	318
Fi mArray/BioFire Respiratory Pane 2.1 (BioFire Diagnostics, USA)	RT-PCR	S + M	NPS	H, M	2-min hands-on time/1 h per run	160 copies/m	579
eP ex/eP ex SARS-CoV-2 (GeneMark Diagnostics, USA)	RT-PCR	N	NPS	H, M	2-min hands-on time/1.5 h per run	750 copies/m	319
GeneXpert Xpress/Xpert Xpress SARS-CoV-2 (Cepheid, USA)	RT-PCR	E + N2	NS, NPS, OPS, MTS, NW, NA	H, M, W	1-min hands-on time/45 min per run	0.02 PFU/m	580
Accu a Dock/Accu a SARS-CoV-2 (Mesa Biotech, USA)	RT-PCR	N	NS, MTS	H, M, W	5-min hands-on time/30 min per run	150 copies/reaction	320
D Now/ D Now COV D-19 (Abbott Diagnostics, USA)	NEAR	RdRp	NS, NPS, OPS	H, M, W	2-min hands-on time/13 min per run	125 copies/m	581
SHERLOCK CR SPR SARS-CoV-2 kit (Sher ock Biosciences, USA)	RT-LAMP, CR SPR-Cas13	ORF1ab + N	NS, NPS, OPS, NPW, NPA, NA, BAL fluid	H	1 h per run	6,750 copies/m	582
SARS-CoV-2 DETECTR reagent kit (Mammoth Biosciences, USA)	RT-LAMP, CR SPR-Cas12	N	NPS, OPS, MTS, ANS, NPW, NPA, NA	H	45 min per run	20,000 copies/m	583
NovaSeq 6000/ umina COV DSeq test (umina nc., USA)	Next-generation sequencing	98 targets on the virus	NPS, OPS, MTS, ANS, NPW, NPA, NA, BAL fluid	H	3,072 samp es per 12 h	500 copies/m	584

[a]The fu ist is avai ab e in reference 29. Abbreviations: RT-PCR, reverse transcription-PCR; TMA, transcription-mediated amp ification; NEAR, nicking enzyme amp ification reaction; RT-LAMP, reverse transcription– oop-mediated isotherma amp ification; NS, nasa swab; NPS, nasopharyngea swab; OPS, oropharyngea (throat) swab; BAL, bronchoa veo ar avage; MTS, midturbinate nasa swab; NPW, nasopharyngea wash; NPA, nasopharyngea aspirate; NA, nasa aspirate; NW, nasa wash; ANS, anterior nasa swab; H, aboratories certified under the C inica Laboratory mprovement Amendments of 1988 (CL A), 42 U.S.C. §263a, that meet requirements to perform high-comp exity tests; M, aboratories certified under CL A, 42 U.S.C. §263a, that meet requirements to perform moderate-comp exity tests; W, patient care settings operating under a CL A certificate of waiver; TC D_{50}, median tissue cu ture infectious dose.

[b]The LoD (imit of detection) of each assay is the owest LoD reported in the instructions for use for that assay, regard ess of the specimen types.

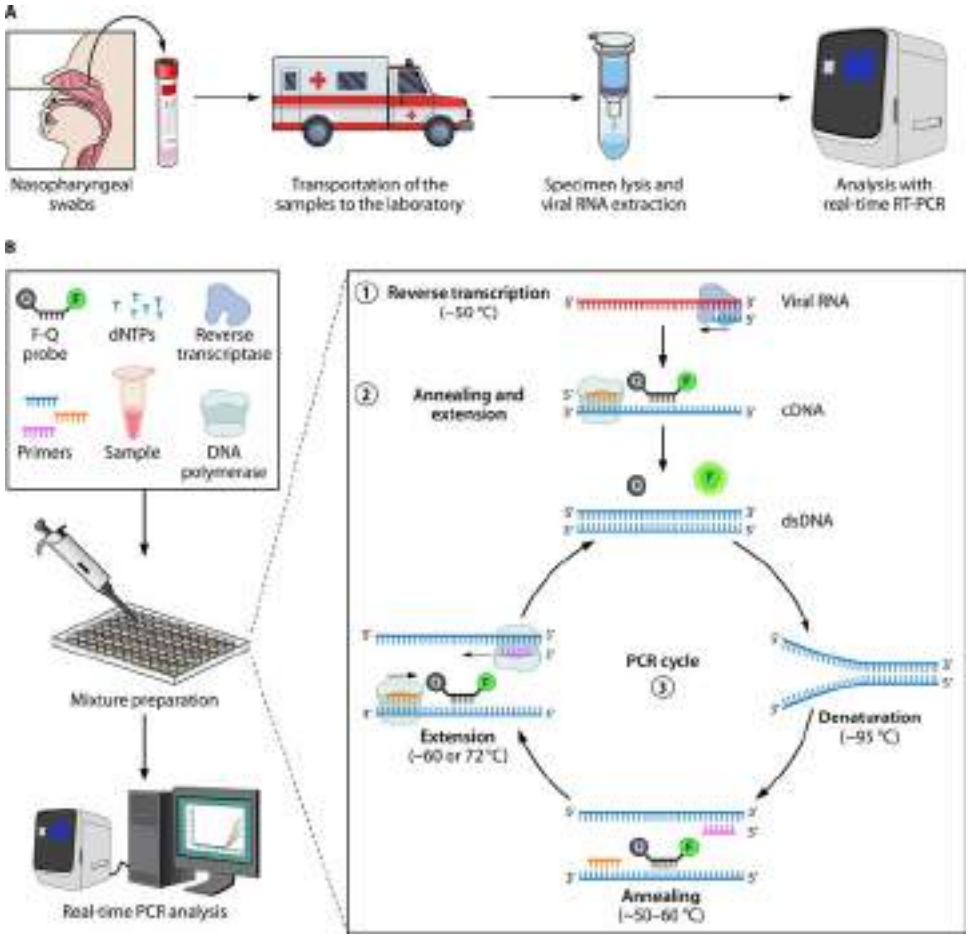

FIG 3 Real time RT PCR analysis. (A) Typical steps required for the detection of SARS CoV 2 with real time RT PCR. (B) Principle of real time RT PCR. (1) During reverse transcription, reverse transcriptase (RT) creates a cDNA from the viral RNA template, with the aid of the reverse primer (or random oligonucleotides). The RNase H activity of the RT digests the initial RNA template. (2) The DNA polymerase activity of RT (or of the *Taq* polymerase) completes the second DNA strand guided by the forward primer and cDNA. (3) The newly formed double stranded DNA (dsDNA) is used as a template for the PCR portion of the assay. At the annealing stage, the reverse primer binds to the sense strand of dsDNA in a sequence specific manner, and the forward primer and a dually labeled probe bind to the antisense strand of the DNA. In this stage, the fluorophore (F) present on the probe is masked by the quencher (Q). During the extension step, the DNA polymerase extends the forward primer and, in the process, hydrolyzes the probe, resulting in the release of the fluorophore. Next, following excitation, fluorescence emission can be captured by the real time thermocycler. With each round of PCR amplification, the dsDNA amplicon is multiplied by a 2 fold factor, with a proportional increase in the overall fluorescence signal. After 30 to 40 cycles of amplification, the RT PCR is complete. The PCR cycle at which the fluorescence signal crosses the threshold for positivity is called the threshold cycle (C_T), and C_T values are inversely proportional to the quantity of the target present in the reaction mixture.

occurred is termed the threshold cycle (C_T). C_T values help interpret results as positive, negative, or indeterminate (or equivocal), and each real-time RT-PCR method must validate its cutoff values, as they may differ among methods and instruments (40, 53, 274).

The performance of real-time RT-PCR depends on a number of factors, including the specimen type, the timing of collection, the quality and quantity of viral RNA, the primers and probes designed and their viral RNA target, the reagents used for the RT-PCR(s), the instrument and its operational parameters, and the signal/cutoffs used for result interpretation (23, 40, 53). Typically, real-time RT-PCR assays demonstrate high sensitivity and specificity for SARS-CoV-2. In a systematic review and meta-analysis by Mustafa Hellou et al., the pooled sensitivity for SARS-CoV-2 detection from 29 studies was 96.2% (95% CI, 91.0% to 98.4%), and the pooled specificity was 98.1% (95% CI, 95.9% to 99.2%) (106). Sensitivity is of the utmost importance to ensure that cases in a population are identified, and specificity is important to ensure that no false-positive

results occur. SARS-CoV-2 NAATs like real-time RT-PCR do not cross-react with other respiratory viruses, including human coronaviruses.

(iii) SARS-CoV-2 targets and data interpretation. Various targets have been used for SARS-CoV-2 real-time RT-PCR, but the genes encoding E, N, S, and ORF1ab are used widely (40, 41, 53, 275–279). Despite limited access to control materials early in the pandemic, LeBlanc et al. assessed the analytical performances of various LDTs and commercial RT-PCR assays and found that most of them had a high sensitivity with similar limits of detection (LoDs) in the range of 3.4 to 4.5 $\log_{10}$ copies/ml (11.2 to 141 copies/reaction) (40). Similar proficiency testing across laboratories has been performed by others, demonstrating high sensitivity and specificity across different NAAT methods and instruments (280–282).

In the initial stages of the pandemic, dual- or multigene detection strategies were adopted for real-time RT-PCRs to ensure assay specificity (40). As the pandemic progressed and the disease prevalence increased, some laboratories implemented single-target detection of SARS-CoV-2 in LDTs to streamline the workflow; however, many commercial methods continue to rely on detection using two or more targets (283). In duplex or multiplex real-time RT-PCR assays, if the identification of any target is considered a positive result, sensitivity would be enhanced compared to the requirement of at least two targets to be positive for a SARS-CoV-2 result to be released as such (40). However, this strategy comes at the risk of decreasing the specificity and potentially increasing the false-positivity rate (40). Regardless of the approach for testing, each target should have a validated range of values that define a positive, negative, or indeterminate result as well as conditions that would trigger an invalid result (e.g., processing or quality failures) (40, 284). C_T values can be used in real-time RT-PCR to define these cutoffs, and indeterminate (or equivocal) results arise for values falling between the C_T cutoff values of negative results and the reproducible C_T value cutoff for positivity. This is sometimes termed the diagnostic gray zone for result interpretation (40, 285).

Low C_T values suggest that more viral RNA was present in the specimen, whereas high C_T values represent specimens with lower virus burdens, as more cycles were required to amplify the viral target. Therefore, C_T values are sometimes used as a surrogate for viral load. While low viral loads (indicated by high C_T values) could represent early or late disease, they could also be explained by nonspecific reactions (i.e., false-positive reactions), poor collection techniques, specimen integrity issues during storage or transport, or a problem occurring during laboratory processing. As discussed in the section on the timing of specimen collection above, some studies have evaluated the correlation between C_T values and infectivity (208, 211–217). There are some data to suggest that specimens that have SARS-CoV-2 RT-PCR results with C_T values of >24 cannot be effectively grown in tissue culture (212), yet other data have shown that SARS-CoV-2 can be recovered from cultured specimens with a C_T value of >35, at a lower frequency (213, 214). While methodologies may have differed between studies to explain these differences (e.g., fresh versus frozen specimens), it should be noted that the infectious dose required for human infection with SARS-CoV-2 is unknown and influenced by many biological and environmental variables. Given the variability that can occur in specimen collection, transport, and processing, there are no biological correlates accurately linking C_T values to infectivity or the potential for transmission. Detectable virus by NAATs does not imply infectious virus. Of note, even if such a correlate existed, C_T value cutoffs cannot be applied universally to all NAATs, as they are method, reagent, and target specific, and to date, there is no international standard that can be used for calibration. Of note, other studies have investigated the role of C_T values in predicting the clinical course of COVID-19 or prognosis (286, 287); however, given the number of factors that could influence C_T values, along with the inability to standardize respiratory specimens, the role of C_T values in accurately predicting clinical outcomes would likely be inconsistent, and further research is needed. While the interpretation of C_T values requires careful consideration, it is clear that C_T values vary based on the viral burden, which itself varies throughout SARS-CoV-2 infection. Staging

infection can provide epidemiological clues and can help with patient management. For example, low viral loads (i.e., high C_T values) are seen during presymptomatic, early, or late stages of infection, whereas low C_T values are seen between the early and late stages. If clinically indicated, patients with high C_T values should undergo repeat testing within 24 to 48 h to determine if the C_T value is stable, rising, or declining to help stage potential exposures in contact tracing (167, 168, 230, 288). However, C_T value interpretation is complicated in asymptomatic infections, where the time of infection onset may be unknown. Therefore, to rule out potential false-positive results, repeat testing is recommended for patients with high C_T values suggestive of low viral loads (167, 168, 230, 288).

(iv) Automation. LDTs and commercial assays for moderate- to high-throughput testing for SARS-CoV-2 require relatively expensive equipment and experienced personnel to obtain accurate and robust data, and the turnaround time for results can take several hours. Real-time RT-PCR assays are constantly being improved to increase specimen throughput, provide rapid specimen turnaround times, reduce the hands-on time, and facilitate result interpretation and reporting. Automated high-throughput instruments are capable of performing over 1,000 tests daily, with performance characteristics greater than or equivalent to those of LDTs (167, 168, 251, 289–295). LDTs typically require separate nucleic acid extraction and amplification steps, but these processes can occur simultaneously with high-throughput instruments, along with full traceability, and results can be directly reported through interfacing with the laboratory information system. One of the first high-throughput instruments with a commercially available SARS-CoV-2 detection assay was the cobas 6800 instrument (Roche Molecular Systems, USA), but other highly automated instruments relying on NAAT technology are now available, with similar performances, testing capacities, and workflow benefits. These include the Abbott RealTime SARS-CoV-2 assay on the m2000 instrument (Abbott Molecular, USA), the Hologic Panther SARS-CoV-2 assay (Hologic, USA), the NeuMoDx SARS-CoV-2 assay (NeuMoDx Molecular, USA), and BD Max reagents (Becton, Dickinson, USA) (296–302). Advances have also been made for LDTs for SARS-CoV-2 testing using semiautomated robotics to streamline specimen processing, nucleic acid extraction, RT-PCR setup and amplification, data interpretation, and interfacing for data reporting (295). LDTs for SARS-CoV-2 have also been adapted for other instruments, such as droplet digital PCR (ddPCR). In ddPCR, water-oil emulsions are used to partition nucleic acid samples into thousands of nanoliter-sized droplets, and PCR amplification is carried out within each droplet (303–306). To date, the performance of ddPCR has been shown to be equivalent to or slightly more sensitive than LDT comparators, but limited data are available for its use in clinical laboratories (303–306).

(v) Specimen pooling. Regardless of the NAAT used for SARS-CoV-2 detection, manufacturers of nucleic acid purification kits or RT-PCR reagents and consumables have been challenged with the rapid increase in testing demands that came with the global spread of SARS-CoV-2. With challenges to meet testing resources and limitations in the supply chain, research into alternative testing strategies has been explored (254). A possible strategy to increase testing capacity and gain laboratory efficiencies is group testing (i.e., specimen pooling) (307). While many pooling permutations are possible, its simplest application involves combining patient samples before testing and retesting individual specimens following the identification of a positive pool (308–312). The optimal number of specimens within pools (i.e., pool depth) varies with disease prevalence and assay performance (307, 311, 312). While larger pool depths may achieve higher efficiency, particularly for high-throughput instruments, the trade-off is the accompanying reduced sensitivity, with the potential generation of false-negative results (307). When prevalence is low, typically only a subset of specimens with low viral loads pass undetected, while the testing capacity is increased and the cost of testing is reduced (307, 311, 312). In settings of high disease prevalence, the merits of pooling are lost given the high number of pools that need to be resolved. Other

challenges for pooling include the increased human resource requirements for specimen registration and processing, but robotics and pooling software can help mitigate some of these issues (311). For lower-throughput analyzers like NAAT-based RDTs, pooling can also be considered (312). Overall, while thorough validation and careful consideration of potential impacts of pooling should be considered before implementation on any instrument, pooling can offer an opportunity for clinical laboratories to increase testing capacity, reduce costs, and mitigate the supply chain limitations of laboratory testing (311).

(vi) RT-PCR-based rapid diagnostic tests. Unlike high-throughput automated instruments that are focused on large specimen volumes, rapid diagnostic tests (RDTs), as their name implies, are focused on speed. While this is acceptable for routine testing, RDTs have been developed to provide rapid results with easy-to-use testing, with minimal hands-on processing steps to facilitate training and testing. The first RDT based on real-time RT-PCR that obtained EUA from the FDA and Canada was the Xpert Xpress SARS-CoV-2 assay on the Cepheid GeneXpert platform (Cepheid Inc., USA), which provides results in about 45 min, with a <5-min hands-on specimen processing time (27). This NAAT-based RDT showed analytical and clinical performance characteristics often greater than those of LDTs and other commercial NAATs (99, 167, 168, 290–292, 296, 313, 314). It should be noted that while Xpert Xpress is often referred to as a point-of-care (POC) test, this testing is not typically performed at the time and place of patient assessment and is more commonly performed in a laboratory setting; therefore, the term RDT would be more appropriate. The most current version of the Xpert SARS-CoV-2 assay is multiplexed with influenza A and B viruses as well as respiratory syncytial virus (RSV), which can present with similar respiratory symptoms (315). More highly multiplexed assays like BioFire Respiratory Panel 2.1 with SARS-CoV-2 (BioFire Diagnostics, USA) are also available, which allow a syndromic approach with the simultaneous detection of SARS-CoV-2 and several other respiratory viruses (316, 317). While syndromic testing is also being developed for larger instruments, such assays on RDTs are particularly useful for remote communities or resource-limited settings or for testing of populations where rapid diagnosis would be of benefit (e.g., patients admitted to the ICU).

Other devices with a focus on potential POC applications have integrated RT-PCR with rapid (5- to 30-min) technologies such as digital microfluidics, visual lateral flow readouts, and portable instruments (318–325). All these assays have the advantage of speed and simplicity but are prone to limitations such as low sensitivity, low specimen throughput, and minimal scalability (288). For developing countries or other resource-limited settings where instrumentation is lacking, other cost-sparing testing alternatives are being explored. Arumugam et al. demonstrated a proof of principle of an RT-PCR that could be conducted in 12 min using a setup consisting of thin-walled PCR tubes, *sous vide* immersion heaters/circulators, and an endpoint readout performed with a light-emitting diode (LED) gel-viewing box (326). Such creative and innovative solutions from industry and academic settings help meet the global needs for SARS-CoV-2 laboratory testing, besides other NAATs rapidly being developed and validated.

Isothermal amplification technologies. In efforts to develop portable and rapid diagnostic tests for SARS-CoV-2, NAATs other than RT-PCR have been investigated. Isothermal amplification technologies (IATs) are conducted at a constant temperature, eliminating the need for expensive equipment such as thermocyclers. The principles behind IATs rely on thermal or enzymatic denaturation of nucleic acids, followed by nucleic acid amplification reactions, and have been reviewed in detail elsewhere (244). Isothermal NAAT technologies include transcription-mediated amplification (TMA), nicking enzyme-assisted reaction (NEAR), loop-mediated isothermal amplification (LAMP), recombinase polymerase amplification (RPA), and systems using clustered regularly interspaced short palindromic repeat (CRISPR)–CRISPR-associated (Cas) (CRISPR-Cas) systems. While most IAT methods have been applied to DNA, they can often be adapted to RNA amplification by adding an RT step (e.g., RT-LAMP and RT-RPA) (244, 271, 327, 328). Other IATs were designed for the intent of RNA amplification (e.g., TMA). Only TMA

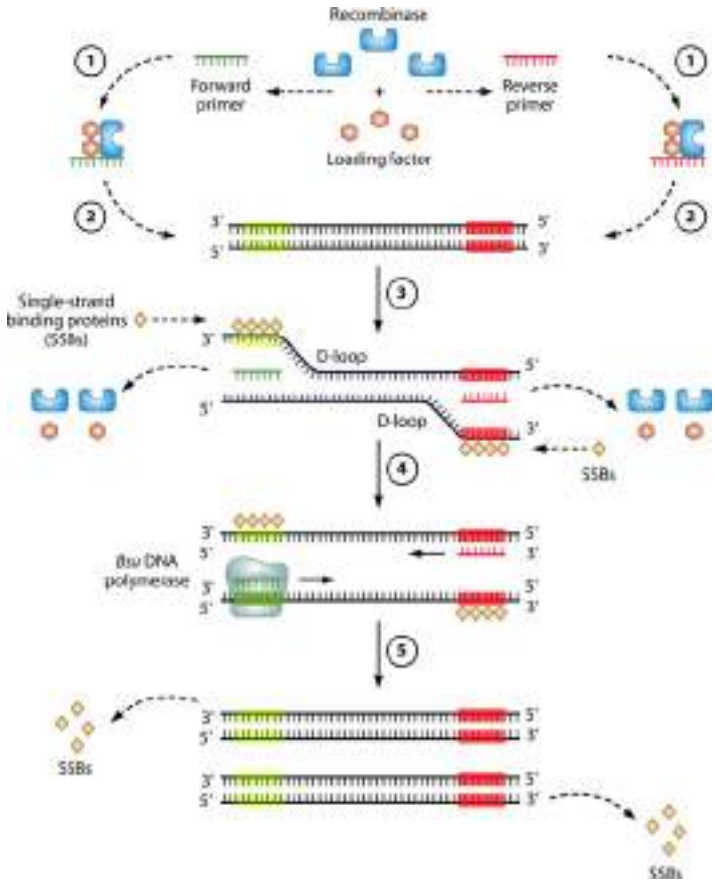

FIG 4 Mechanism of RT RPA. The RT RPA reactions typically occur at between 37°C and 42°C in the following steps. (1) The reaction is initiated by the binding of a recombinase (e.g., T4 UvsX) and a loading factor (e.g., T4 UvsY) to each of the forward and reverse primers. (2) These recombinase/loading factor/oligonucleotide complexes search for homologous sequences in dsDNA, formed in the RT reaction from viral RNA (not depicted). (3) Once sequence homology is found, the recombinase complex invades the duplex DNA, forming a structure called a D loop in an ATP dependent reaction, where there is the unwinding of dsDNA and binding of the primer to its complementary sequence. Access to the primer binding sequence is possible due to the stabilization of the opposite strand by SSBs (e.g., T4 gp32). Subsequently, the recombinase and loading factor disassemble and are released to initiate other rounds of target recognition. (4) Following the binding of the forward and reverse primers, these primers are extended at their 3′ ends using a strand displacement DNA polymerase (e.g., *Bsu*), and during the elongation process, there is a further separation of the two strands. (5) Eventually, SSBs are displaced, and the replication of both strands is complete.

has been commercialized on a high-throughput instrument, but other IATs have been explored for uses as RDTs or for potential POC applications (e.g., RT-RPA, RT-LAMP, NEAR, and CRISPR-Cas) (244). The following sections describe examples of IATs and current and potential applications.

(i) Reverse transcription-recombinase polymerase amplification. As shown in Fig. 4, the mechanism of RPA relies on homologous recombination (329). RT-RPA uses a DNA polymerase to extend forward and reverse primers and make copies of each DNA strand (like PCR). However, to unwind and copy the DNA strands generated from reverse transcription, RPA requires the ATP-dependent targeting activity of a recombinase complex as well as the polymerase activity of a strand displacement DNA polymerase (e.g., *Bsu*) (329, 330).

While the mechanisms for RT-RPA are relatively simple, the reaction components are fairly complex. Single-tube RT-RPA reactions include forward and reverse primers, core enzymes (e.g., reverse transcriptase, recombinase, recombinase loading factor, and a strand displacement DNA polymerase), proteins like single-stranded binding protein (SSB), and a number of ancillary components such as deoxynucleoside triphosphates (dNTPs), salts, buffers, cofactors, crowding agents, ATP, and an enzymatic

system to generate additional ATP (phosphocreatine and creatine kinase [CK]). Once added, magnesium (Mg^{2+}) initiates the RPA reaction. Fortunately, various kits are now commercially available for RPA (e.g., TwistDx, United Kingdom), with variations for the probe used in the detection step (329). For example, the TwistAmp exonuclease (exo) probes are used for fluorescence detection through a mechanism involving exonuclease III, whereas a detection system designed for a lateral flow assay (LFA) output can be incorporated using endonuclease IV (nfo) probes (329). Alternative fluorescence technologies have also been used, such as fluorescence resonance energy transfer (FRET) probes or CRISPR-Cas technology (271, 327).

Unlike real-time RT-PCR, RT-RPA does not require sophisticated instrumentation like thermocyclers, thereby simplifying the testing process. The ease of use of this isothermal technology makes RT-RPA an attractive candidate for point-of-care molecular tests. RT-RPA technology has been applied to the detection of other RNA viruses like Ebola virus (329); however, to date, data presenting its use for the detection of SARS-CoV-2 are scarce (271, 327, 331). Kim et al. used a modified version of RT-RPA to detect SARS-CoV-2 and achieved a sensitivity of approximately 4 copies/reaction in a 10-min reaction that used a lateral flow immunoassay (LFIA) readout. Their RT-RPA correctly identified all 18 contrived specimens generated by spiking heat-inactivated virus into NP swabs or saliva (327). A second publication by Xia and Chen described another modified single-tube version of RT-RPA introduced by GenDx called reverse transcription-enzymatic recombinase amplification (RT-ERA) as well as the whole-course encapsulated procedure for exponential amplification from RNA (WEPEAR) protocol (271). The WEPEAR protocol contains all the reaction components necessary for RT-ERA, except the activator Mg^{2+}, which is loaded into the microtube's lid. Following the RT reaction, the tube can be spun and mixed to initiate the modified RPA reaction. Using FRET probes for a fluorescence output or nfo probes for LFIA-based detection, the WEPEAR protocol achieved high sensitivity in the range of a single copy per reaction. Unfortunately, this method was attempted on only a single clinical specimen and would require further validation. Other applications of the RT-RPA for the detection of SARS-CoV-2 involve the use of CRISPR-Cas technology, which is covered in a later section [see "Isothermal amplification technologies. (v) CRISPR-Cas technology," below].

(ii) Transcription-mediated amplification. Transcription-mediated amplification (TMA) is an IAT that amplifies RNA from an RNA template (41, 332–334), and this technology has been applied to SARS-CoV-2 diagnostics on high-throughput analyzers (296, 322, 335, 336). Figure 5 illustrates the principle of TMA.

The Aptima SARS-CoV-2 assay is performed on the Hologic Panther instrument, a highly automated instrument capable of processing over 1,000 specimens daily (41). Its principle combines a purification step using target capture, TMA for RNA amplification, and chemiluminescent probes for RNA detection. In the target capture step, SARS-CoV-2 RNA is isolated from specimens using magnetic microparticles coupled to oligomers containing sequences complementary to specific regions of the target RNA molecules as well as polydeoxyadenosine residues. By modifying the temperature, sequential hybridization can occur between the RNA target and the sequence-specific portion of the capture oligomers, and a hybridization step then occurs between the polydeoxyadenosine region of the capture oligomer and the polydeoxythymidine sequence that is covalently bound to the magnetic microparticles (337). After the purification step, TMA reactions occur, while detection is achieved through the hybridization of sequence-specific single-stranded oligonucleotide probes labeled with acridinium ester. A reagent is applied to generate a chemiluminescence signal that can distinguish between free and bound probes. A luminometer captures the resulting light emitted from bound probes, expressed as relative light units (RLU).

The Hologic Aptima SARS-CoV-2 assay has only recently been authorized by the FDA and Health Canada, but data on its performance are scarce. The Aptima SARS-CoV-2 assay showed higher analytical sensitivity than some LDTs using real-time RT-PCR, and the performance against other high-throughput analyzers was equivalent (296, 335, 336).

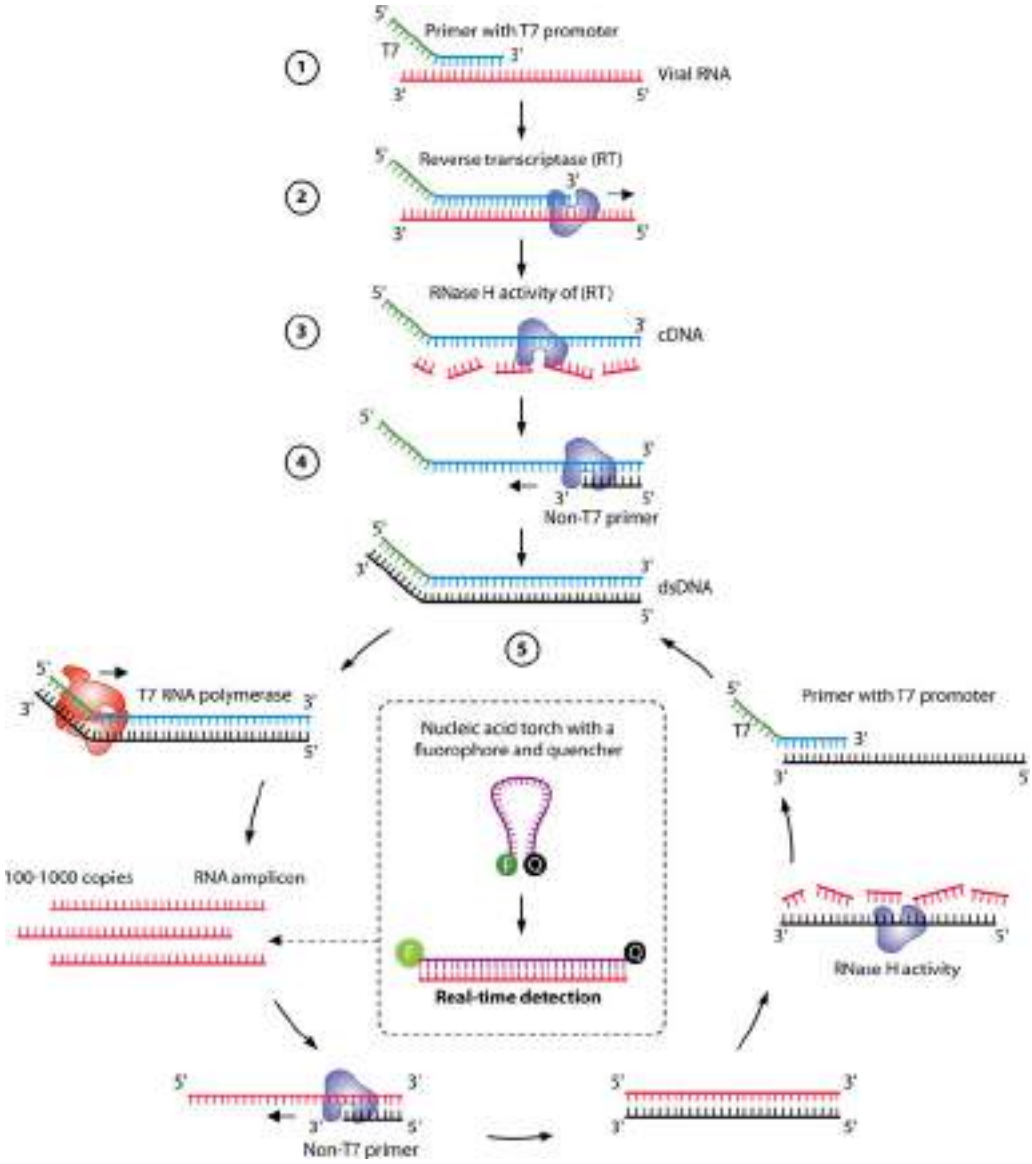

FIG 5 Principle of TMA. (1) The reactions use a reverse primer that is complementary to the sequence of the RNA template, but the reverse primer also contains an overhang with a promoter sequence for T7 RNA polymerase at its 5′ end. (2) Reverse transcription is conducted by the RT; the newly transcribed cDNA includes both the target sequence and the T7 promoter. (3) The RNA template is digested by the RNase H activity of the RT. (4) dsDNA is produced by the DNA polymerase activity of the RT. (5) The produced dsDNA is used as the template for transcription mediated by the T7 RNA polymerase. RNA is thereby amplified severalfold and, through the activity of the same enzyme(s), can serve as the template for a new TMA reaction. As the cycle progress, exponential amplification ensues. Detection of the amplified RNA is usually accomplished using sequence specific molecular beacons ("torch") or hybridization probes targeting the single stranded RNA (ssRNA).

Compared to the Hologic Panther Fusion SARS-CoV-2 assay (i.e., real-time RT-PCR on a highly automated instrument), the Aptima SARS-CoV-2 assay showed similar analytical sensitivity, with LoDs ranging between 62.5 and 125 copies/ml, and the clinical performance was equivalent (322). Given the widespread use of Panther instruments in clinical laboratories for other pathogens (e.g., *Chlamydia trachomatis* and *Neisseria gonorrhoeae*) (338), the SARS-CoV-2 assay on this high-throughput instrument was highly anticipated.

(iii) Nicking enzyme-assisted reaction. The ID Now COVID-19 (IDNCOV) assay performed on the ID Now instrument (Abbott Diagnostics Inc., USA) is an IAT that uses nicking enzyme-assisted reaction (NEAR) technology, and this RDT was recently authorized for use for POC testing in the United States and Canada. NEARs are typically coupled to

fluorescence detection following exponential amplification of DNA but can be used to detect an RNA template with the addition of a reverse transcription step (339, 340). NEARs occur under isothermal conditions (at 60°C) and in several steps mediated by two main enzymes: (i) a nicking endonuclease that recognizes specific restriction endonuclease sites in DNA (e.g., Nt.*Bst*NBI [5′-GAGTCNNNN^N-3′]) but nicks only one strand and (ii) a strand-displacing DNA polymerase like *Bst* that can displace downstream DNA during synthesis at temperatures of around 65°C (Fig. 6). Strand displacement is possible due to the fact that the *Bst* DNA polymerase lacks 5′→3′ exonuclease activity common to other DNA polymerases (e.g., *Taq* polymerase).

While the mechanism for nucleic acid amplification with NEAR may be complex, IDNCOV testing is simple and rapid. The assay has processing times as low as 5 min for positive results with high viral loads and 15 min for specimens with lower viral loads or negative results. Compared to LDTs or commercial NAATs, many recent studies have demonstrated an excellent specificity/negative percent agreement (NPA) near 100% but relatively poor sensitivity/positive percent agreement (PPA) of between 48% and 70% for the detection of SARS-CoV-2, while other studies showed a high specificity/NPA (~100%) as well as high sensitivity/PPA values above 90% (290, 301, 341–347).

The reasons for the disparities in sensitivity/PPA between studies are likely multifold and include differences in the patient population (setting, host factors, and the presence or not of compatible symptoms), the specimen type, the timing between collection and testing, the transport conditions used (dry swabs or transport media), the quality of specimens (prospective versus retrospective), the spectrum of viral loads in the specimens evaluated (proportion of specimens with low viral loads), or differences in performance characteristics of the comparator method(s) (290, 301, 341–347). For example, the swab type affected IDNCOV performance, where NP swabs showed a PPA of 64%, compared to 48% with nasal swabs (348). Using residual positive and negative NP swabs collected in VTM, Mitchell and St. George compared IDNCOV to the CDC real-time RT-PCR, and IDNCOV showed sensitivity and specificity of 71.7% and 100%, respectively (341). All false-negative results corresponded to specimens for which C_T values were between 35 and 40, suggesting low viral loads. Smithgall et al. used residual NP swabs tested with the Roche cobas assay and found NPAs of 100% and 92.0% for INDCOV and Cepheid Xpert Xpress and overall PPAs of 73.9% and 98.9%, respectively (290). However, they also noted that the PPA varied with viral loads. When specimens were categorized by C_T values, both INDCOV and Xpert showed 100% PPA for specimens with medium to high viral loads (C_T values of <30), but at low viral loads (C_T values of >30), the PPA for IDNCOV was 34.3%, versus 97.1% for Xpert (290). In a recent study, Stokes et al. compared IDNCOV to an LDT and showed an excellent PPA of 89.1% (95% CI, 82.0% to 94.1%) for IDNCOV (347). Notably, the PPA increased to 98.2% by following the manufacturer's recommendations for testing under EUA for symptomatic individuals tested ≤ 7 days after symptom onset and within an hour of collection using the appropriate swab (347). Overall, these studies not only demonstrate that the performance characteristics of a test are dependent on numerous factors but also reflect the need for validations or verification of these factors in the settings and conditions where NAAT-based RDTs are applied (274, 288).

(iv) Reverse transcription–loop-mediated isothermal amplification. Reverse transcription–loop-mediated isothermal amplification (RT-LAMP) is an IAT that is gaining interest for potential POC applications and is also being explored for routine diagnostic testing (41, 53, 54, 244, 349–351). Like RT-PCR, RT-LAMP begins with reverse transcription of the target RNA into cDNA by reverse transcriptase, which is done either in a separate reaction or in the same tube as the LAMP reaction. The LAMP reaction can take place in a single tube at 60°C to 65°C (260, 352, 353), and the process can be performed in as little as 20 to 60 min (353, 354). LAMP reactions consist of a strand displacement DNA polymerase (e.g., *Bst* polymerase); a DNA template; dNTPs, typically from 4 to 6 primers; and, depending on the LAMP permutation for signal detection,

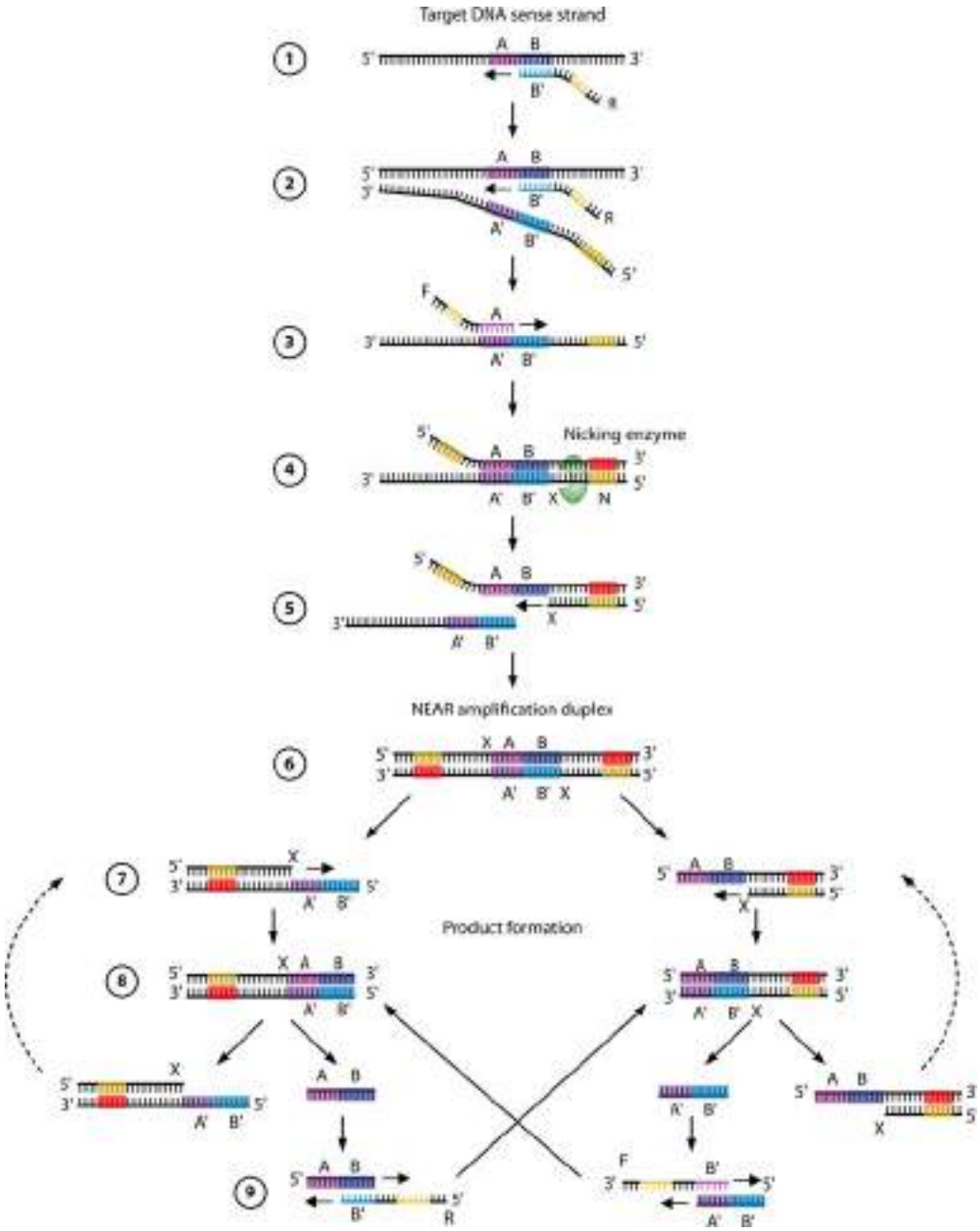

FIG 6 Principle of NEAR technology. The NEAR amplification reactions occur at 60°C and can be broken down into two milestones: NEAR amplification duplex formation and product formation. (1) The target recognition region (B′) of the reverse primer (R) binds to the complementary sequence (B) of the target DNA sense strand and is fully extended by the strand displacement DNA polymerase. (2) A second R primer binds to the template DNA and, during extension, displaces the elongated product of the first R primer extension. (3) The recognition region (A) of the forward primer (F) binds to its complementary sequence (A′) in the R extension product, and F is extended to create a double stranded nicking enzyme recognition site (N). (4) The nicking enzyme recognizes N and cleaves a single strand of DNA in a sequence specific manner at the cut site (X). (5) This releases a fragment of the R extension product. The remaining fragment serves as a primer and is extended at its 3′ end. (6) This extension completes the double stranded complex, termed the NEAR amplification duplex, which is the starting point for product formation. (7) Nicking enzymes bind to the nicking enzyme recognition sites on both ends of the NEAR amplification duplex and cleave at X. (8) The resulting single strand nicks create two complexes, each consisting of a single stranded target region flanked by a nicking enzyme recognition region. (9) Repeated nicking, polymerization, and strand displacement activities result in the amplification of the AB and A′B′ target products. Cleaved complexes are regenerated, while the AB and A′B′ products can anneal to R and F primers, respectively. In turn, the bidirectional extension of the primer and product each creates duplexes that lead to the generation of the opposite product upon cleavage. Product amplification continues until reagents or enzymes are depleted.

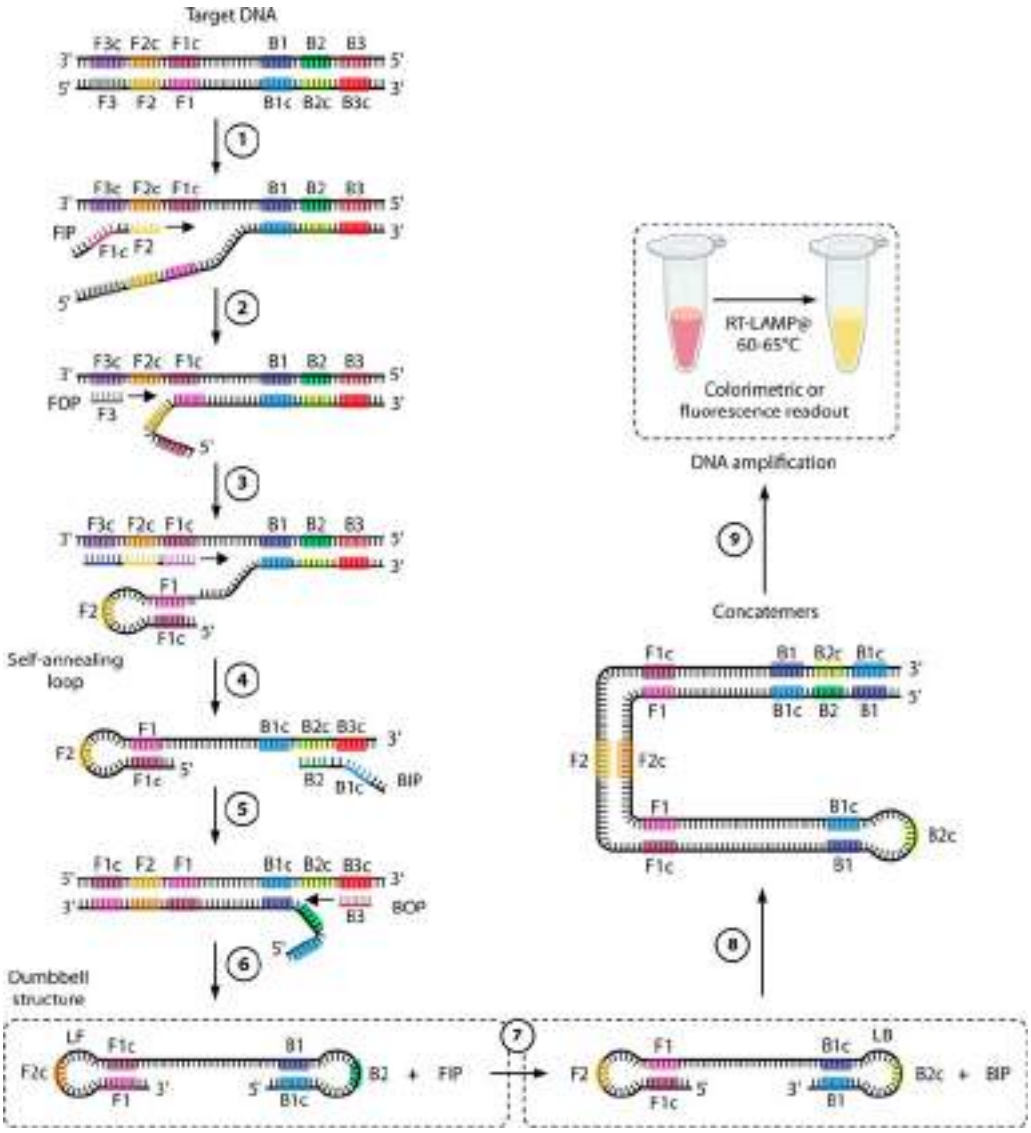

FIG 7 Amplification of nucleic acids using RT LAMP. Overall, there are four core primers that mediate all the processes in a LAMP reaction by recognizing six distinct regions of the target DNA through several steps. (1) After the conversion of the template RNA into dsDNA via reverse transcription (not shown), the LAMP reaction starts from strand invasion by the forward inner primer (FIP), which hybridizes through its F2 region to the F2c region of the target DNA. This initiates complementary strand synthesis using a strand displacement DNA polymerase. (2) The forward outer primer (FOP) (also termed the F3 primer) then hybridizes to the F3c region of the target DNA and, during extension, displaces the newly elongated strand from the FIP. (3) Given that the FIP also contains an F1c sequence, the strand displacement triggered by the DNA polymerase and the FOP leads to the formation of a self annealing loop in the 5′ end of the FIP linked strand (regions F1 and F1c). (4) This single stranded DNA with a stem loop at its 5′ end then serves as a template for the backward inner primer (BIP), which hybridizes to the B2c region of the template DNA through its B2 sequence. (5) During elongation, the complementary strand opens the 5′ end stem loop. Next, the backward outer primer (BOP) (also termed the B3 primer) hybridizes to the B3c region of the target DNA, and its elongation displaces the BIP linked complementary strand. (6) The displacement of the BIP linked strand results in self hybridization on both the 5′ and 3′ ends, leading to two stem loops and the formation of a dumbbell shaped DNA. (7 to 9) The amplification of the dumbbell structure with the FIP leads to a concatemer and the formation of a second dumbbell structure that can be amplified with the BIP. Amplification can occur from the 3′ end of each dumbbell structure or with the annealing of primers such as the FIP and BIP. Additional loop primers (i.e., loop F [LF] and loop B [LB] primers) can also be used to increase the speed and sensitivity (41, 350, 351). Visualization of LAMP amplification is typically done by using pH sensitive colorimetric or intercalating fluorescent dyes.

either a pH-sensitive colorimetric dye or a fluorescent dye (41, 54, 244, 350, 351, 355, 356). The mechanism for DNA amplification using LAMP is summarized in Fig. 7.

Variations of LAMP have been developed for potential POC applications with reactions that are monitored in one of three ways. (i) Turbidity can be measured with a

spectrophotometer at an optical density (OD) of 400 nm, as magnesium pyrophosphate precipitates in the solution as a by-product of the LAMP reaction (41, 357–359). (ii) Colorimetric detection can be performed using pH-sensitive dyes (e.g., cresol red or phenol red) that change color from the incorporation of dNTPs during amplification or using a metal indicator (e.g., hydroxynaphthol blue) that would assess the concentration of Mg^{2+}, used as a cofactor for dNTP incorporation during DNA synthesis (349, 360–362). Color changes can be read by the naked eye or spectrophotometry (359, 362). (iii) Fluorescence detection can be performed if an intercalating dye (e.g., SYBR green) is used in the LAMP reaction. When complexed with dsDNA, intercalating dyes can be excited to emit fluorescence, which can then be captured in real time with a fluorometer or a compatible thermocycler (354, 360). Alternative detection systems for RT-LAMP include CRISPR-Cas technology, and these are covered in a later section of this review.

Fluorescence detection tends to be the most sensitive of the visualization methods, which makes the LAMP technology amenable to real-time monitoring and high-throughput testing (349, 354). However, to our knowledge, no high-throughput instruments have adopted this technology to date. On the other hand, a commercial kit for real-time SARS-CoV-2 RT-LAMP (Variplex; Amplex Diagnostics, Germany) has been developed and compared to real-time RT-PCR. The commercial RT-LAMP kit showed moderate agreement with real-time RT-PCR, with a clinical sensitivity of 76.3% (363, 364). Given its simplicity, RT-LAMP technology has also been used to develop rapid POC products (349). Results are ready in 30 min using RapiPrep COVID-19 (MicrosensDX, England), which integrates magnetic bead-based RNA extraction with LAMP technology. However, a relatively low sensitivity of 80% and a specificity of 73% were observed when tested on 21 nasal swabs compared to real-time RT-PCR (365). The authors of that study suggested that while the sensitivity and specificity were poor, the assay still had merit in some clinical applications such as algorithms using repeat testing over time. Other studies that used RT-LAMP demonstrated varying performance compared to LDTs based on real-time RT-PCR for commonly used specimen types (357, 366). The analytical sensitivity of most RT-LAMP assays was found to be in the range of 100 to 200 copies per reaction (360, 367), while others have reported analytical sensitivities of as low as 10 copies/reaction (354, 368). Altogether, this range is consistent with those of some LDTs and commercial real-time RT-PCR assays (e.g., cobas SARS-CoV-2 test) (40, 278, 368, 369). The variability in the performance of RT-LAMP assays could be attributed to differences in processing steps, specimen types, the quality of the nucleic acid extraction, LAMP reagents, viral targets, detection methods (manual versus automated), the methodology (e.g., measuring turbidity, using colorimetry, or using fluorescence), viral loads, patient populations tested, numbers of specimens evaluated, methods used as a comparator, or other undefined or uncharacterized factors like inhibition rates (244, 260–262, 354, 357, 367, 370–372). Overall, RT-LAMP technology shows promise for large-scale testing (373) and POC testing (260, 278, 368, 369, 374, 375), but further optimization is still required.

(v) CRISPR-Cas technology. CRISPR and its Cas proteins are derived from prokaryotic defense systems against foreign nucleic acids (376–381). When activated, Cas proteins can exhibit local DNase or RNase activity resulting in local cleavage (*cis*-cleavage) of the target DNA or RNA as well as collateral damage (*trans*-cleavage) to neighboring single-stranded DNA (ssDNA) or RNA. A number of different Cas proteins have been identified that differ in nucleotide specificity for their *cis*-cleavage targets and in their ability to cause collateral damage to nearby nucleic acids (331, 382–384). The high degree of collateral damage caused by Cas12a or Cas13 can break down neighboring RNA or ssDNA, which can be exploited for detection. For example, dually labeled ssDNA or RNA probes with a fluorophore-quencher combination can be used, and when the Cas12a or Cas13 system binds to the target DNA or RNA, the Cas proteins are activated to cleave the target and the probe. With a blue-light generator, fluorescence is generated and visualized or captured by a fluorometer (385–387). Alternatively, the RNA or ssDNA probe can be labeled with biotin, and the cleavage reaction can be observed with the aid of a specific immunochromatographic device (e.g., LFIA) and

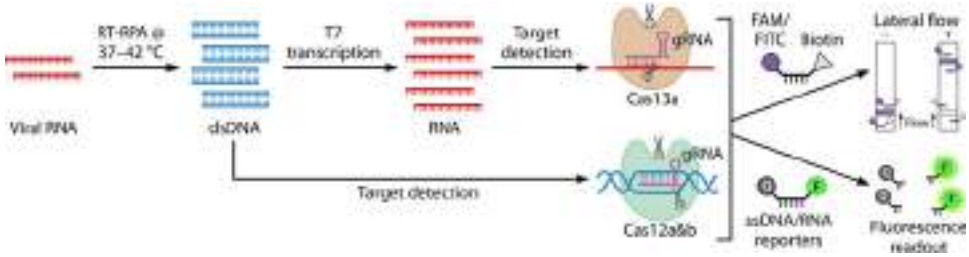

FIG 8 Principle of CRISPR Cas technology for viral RNA detection. First, the viral RNA is subjected to reverse transcription and amplification, e.g., in an RT RPA reaction at 37°C to 42°C, to generate dsDNA. The dsDNA can be targeted by guide RNAs (gRNAs) directly in a CRISPR Cas12 detection system, whereas RNA detection using the CRISPR Cas13 system requires an additional T7 transcription step. When Cas12 or Cas13 is activated by the recognition of gRNA, there will be cleavage of the target as well as nonspecific cleavage of dually labeled oligonucleotide probes. The probes are ssDNA or ssRNA for the CRISPR Cas12 or CRISPR Cas13 systems, respectively. The readout for either method can be colorimetric by the incorporation of fluorescein amidite (FAM)/fluorescein isothiocyanate (FITC) biotin probes and the use of lateral flow dipsticks, or fluorometric readouts can be used by the incorporation of dually labeled fluorophore (F) quencher (Q) probes. Upon collateral cleavage, the unquenched fluorophore can be excited with blue light, and the resulting emission of fluorescence can be visualized or captured with a fluorometer.

colorimetric detection (385–387). Understanding the mechanism and permutations of CRISPR-Cas systems led to many technological advances in genome editing (388, 389) and diagnostic applications such as the detection of RNA viruses (Fig. 8) (382–384, 386, 387, 390, 391).

The use of CRISPR-Cas as a diagnostic tool was proposed by two laboratories, which founded the Cas12a-based system named DETECTR (DNA endonuclease-targeted CRISPR *trans*-reporter) (392) and the Cas13-based system termed specific high-sensitivity enzymatic reporter unlocking (SHERLOCK) (393, 394) (Fig. 8). Recently, a SHERLOCK-based COVID-19 test received EUA from the FDA, which is the first EUA for any CRISPR technology. However, many variations of CRISPR-Cas12 and CRISPR-Cas13 systems have emerged for the detection of SARS-CoV-2 in a variety of clinical specimens, in both potential POC and high-throughput testing formats (395). These include the SHERLOCK testing in one pot Covid test (STOPCovid), all-in-one dual CRISPR (AIOD-CRISPR), Cas12b-mediated detection (CDtection), CRISPR-assisted detection (CASdetect), and Cas13-based, rugged, equitable, scalable testing (CREST) (387, 392, 395–399).

The composition and conditions of each stage of a CRISPR-Cas detection system can affect its speed and performance. For SARS-CoV-2 detection, the initial step in the CRISPR-Cas system can be the lysis of the specimens, with or without an RNA extraction step; however, purified RNA showed higher sensitivity (392, 395, 396). For example, Broughton et al. demonstrated a DETECTR system that had an LoD of approximately 10 copies/μl using purified RNA, but removing the nucleic acid extraction step decreased the LoDs to 15,000 and 500 copies/μl for contrived specimens consisting of spiked SARS-CoV-2 in $\geq$10% UTM and $\geq$20% PBS, respectively (392). As such, the purification of RNA was recommended. Next, the time to results for CRISPR-Cas-based methods was low compared to real-time RT-PCR, at 20 min (395), 40 min (386, 392, 397), 50 min (331), 60 min (387), or 70 min (396), but varied between methods and detection systems. All CRISPR-Cas methods described here require the conversion of SARS-CoV-2 RNA into dsDNA, which can be accomplished by RT-PCR, RT-LAMP, or RT-RPA. Huang et al. compared the CDC real-time RT-PCR to a DETECTR assay using either RT-PCR or RT-RPA with a fluorescence readout and achieved low analytical sensitivity (2 copies per sample, regardless of the method used for amplification) (331). Cas12-based CRISPR systems are typically faster than Cas13-based methods, as Cas12 directly detects dsDNA, but the latter requires an additional transcription step to RNA (Fig. 8).

The methods used for SARS-CoV-2 result readout can also affect the speed and performance of the assays. While initially, CRISPR-Cas assays used visual readouts on commercial lateral flow assays, coupling the CRISPR-Cas technology to fluorescent reporters

instead leads to more rapid results and sensitive detection (392, 393, 400). For example, Joung et al. validated a SHERLOCK-based method that returned results in 70 min using the LFIA readout, while fluorescence testing was completed in 40 min (396). Guo et al. demonstrated that the analytical sensitivity of CASdetec, a CRISPR-Cas12b assay based on reverse transcription recombinase-aided amplification (RT-RAA) and fluorescence output, was 10^3 copies/ml, whereas the sensitivity of DETECTR and SHERLOCK ranged between 10^4 and 10^5 copies/ml using an LFIA for detection (387). Also, CRISPR-Cas systems have been adapted to one-tube reactions using fluorescence rather than amplification followed by detection using lateral flow methods, not only to reduce processing steps but also to decrease the potential for contamination (395–397). To optimize the reaction in single-tube formats, the temperature for the IAT must be compatible from the RT step to Cas-based detection. Ding et al. described a one-pot reaction at 37°C combining RT-RPA and a CRISPR-Cas12a system and could achieve detection of 1.3 copies of SARS-CoV-2 RNA (397). With the high temperatures required for RT-LAMP (55°C to 65°C), CRISPR-Cas12b systems have been developed with a thermostable Cas12b protein derived from *Alicyclobacillus acidiphilus* that could maintain activity at higher temperatures (396, 401). A similar approach was used by Ali et al., who developed a single-tube RT-LAMP- and CRISPR-Cas12a-based system able to reach an analytical sensitivity (10 copies/reaction) comparable that of to the CDC real-time RT-PCR (5 copies/reaction) (395). Given the many variables for CRISPR-Cas technology, optimization of this methodology for SARS-CoV-2 and other diagnostic testing is an active area of research.

While the analytical performances of CRISPR-Cas technology showed some promise for detecting SARS-CoV-2, validation on clinical specimens has been scarce to date. Hou et al. showed that an RT-RPA CRISPR-Cas13a system with fluorescence detection was able to correctly identify 52 positive specimens for SARS-CoV-2, whereas an undefined real-time RT-PCR failed to identify 5 specimens with low viral loads (402). Huang et al. compared the CDC real-time RT-PCR to a DETECTR assay using either RT-PCR or RT-RPA with fluorescence detection on 19 positive clinical specimens and identified all of them; however, 3 additional positive specimens were detected (331). These could represent false-negative results for the real-time RT-PCR or false-positive results for the CRISPR-Cas12 assay (i.e., specificity would be 71.4% for the latter). The LoD for the CRISPR-based method was 2 copies/reaction, compared to 5 copies/reaction for the CDC real-time RT-PCR, suggesting that CRISPR-based detection may be able to identify SARS-CoV-2 at lower viral loads. Broughton et al. compared the CDC real-time RT-PCR to an RT-LAMP DETECTR system with LFIA or fluorescence readouts using 83 clinical specimens (41 positive and 42 negative specimens) and demonstrated 95% positive agreement (392). Of the 21 specimens positive for SARS-CoV-2 identified by the CDC real-time RT-PCR, Ali et al., using an RT-LAMP CRISPR-Cas12 system, were able to identify 18 (85.7%) using the fluorescence readout, but weak or absent signals were noted with LFIA detection (395). Overall, these data show variability in performance for CRISPR-based assays, ranging from 80 to 100% sensitivity.

While CRISPR-based methods are showing promise for SARS-CoV-2 detection, research into this technology is evolving. Recently, an RT-LAMP-based CRISPR-Cas12 system was developed using an electric field gradient on a microfluidic device (403). This allowed for on-chip, automated separation of nucleic acids from nasopharyngeal swab samples in 30 min, followed by CRISPR-based detection (403). While further validation is required to fully understand the benefits of CRISPR-Cas technology, it has much potential for applications for POC devices or high-throughput testing platforms (331, 395).

SARS-CoV-2 next-generation sequencing. Understanding the genomic sequence of SARS-CoV-2 obtained from clinical specimens can help identify the COVID-19 pandemic origins, delineate transmission events, unravel clues to pathogenesis, and monitor viral evolution over time (404–408). Over the last few decades, DNA sequencing technologies have relied on modifications of Sanger sequencing, which was developed in the 1970s (409). While Sanger sequencing technology is still used for small sequences (~0.5 to 1 kb) such as single-gene targets, next-generation sequencing (NGS)

technologies have allowed sequencing to be performed as massively paralleled reactions, allowing rapid access to complete genomes at a scale and cost that are feasible for many laboratories (404–406, 410–412). For SARS-CoV-2 genomes of <30 kb, high-quality sequences can readily be obtained with NGS directly from clinical specimens using strategies like amplicon enrichment or bait capture techniques to favor the sequencing of the viral targets (413). NGS involves technologies such as sequencing by synthesis, sequencing by ligation, and ion semiconductor sequencing (e.g., nanopore sequencing), each with its own advantages and limitations (404–406, 410–412). The principle of each NGS technology has been reviewed elsewhere (404–408), and some of them are illustrated in Fig. 9.

To date, a single commercial kit (Illumina Inc., USA) for NGS has been approved as a clinical diagnostic test under FDA EUA guidelines for COVID-19, which is based on sequencing by synthesis (414). However, no data are available to date to describe its performance, advantages, or limitations compared to commonly used detection methods like real-time RT-PCR. Also, only a limited number of studies that have explored the use of NGS for SARS-CoV-2 detection for the purpose of diagnostic testing are available (413, 415–417). For example, using a laboratory-developed protocol for NGS, Bhoyar et al. compared NGS and real-time RT-PCR on 752 clinical specimens processed in duplicate on a single flow cell (417). They demonstrated high concordance between the methods and a diagnostic increase in the positivity of 5.7% with NGS (with the detection of 6 cases that tested negative by PCR and 21 cases where PCR results were inconclusive). This study demonstrates the feasibility of processing 1,536 specimens in a total of 17 h (11 h for sequencing and 6 h for analysis) (417). In another study, a low-cost NGS approach was shown to achieve high sensitivity for the detection of SARS-CoV-2 (84 genome units/ml), which is equal to or higher than those of some RT-PCR methods; however, this study tested only 10 specimens (5 positive and 5 negative specimens) (415). It is unclear whether high sensitivity would still occur if the throughput would be increased to their proposed workflow of 192 specimens in 8 h. Bloom et al. showed 100% concordance between NGS and RT-PCR with a limited number of specimens (31 positive and 33 negative NP swabs) (416). These authors propose NGS as a tool for population-based surveillance rather than individualized testing for medical decisions. While postulated to be able to achieve screening of thousands of samples on high-throughput NGS platforms, no data were provided to support the feasibility of this approach or the impact of such a high level of specimen pooling. Overall, some data support the potential of NGS as a diagnostic tool for SARS-CoV-2, yet further analyses are required to understand its benefits and limitations.

Despite the potential for NGS as a diagnostic tool, the limitations of SARS-CoV-2 genome sequencing using NGS technologies should also be recognized. For example, NGS technologies are challenged with specimens with low viral loads (413, 418), as insufficient data or poor-quality results are obtained for subsequent analyses. Efforts to increase sensitivity and quality are under way using target enrichment processes with NGS techniques such as multiplex PCR amplicon-based sequencing, hybrid capture-based sequencing, and ultrahigh-throughput metatranscriptomic sequencing (413, 419). Another limitation of NGS technologies is cost, which may be prohibitive for many diagnostic laboratories. Furthermore, the complexity of the NGS workflow and requirement for sophisticated instrumentation and bioinformatics expertise may pose significant barriers to NGS access in many laboratories. If resources are limited, specimens could be prioritized and sent to referral laboratories to help inform public health responses and global surveillance initiatives.

While not routinely used for SARS-CoV-2 diagnostic testing in clinical laboratories, genome sequencing of SARS-CoV-2-positive specimens with NGS technologies has paved the way for numerous applications, including investigations of disease pathogenesis, epidemiology, virus phylogenetics, SARS-CoV-2 evolution, and the impact of viral evolution on diagnostic testing or interventions like therapeutics and vaccines (420–424). For example, Meredith et al. used SARS-CoV-2 nanopore sequencing on

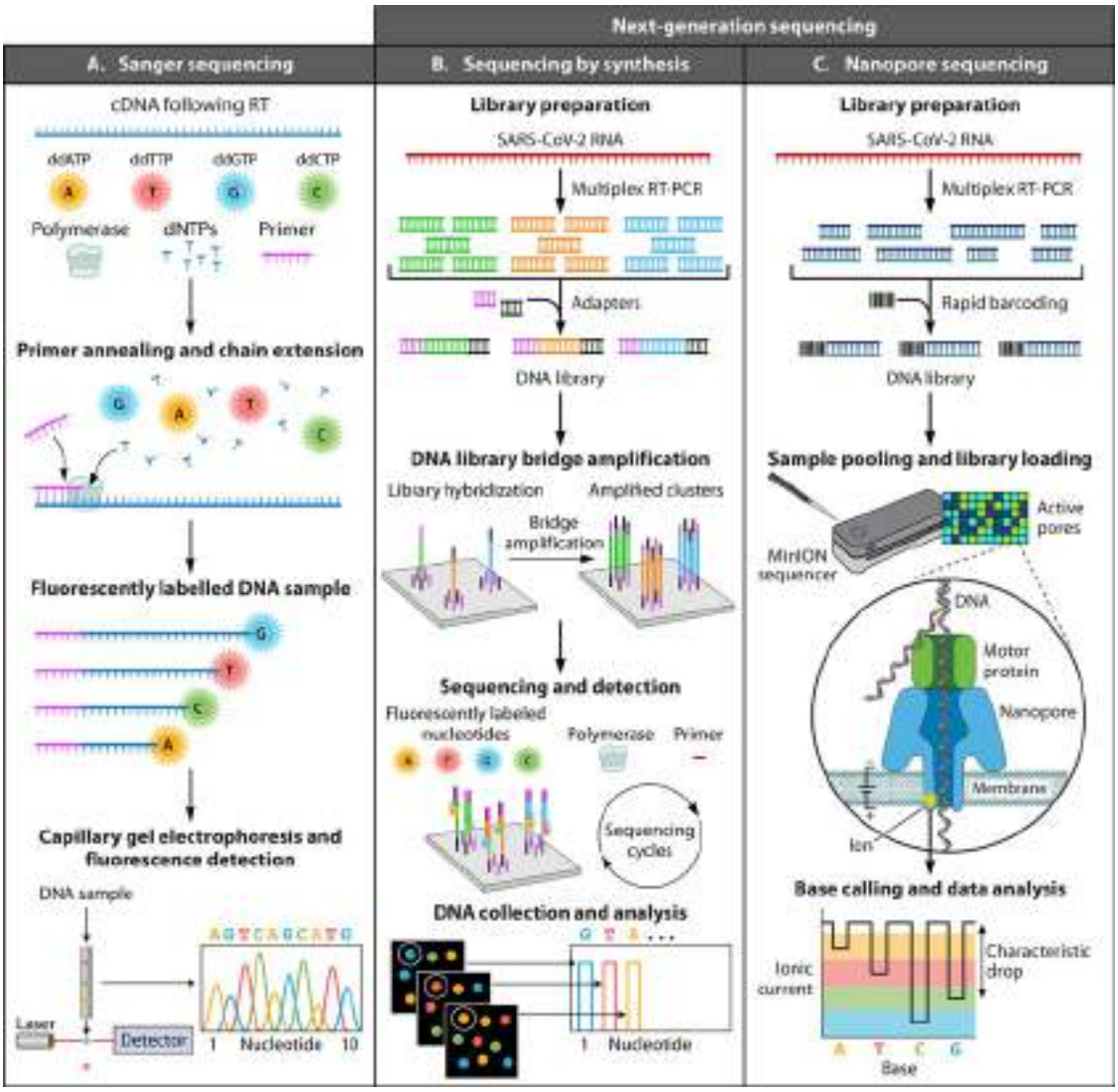

FIG 9 Sequencing techniques for identification of SARS CoV 2. (A) Sanger sequencing. First, SARS CoV 2 RNA is often amplified by RT PCR (not depicted). Sanger sequencing reactions can be undertaken to analyze either of the DNA strands, but only one strand per reaction can be assessed. The extension of the primer annealing to the template DNA occurs in the presence of DNA polymerase, buffer, cofactors, deoxynucleotide triphosphates (dNTPs), and fluorescently labeled dideoxynucleotide triphosphates (ddNTPs). The binding of the ddNTPs to the oligonucleotide strands will cease the extension, resulting in various DNA structures with different lengths. Next, the extended DNAs undergo capillary gel electrophoresis in which the shorter DNA strands move faster, resulting in the detection of the fluorescently labeled nucleotides in the order of the size of the DNA strands. Finally, as DNA fragments are resolved and nucleotide specific fluorescence signals are captured by a detector, a chromatogram is assembled to reveal the sequence of the template. (B) Next generation sequencing (NGS) by synthesis. First, a library of millions of DNA fragments is created from the template (or enhanced by multiplex RT PCR for SARS CoV 2). Adapters are bound to the two ends of each DNA fragment. The adapters consist of a universal primer binding site and a unique sequence (i.e., barcode) that can be hybridized to a specific sequence on the support (e.g., flow cell). Following hybridization, with complementary sequences of the adapters, bridge amplification is used to amplify each DNA fragment at a defined physical position. In the sequencing and detection steps, fluorescently labeled nucleotides are bound to the forward strands in the presence of a primer and a polymerase, which results in the generation of fluorescent light that is detected by an analyzer in real time. Many other NGS technologies are also available. (C) For example, NGS by nanopore technology is presented. After creating a library of DNA fragments by multiplex RT PCR and barcoding, the library is loaded onto a membrane containing nanopores. The nanopores are proteins that open the DNA double strand, and as each nucleotide is passed through the membrane, it causes a specific change in the ionic current that can then be translated into the nucleotide sequence of the templates.

PCR-positive specimens combined with epidemiological data to help identify nosocomial transmission events and inform infection control interventions (418). They demonstrated the feasibility of rapid NGS in a health care setting by providing sample-to-sequence information in less than 24 h. From the discovery of SARS-CoV-2, NGS has been used to understand its origins and transmission. Initial phylogenetic analysis of the genomes of

SARS-CoV-2 showed that it was closely similar to human SARS-CoV and potentially used the same cell entry receptor (i.e., ACE2) and helped postulate the probable zoonotic origins of the virus (i.e., bats) (10, 425–429). Next, the first SARS-CoV-2 genomes were made available less than a month from the first recognition of disease reported from Wuhan, Hubei, China (10). With rapid access to SARS-CoV-2 genome data, molecular methods like real-time RT-PCR were rapidly developed at the early stages of the COVID-19 pandemic and became the method of choice for SARS-CoV-2 detection worldwide. Through remarkable efforts from public health agencies and researchers, SARS-CoV-2 genome sequences have been made available in public data repositories such as the Global Initiative on Sharing All Influenza Data (GISAID) (https://www.gisaid.org/) and the National Center for Biotechnology Information (NCBI) GenBank database (https://www.ncbi.nlm.nih.gov/). These data help provide a snapshot of global diversity and data that could be used for epidemiological investigations. In the initial stages of the pandemic, the high diversity of SARS-CoV-2 genomes was attributable to multiple independent importations of SARS-CoV-2 by travel overseas in countries of initial virus activity, and transmission routes could be investigated (418, 430–434). Following global spread and closure of international borders, sequence diversity was more limited, and sequencing of SARS-CoV-2 genomes was used in outbreak investigations and became particularly useful for cases in areas of unknown community transmission (418, 430–434). However, with natural evolution in the human host, or selective pressures from the recent introduction of SARS-CoV-2 vaccines or exploratory therapeutics (i.e., antivirals or convalescent-phase sera), there are increasing chances for SARS-CoV-2 to further diversify and acquire mutations (435–439).

The genetic diversity of SARS-CoV-2 stems from naturally occurring mutations in its genome, which is common at higher frequencies in RNA viruses (440). Some mutations might have no impact on SARS-CoV-2 protein sequences (i.e., synonymous substitutions), but these may affect the performance of diagnostic tests using NAATs if they occur in the target region for the assays (40, 441–443). From the various genomes of SARS-CoV-2 that have been sequenced since its discovery, the M, E, and RdRp genes were shown to be fairly conserved compared to the high divergence observed in some regions of the S genes (420, 421, 439, 444–450). Mutations in the genome of SARS-CoV-2 could also occur from point mutations, insertions, deletions, or recombination events that could affect protein sequence, structure, and function (i.e., nonsynonymous substitutions). Both synonymous and nonsynonymous mutations can be useful for epidemiological investigations, but it should be noted that nonsynonymous mutations are of significant interest as they could have impacts in terms of disease transmissibility and severity or could help the virus escape from therapeutic (i.e., convalescent-phase sera or antivirals) or preventative (i.e., vaccines) interventions. Mutations in S are of particular concern as S glycoprotein epitopes are major targets for current and exploratory vaccines (35, 451, 452). Multiple SARS-CoV-2 strain variants are circulating globally, but few are variants of concern (VOCs) (439). In the United Kingdom, a novel variant of SARS-CoV-2 (0B/501Y.V1, VOC 202012/01, or B.1.1.7 lineage) emerged, with an unusually large number of mutations. This VOC has since been reported in several countries, including Canada and the United States. It contains a number of mutations in the S gene (e.g., N501Y, 69/70 deletion, and P681H), and while these mutations have yet to show any impact on disease severity or vaccine effectiveness, some preliminary epidemiological data suggest that this variant is associated with increased transmissibility (439). In Brazil, a SARS-CoV-2 variant from lineage B.1.1.248 was reported, with an E484K S gene mutation associated with reduced neutralization capability by convalescent-phase plasma (453–455). Such mutations are concerning due to potential failures of therapeutic options or prevention strategies like vaccines that target similar viral protein epitopes. Furthermore, a novel VOC from lineage B.1.1.248 called P1 was identified, with 12 mutations in the S gene, including both E484K and N501Y, suggesting the potential for increased transmissibility and immune escape (438, 439). Ongoing surveillance should be encouraged to identify novel SARS-CoV-2 variants and characterize the potential impacts of VOCs.

Overall, sequence-based surveillance of SARS-CoV-2 is important to ensure that diagnostic tests accurately identify the virus and that there are no changes with novel

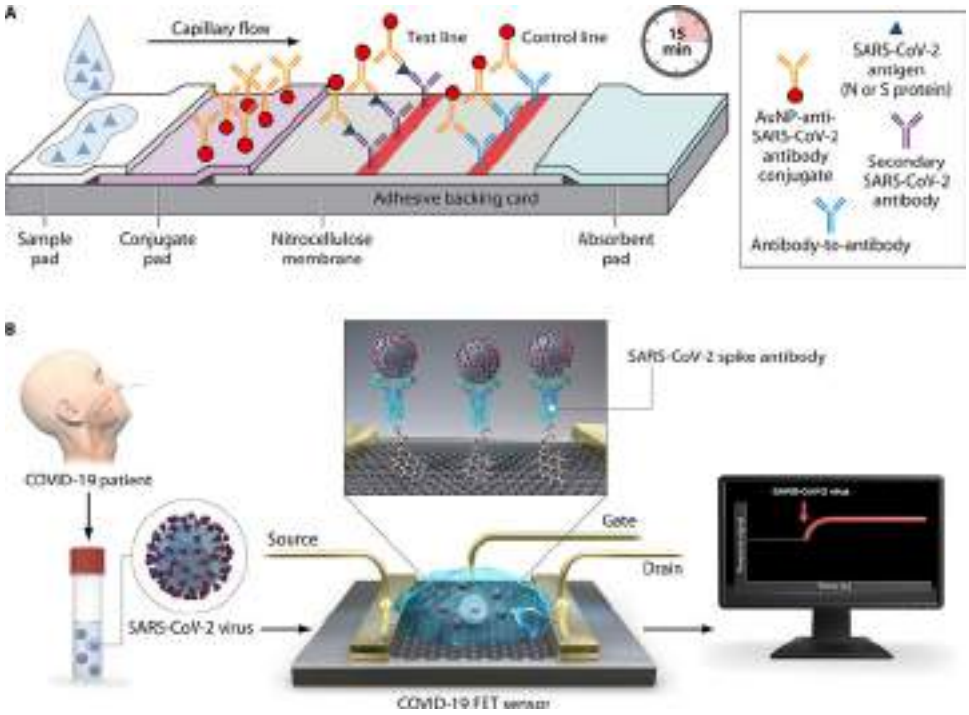

FIG 10 Antigen testing for the detection of SARS CoV 2. (A) Principle of a lateral flow immunochromatographic assay (LFIA). The design of the LFIA for antigen detection is a qualitative immunological reaction confined to a small portable device (e.g., cassette or dipstick) that can be performed in the laboratory or a POC setting. Briefly, antigens in specimens (e.g., nasal swabs, nasopharyngeal swabs, and saliva) are placed in a well with a sample pad, and the fluid containing the antigen flows through the device via capillary action. The bottom of the well where the specimen is inoculated contains a sample pad, which is in contact with the conjugate pad used as a support for SARS CoV 2 specific monoclonal antibodies (mAbs) that are labeled with colloidal gold nanoparticles (AuNPs) or other tags. If present, SARS CoV 2 antigen (usually S or N protein) forms a complex with the mAbs bound to the AuNPs, and the entire complex migrates via capillary action until it is captured by other SARS CoV 2 antigen specific mAbs immobilized on the nitrocellulose membrane (i.e., the test line). As antigen antibody complexes are trapped at this location, they form a line that can be visualized by the naked eye or with the aid of a detector. Also, mAbs AuNPs, whether conjugated with antigens or not, continue to migrate until captured by an isotype specific antibody directed against the fragment crystallizable (Fc) portion of the mAb at the control line. This ensures proper liquid flow through the device and test validity. (B) Point of care detection of SARS CoV 2 antigen using a FET based sensor. Upon binding of spike (S) proteins to the anti S monoclonal antibodies immobilized on the graphene sheet via the PBASE linker, a change in the voltage ampere diagram reveals the presence of the virus. (Panel B is adapted from reference 465 with permission of the American Chemical Society.)

variants in disease spread, disease severity, or the effectiveness of vaccines or antivirals. Whether NGS will eventually become a common diagnostic tool remains to be determined.

SARS-CoV-2 Antigen Detection

Antigen detection methods, like NAATs, are used to detect active replicating viruses in the early stages of SARS-CoV-2 infection. Unlike NAATs that rely on the detection of viral RNA, antigen detection is based on the identification of SARS-CoV-2 proteins. The two main antigens in SARS-CoV-2 detection assays are S and N proteins. Antigen detection assays use technologies similar to those of serological methods. Like serology, high-throughput antigen-based testing can be performed on semiautomated or automated instruments using enzyme immunoassay (EIA) technologies like enzyme-linked immunosorbent assays (ELISAs) or chemiluminescence immunoassays (CLIAs). However, most antigen detections to date have aimed for methods allowing easy-to-use and rapid testing using portable devices, like LFIAs (also termed lateral flow immunochromatographic assays or lateral flow assays [LFAs]). The mechanism for LFIAs is shown in Fig. 10A, and other technologies (e.g., ELISA and CLIA) are covered in the subsequent serology sections. This section summarizes the current knowledge on the

clinical performance of antigen-based detection assays and their potential applications to support COVID-19 responses.

Hundreds of companies have been developing antigen rapid diagnostic tests (Ag-RDTs) for SARS-CoV-2 detection (238). Ag-RDTs (e.g., LFIAs) are often promoted as POC devices for rapid testing and immediate management of patients in settings such as physicians' offices or clinics; however, these tests are not always performed in these settings. RDT is a more appropriate term if performed in a laboratory setting. At the time of this review, few antigen-based detection assays have received EUA approval in the United States and Canada, but many more applications have been submitted as laboratory and/or POC tests (29, 30, 456, 457). Examples of SARS-CoV-2 Ag-RDTs that have received EUA for testing in laboratory or POC settings in the United States or Canada include technologies relying on a colorimetric LFIA with a visual readout, instrument-based antigen detection using a fluorescence-based LFIA, a microfluidic immunofluorescence assay, and a chromatographic digital immunoassay (Table 2).

While EUA was granted for some Ag-RDTs, at the time of this review, limited data have been published on their clinical performance characteristics. The performance of antigen- and molecular-based POC tests for detecting SARS-CoV-2 was the subject of a recent Cochrane review (203), but limited data were available to be summarized (369, 458–463). Briefly, the review summarized data from five studies, representing 943 samples. The average sensitivity of Ag-RDTs was found to be 56.2% (95% CI, 29.5% to 79.8%), and the average specificity was 99.5% (95% CI, 98.1% to 99.9%). In comparison, NAAT-based RDTs had an average sensitivity of 95.2% (95% CI, 86.7% to 98.3%) and an average specificity of 98.9% (95% CI, 97.3% to 99.5%). High specificity was observed for both molecular and antigen-based detection methods; however, low sensitivity was noted for Ag-RDTs, but a high level of heterogeneity was noted between studies. This variability could be explained by factors including the methods used for SARS-CoV-2 detection, the comparator methods during the evaluation, the patient populations assessed, SARS-CoV-2 prevalences, the timing of specimen collection, the specimen types used, and antigen stability during analyses.

Consistent with the low clinical sensitivity of Ag-RDTs, the analytical sensitivity was defined in some studies, which described LoDs of Ag-RDTs that were approximately 1,000-fold lower than those of culture-based detection of SARS-CoV-2 and 10,000-fold lower than those of NAATs (463). Mertens et al. noted that when specimens with high viral loads were evaluated (defined as specimens with real-time RT-PCR C_T values of <25), the sensitivity of Ag-RDTs increased to 74.8%, compared to an overall sensitivity of 57.6%, when all specimens were considered (459). Scohy et al. observed an overall sensitivity of Ag-RDTs of 30.2% (461). When specimens were further characterized by real-time RT-PCR C_T values, the impact of the poor sensitivity of Ag-RDTs was clear. With specimens with C_T values of <25 (1.8×10^5 copies/ml), C_T values of <30 (9.4×10^3 copies/ml), and C_T values of <35 (4.9×10^2 copies/ml), the sensitivities of Ag-RDTs were shown to be 100%, 70.6%, and 46.9%, respectively. Linares et al. showed that an Ag-RDT achieved 86.5% sensitivity (95% CI, 75.0% to 97.0%) if symptomatic patients with high or moderate viral loads were tested within 7 days of symptom onset (457). As seen with all other SARS-CoV-2 tests, the timing of testing likely plays an important role in assay performance. Recognizing the relatively poor sensitivity compared to NAATs but the potential role for Ag-RDTs, WHO interim guidance described situations where such tests could be considered (238). The WHO supports the use of Ag-RDTs for conditions such as (i) testing in areas where NAATs are not available (e.g., remote areas) or when the result turnaround times using NAATs are long; (ii) in outbreak investigations, but the frequency of testing in these settings remains unclear; (iii) in areas where the prevalence is high; and (iv) for testing of asymptomatic contacts of positive cases.

Given the poor sensitivity of Ag-RDTs for detecting SARS-CoV-2, research is being performed to improve sensitivity using novel sensor and biosensor technologies (464). So far, a few studies have leveraged the power of electronic and electrochemical

TABLE 2 Examp es of ant gen tests approved for emergency use by the U.S. FDA for detect on of SARS-CoV-2[a]

Device or assay (manufacturer)	Methods	Target antigen protein	Specimen type(s)	Authorized detection window (dpo)	Authorized settings	Time (min)	LoD ($TCID_{50}$/ml)[b]	Reference
BinaxNOW COV D-19 Ag card home test[c] (Abbott Diagnostics, USA)	LF A, visua readout	N	NS, ANS	7	Home, H, M, W	15	140.6	585
CareStart COV D-19 antigen test (Access Bio, USA)	LF A, visua readout	N	NPS	5	H, M, W	10	800	586
QuickVue SARS antigen test[c] (Quide Corporation, USA)	LF A, visua readout	N	ANS	5	H, M, W	10	7,570	587
Veritor system for rapid detection of SARS-CoV-2 (BD, USA)	LF A, instrument readout	N	NS	5	H, M, W	15	140	588
Sofia 2 F u + SARS antigen F A[c] (Quide Corporation, USA)	LF A, FA, instrument readout	N	NS, NPS	5	H, M, W	15	91.7	589
LumiraDx SARS-CoV-2 Ag test[c] (LumiraDx Ltd., UK)	Microfluidics, FA, instrument readout	N	NS	12	H, M, W	12	32	590
C ip COV D rapid antigen test[c] (Luminostics nc., USA)	LF A, LA, instrument readout	N	ANS	5	H, M, W	30	88	591
E ume COV D-19 home test[c] (E ume Limited, Austra ia)	LF A, FA, smartphone readout	N	MTS	NA	Home, H, M, W	15	6,309	592

[a]The fu ist is avai ab e in reference 29. Abbreviations: LF A, atera flow immunoassay; FA, immunofluorescence assay; LA, immuno uminescence assay; BD, Becton, Dickinson and Company; dpo, days post-symptom onset; NS, nasa swab; ANS, anterior nasa (naris) swab; NPS, nasopharyngea swab; MTS, midturbinate nasa swab; H, aboratories certified under the C inica Laboratory mprovement Amendments of 1988 (CL A), 42 U.S.C. §263a, that meet requirements to perform high-comp exity tests; M, aboratories certified under the CL A, 42 U.S.C. §263a, that meet requirements to perform moderate-comp exity tests; W, patient care settings operating under a CL A certificate of waiver; TC D_{50}, median tissue cu ture infectious dose.

[b]The imit of detection (LoD) of each assay is the owest LoD reported in the instructions for use of that assay, regard ess of the specimen types.

[c]The assay does not differentiate between SARS-CoV-2 and SARS-CoV.

methods to create fast and sensitive diagnostic devices for SARS-CoV-2 detection. For example, Seo et al. described a field-effect transistor (FET)-based biosensing device that detected SARS-CoV-2 at concentrations of 2.42×10^2 copies/ml in clinical specimens, without sample pretreatment, in approximately 3 min (465). The FET sensor used SARS-CoV-2 monoclonal antibodies (mAbs) to spike proteins, which were coupled to graphene sheets through a 1-pyrenebutyric acid *N*-hydroxysuccinimide ester (PBASE) linker (Fig. 10B). With the high conductivity and other properties of graphene, real-time dose-dependent detection of SARS-CoV-2 antigen can be achieved down to 1 fg/ml. While further optimization is needed to commercialize this technology, it has the potential to help increase the sensitivity of antigen detection. In another study, Mahari et al. developed an electrochemical device using a screen-printing technique. They immobilized antibodies against SARS-CoV-2 spike proteins on screen-printed carbon electrodes (SPCEs) to detect the virus and developed an integrated in-house-built portable device that could measure the changes in electrical conductivity upon the reaction between antigens and antibodies. The device was able to detect spiked SARS-CoV-2 antigens in saliva with an LoD of 90 fM within 10 to 30 s (466).

While FETs and electrochemical sensors show promise to increase the sensitivity of antigen detection, the desire to achieve the highest sensitivity possible with RDTs has been the subject of recent debate (288, 299, 301, 467, 468). Some authors have proposed that with repeat testing, the chance of identifying SARS-CoV-2-infected individuals increases (288, 467–470). This may be true on a population level, where testing may otherwise not have been performed (e.g., asymptomatic testing), and there would be fewer consequences if detection of the virus is missed. However, repeat testing and the possibility of false-negative results in an acute-care setting pose many more challenges, particularly when decisions have to be made at the time of or shortly after the time of presentation. For existing or novel technologies, studies with more robust data are needed to better define the utility of Ag-RDTs in various settings. These should include prospective analyses that consider factors such as the timing of collection, time of symptom onset, symptomatic and asymptomatic patient populations, disease prevalence, stability, and following the manufacturer's recommendations for stability and transport (i.e., direct testing of specimens and not using specimens in transport media).

Serological Immunological Methods for SARS-CoV-2 Detection

Serological assays detect antibodies specific to SARS-CoV-2 in blood sources like serum, plasma, or whole blood (including fingerstick and heel pricks sometimes used in POC testing), and the possibility of antibody detection in other body fluids such as saliva is being explored (471–473). Given that the typical time required to detect immune responses to SARS-CoV-2 is around 1 to 2 weeks, serological tests have limited utility for SARS-CoV-2 diagnostics in the acute stages of the illness but could have value once immune responses have had time to occur (241, 474–478). Many serological assays for detecting SARS-CoV-2 antibodies have been developed and commercialized, and a list of authorized medical devices related to COVID-19 in the United States and Canada is regularly updated online (29, 30, 472, 479). Despite access to serological assays, the interpretation of their results is further complicated in the postvaccine era for SARS-CoV-2, and the relevance of antibody detection must be considered in the context in which it is used and its limitations. Following a section describing serological methods, a discussion on the relevance and possible applications is provided.

Serological assays often use recombinant antigens to capture SARS-CoV-2-specific antibodies, with the N protein and the receptor-binding domain (RBD) of the S1 subunit of the S glycoprotein being the most commonly used antigens. Serological methods can target one or more immunoglobulin isotypes (i.e., IgA, IgM, or IgG) or total antibody, and theoretically, any of these isotypes could provide neutralizing activity against SARS-CoV-2 (480). IgM and IgG are commonly used immunoglobulins in serological assays for SARS-CoV-2, while IgA detection is less commonly used (479). IgA and IgM have shown some merits for the detection of early immune responses to

SARS-CoV-2, but there has been some concern regarding the rapid decay of IgA and IgM in serum and saliva compared to IgG (242, 481, 482). While more data are needed to fully understand the serological responses in different settings or patient populations, it is clear that IgA, IgM, and IgG all have the potential to generate neutralizing responses to SARS-CoV-2 (242, 481, 482).

The most common methods used are ELISAs in a 96-well plate format and CLIAs for automated higher-throughput instruments (49, 479). LFIAs are also available to provide rapid results. It is unclear whether detectable antibodies in commercial serology methods are associated with immune protection, as large population-level studies and quantitative immunoglobulin analyses are required to assess if detection of SARS-CoV-2-specific immunoglobulins correlates with immune protection. However, studies are under way to investigate the extent of neutralizing antibodies produced over time (242, 481, 482).

The performance of immunological assays remains unclear as there is a lack of a gold standard for method comparison. Methods are often compared among themselves from a consensus standard, but the true performance and relevance of antibody responses, and the optimal testing algorithm, require further investigation (483). For now, the applications of serology include a role as an adjunct to molecular testing to support the identification of SARS-CoV-2 in a patient suspected of having COVID-19 (i.e., persistent or progressing symptoms) but with the absence of testing or repeated negative (or indeterminate) results obtained by NAATs. It should be noted that some patients may be antibody negative at the time of testing, but that does not preclude memory B cell activity or functional T cell responses with subsequent exposures to SARS-CoV-2. Some studies argue that immunological methods could also be used in seroprevalence studies to aid in ongoing outbreak investigations (to identify cases beyond the detectable window of NAATs), to determine past exposures of populations to SARS-CoV-2 (e.g., health care workers or the general population), or to assess attack rates in defined populations or geographical areas. However, correlations to neutralizing antibody titers would be required to fully understand serological data, along with the impact of prior infection with SARS-CoV-2 and other human coronaviruses as well as the impact of vaccines. High sensitivity and specificity are desired, but with these many confounding factors, result interpretation is complicated (49, 484). The following sections describe common methods used for SARS-CoV-2 serology, including ELISAs, CLIAs, and LFIAs, along with a discussion of the potential value and limitations of immunological methods.

Enzyme-linked immunosorbent assay. While many permutations exist, enzyme-linked immunosorbent assays (ELISAs) can be categorized into four main types: sandwich, direct, indirect, and competitive (485). For the detection of SARS-CoV-2, indirect (210, 486–489), modified indirect (210), and double-antigen sandwich (206) ELISAs are the most commonly used methods (Fig. 11A).

In the indirect ELISA method, a solid support, such as wells of a 96-well microplate, is coated with SARS-CoV-2 recombinant antigens (210, 486–489). Patient serum or plasma is added, and if present, SARS-CoV-2-specific antibodies will bind to the immobilized antigens. Following washing steps, a secondary antibody is then added that is specific to the isotype targeted (i.e., anti-human IgM, anti-human IgG, or anti-human IgA). This secondary antibody (or conjugate) is linked to a fluorophore that can generate fluorescence or conjugated to an enzyme for colorimetric or chemiluminescent signal generation following the addition of a substrate. Usually, colorimetric methods are used in which the optical density (OD) (i.e., absorbance) of the solution can be measured using a spectrophotometer and correlated with the concentration of the target antibodies. Other permutations of ELISAs are also possible, but while these techniques all share similarities in terms of their signal generation mechanisms, each can vary in performance. Typically, the time to result for ELISAs is 1 to 5 h (41), and more recently, POC applications of ELISAs for the detection of anti-SARS-CoV-2 antibodies have been explored using microfluidics technology (490). The performance characteristics and limitations of SARS-CoV-2 serology are discussed in a later section.

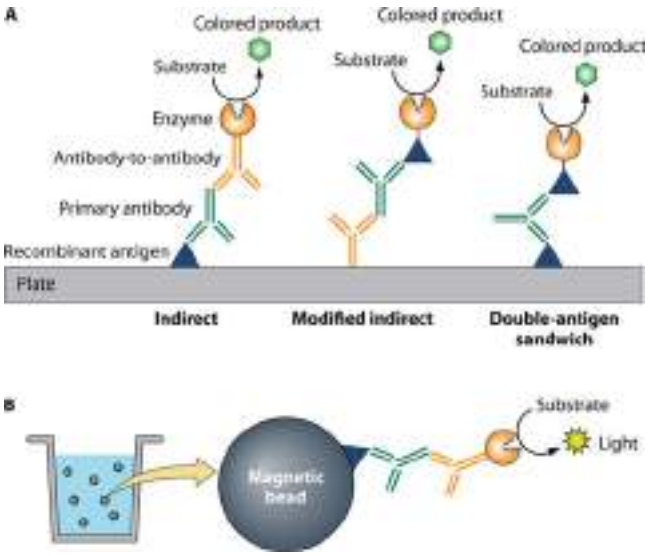

FIG 11 Common serological immunoassays for the detection of SARS CoV 2 specific antibodies. (A) Common designs of ELISA methods, including indirect, modified indirect, and double antigen sandwich assays. (B) Magnetic bead based CLIA.

Chemiluminescence immunoassay. The chemiluminescence assay (CLIA) is an immunoassay that is commonly used in highly automated serological instruments and is known for its high sensitivity compared to other serological assays (491). Similar to ELISAs, variations of CLIAs have been applied for the detection of SARS-CoV-2 antibodies, such as indirect (492, 493) and sandwich (239) methods.

The CLIA has two main differences from colorimetric ELISAs. First, the final reaction produces light, which is detected by a luminometer in relative light units (RLU) rather than the OD, which is an absolute value. To produce light, the conjugate uses an enzyme-substrate reaction such as the alkaline phosphatase (AP) and Lumigen APS-5 substrates. Second, magnetic microspheres in a liquid-phase reaction rather than multiwell plates are coated with the antigenic materials, which allows the easy separation of bound and unbound molecules by a magnet and faster reactions due to providing a large surface area and allowing the reactions to occur entirely in suspension (494–496) (Fig. 11B). Some CLIAs have been commercialized and used on high-throughput automatic analyzers. For example, the Liaison assay (DiaSorin, Italy) uses magnetic beads coated with SARS-CoV-2 S1 and S2 antigens to detect IgG antibodies. This assay is capable of providing up to 170 results/h in a fully automated manner.

Fluorescent microparticle immunoassays. Recently, Norman et al. described a fluorescent nanoparticle immunoassay (FMI)-based single-molecule array assay that consisted of a mixture of four types of dye-encoded beads coupled to S, S1, S2, and N proteins and used for the detection and differentiation of SARS-CoV-2 IgM, IgG, and IgA antibodies (497). In this technique, an excess number of beads is utilized in comparison to the number of antibody molecules in the samples in a way that either zero or one antibody molecule binds to each bead. After the reactions occur between the coated beads and the antibodies and other reagents, the beads are loaded into an array of 216,000 femtoliter-sized wells for imaging, which allows the detection of antibodies with single-molecule resolution. When tested on a set of 81 plasma samples, the technique showed 86% sensitivity and 100% specificity for the samples during the first week after symptom onset and 100% sensitivity and specificity for the samples taken after the first week after symptom onset (497).

Similarly, to facilitate the simultaneous detection of the IgG, IgM, and IgA isotypes of SARS-CoV-2-specific immunoglobulins, a multiplex SARS-CoV-2 antibody immunoassay based on Luminex technology was developed for detection on the Bioplex

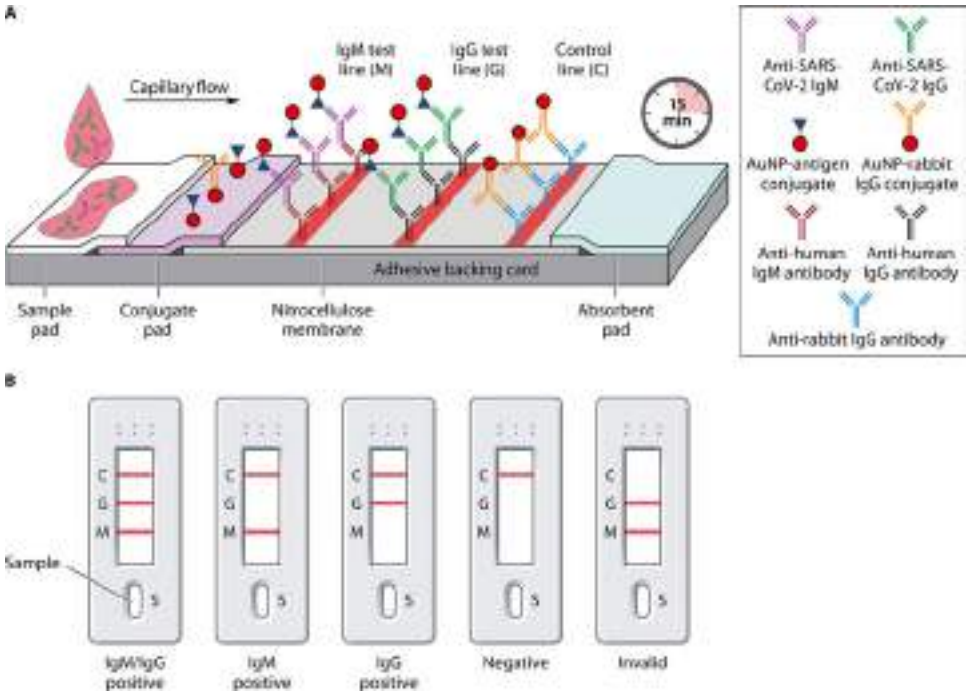

FIG 12 Serological lateral flow immunoassays for the detection of SARS CoV 2 specific antibodies. (A) Schematic of a lateral flow immunoassay device for the simultaneous detection of IgM and IgG antibodies. Upon the addition of the sample, the liquid moves toward the preimmobilized reagents through capillary action and reacts with them. If IgM/IgG antibodies are present in the sample, they bind and form a complex with the recombinant SARS CoV 2 antigen conjugated with colloidal gold nanoparticles (AuNPs). The complex is then captured in one of the test lines by anti human IgM/IgG antibodies, resulting in a pink color due to the accumulation of the AuNPs. There is also an AuNP rabbit IgG conjugate that will be captured in the control line, indicating proper liquid flow through the device. The results will be observable in ~15 min. (B) Variations of results of the lateral flow assay device in a cassette format. (This figure was inspired by the work in reference 498.)

automated flow cytometer (Bio-Rad Laboratories) (473). This multiplex immunoassay was used to demonstrate SARS-CoV-2 antigen-specific antibody responses in 33 saliva and 206 serum samples from participants with RT-PCR-confirmed SARS-CoV-2 infection. Overall, this technology could detect prior SARS-CoV-2 infection with high sensitivity and specificity at ≥10 days after symptom onset, but the performance varied with the targets (473). FMI technology allows robust antibody profiles to be simultaneously Tdetected in a single reaction. A commercial assay for the Bioplex 2200 system has recently received FDA approval, but no data on this assay have been published to date.

Lateral flow immunoassays. As described in the antigen detection section above, lateral flow immunoassays (LFIAs) can be used as an RDT or POC test to detect antibodies against SARS-CoV-2 in blood or serum samples. The most frequently used antigens are recombinant S or N proteins to capture total antibody or detect and sometimes differentiate IgM and IgG antibodies (479). The LFIA devices are low cost, portable, and rapid (~15 min) and require only a few microliters of samples, making them suitable for fingerstick tests (498–500). Figure 12A illustrates an example of an LFIA used for the simultaneous colorimetric detection of SARS-CoV-2-specific IgM and IgG. Many different types of LFIAs have been developed to detect SARS-CoV-2, with variations in antigens used for antibody capture, immunoglobulin isotypes detected, and overall performances (479, 501).

Performance of serological immunological methods for SARS-CoV-2. TIn a systematic review and meta-analysis, the results of 40 studies up to 30 April 2020 were summarized, and differences in sensitivity between serological methods used for SARS-CoV-2 antibody detection as well as antibody classes were presented (49). Data for IgA were scarce, and no conclusions could be drawn. For IgM detection, the pooled sensitivity (95% CI) for LFIAs was

the lowest, at 61.8% (50.8% to 71.8%), whereas that for ELISAs was higher, at 81.7% (71.8% to 88.5%), and that for CLIAs was the highest, at 84.3% (70.7% to 93.0%). Similarly, the pooled sensitivities for IgG detection were 64.9% (53.8% to 75.4%), 80.6% (71.9% to 87.9%), and 93.5% (84.9% to 98.1%) for the LFIA, ELISA, and CLIA, respectively. The pooled specificities were fairly similar among the LFIA, ELISA, and CLIA methods, at 96.6% (93.8% to 98.4%), 99.7% (99.0% to 100.0%), and 96.6% (84.7% to 99.5%) for IgM detection and 97.6% (96.2% to 98.8%), 98.9% (96.7% to 99.8%), and 97.8% (62.9% to 99.9%) for IgG detection, respectively. Other meta-analyses and systematic reviews yielded consistent conclusions for sensitivity and specificity for IgM, IgG, or total antibodies (472, 502, 503).

One important issue affecting the diagnostic performance of serological assays is the time after symptom onset when the samples are taken for serological analyses, as the antibody profiles change over the course of the disease. In a meta-analysis and systematic review (49), the pooled sensitivity (95% CI) for IgM detection was low in the first week after symptom onset, at 25.3% (16.3% to 31.1%), for the LFIA but increased to 51.8% (30.3% to 69.6%) after 2 weeks and to 69.9% (58.4% to 79.9%) after 3 weeks. ELISA detection of IgM showed similar values for weeks 1, 2, and 3 after symptom onset, at 26.7% (15.6% to 35.6%), 57.6% (15.9% to 88.2%), and 78.4% (54.1% to 91.9%), respectively. The CLIA followed the same trend but with higher values, at 50.3% (10.9% to 81.2%), 74.3% (16.1% to 99.4%), and 90.6% (51.8% to 99.4%), respectively. Next, the pooled sensitivities for IgG at weeks 1, 2, and 3 after symptom onset were 13.4% (4.7 to 29.6%), 50.1% (24.8% to 77.0%), and 79.7% (71.4% to 86.9%) for the LFIA; 23.7% (12.7% to 38.1%), 65.3% (46.3% to 79.4%), and 82.1% (76.4% to 89.0%) for the ELISA; and 53.2% (28.7% to 67.6%), 85.4% (48.1% to 98.1%), and 98.9% (86.9% to 100.0%) for the CLIA, respectively (49).

Overall, the performances of serology assays varied between methods and were dependent on the timing of collection, and the applicability of these methods is limited to date. It is important to recognize that other factors such as antigens and the inherent characteristics of a test or instrument used for antibody detection can also impact the performance of immunological assays. Also, data summaries in recent meta-analyses and systematic reviews so far have shown high levels of heterogeneity and a risk of bias and applicability between studies (472, 502, 503). Thus, careful attention should be paid to the design of the studies, their limitations, and whether the conclusions derived from these evaluations are justified. It remains unclear whether antibodies will provide durable protective responses against subsequent SARS-CoV-2 infections or what will be the impact of prior infection with seasonal human coronaviruses (474, 475). It is possible that prior infection with other coronaviruses or other conditions (e.g., pregnancy or chronic illnesses) may cross-react with SARS-CoV-2 serology assays, and robust evaluation of methodologies should include specificity analyses against related viruses and possible interfering substances (504, 505). The recent introduction of vaccine programs will further complicate the use of immunological methods as diagnostic tests but may expand their use to determine whether individuals are immune once exposed to SARS-CoV-2 through natural infection or following immunization. This remains an active area of research that requires comparisons to neutralizing antibody titers and cell-mediated immunity.

Neutralization assays and research areas of interest for serology. The efforts of the scientific community to help understand the host responses to SARS-CoV-2 are fundamental in understanding COVID-19 pathophysiology and the interpretation of SARS-CoV-2 laboratory diagnostics (506–509). There has been an extraordinary effort to rapidly develop serological methods in various formulations, and while some were licensed under EUA in the United States and Canada, their use to make recommendations on a patient's current or future susceptibility to SARS-CoV-2 infection remains unclear (29, 30). Given the timing of the immune responses to SARS-CoV-2 infection, it is clear that serology would not be useful for diagnosis in acute phases of illness; antibodies would not be present in substantial quantities in this time frame to allow public health interventions (133). In fact, positive serology does not preclude viral shedding

(208, 510), and the absence of antibodies does not preclude the possibility of immunity. To date, recommendations for the use of serology include clinical research (e.g., seroprevalence studies) to help inform public health strategies or policies on a population level (102, 133, 241). For example, seroepidemiological studies can support ongoing outbreak investigations or retrospectively assess infection rates in certain populations (133, 511). On an individual level, serology may have considerations for individual patients with multisystem inflammatory syndrome or in situations where suspect cases repeatedly test negative by NAATs, but symptoms persist (and the timing fits into a period of at least 2 weeks after symptom onset) (102, 133, 241). Future research is required to further understand the full value of SARS-CoV-2 serology, especially in the context of immunization with COVID-19 vaccines.

Key areas of research interest should include the relevance and duration of antibody-based immune responses to better understand whether antibody responses in commercial tests or LDTs correlate with protective immune responses against subsequent SARS-CoV-2 infection as well as the magnitude and duration of these responses. Understanding this correlation can be an important function to assess immunity on an individual or population level or even to qualify blood donors desiring to become donors of convalescent-phase plasma that could subsequently be used in clinical trials (512, 513). This would require a quantitative analysis of seroconversion (detection of measurable antibodies following infection), which would not be possible with qualitative assays such as LFIAs but may be possible using semiquantitative ELISAs (where antibody detection relies on a signal value that is normalized to a calibrator to establish a signal-to-cutoff [S/CO] ratio) or, ideally, using quantitative ELISAs. Quantitative detection of SARS-CoV-2 antibodies over time could be used to demonstrate seroconversion, and quantitative ELISAs have become commercially available (e.g., the liquid-based double-antigen sandwich ELISA from Roche [Elecsys anti-SARS-CoV-2 S]). Quantitative antibody analyses, paired with a fundamental understanding of how well serological methods correlate with neutralizing antibodies (nAbs), may help establish a threshold where populations are protected from SARS-CoV-2 reinfection (known as a correlate of protection).

The establishment of a correlate of protection first requires an in-depth understanding of whether nAbs are produced, the extent to which they are produced, whether they provide protection, and the duration of these responses and then analyzing these data in large population studies to correlate a level of nAbs that may confer protection against subsequent infection (514). The quantification of nAbs in serum or plasma is performed using target- and immunoglobulin isotype-specific neutralization assays 9like plaque reduction neutralization tests (PRNTs) (41, 241, 424, 515). Briefly, PRNTs rely on the ability of nAbs to effectively prevent SARS-CoV-2 from infecting cultured cells that would otherwise cause cytopathic effects (i.e., cell death/lysis) (41, 241, 511, 515–517).

Nonetheless, PRNTs are known to be time-consuming and laborious. To increase specimen throughput, microneutralization (MN) tests have been developed to detect nAbs to SARS-CoV-2 that rely on a principle similar to that of PRNTs but are performed in 96-well formats and without the need for semisolid overlays (511, 517). To further automate the detection of nAbs, a focus reduction neutralization test (FRNT) can be used where patient sera/plasma dilutions can be assessed for their ability to reduce viral plaque formation, foci, or individually infected cells using immunocolorimetric staining and visualization using digital imaging (480). Despite MN, FRNTs are amenable to moderate-throughput testing, and alternatives have been developed using fluorescence detection and luminescence to increase sensitivity. On the other hand, MN tests and FRNTs share a challenge similar to that with PRNTs: they all rely on SARS-CoV-2 propagation in cell culture, which requires laboratory facilities with higher levels of biological containment (i.e., biosafety level 3 [BSL3] in Canada or physical containment level 3 [PC3] as defined by the WHO) (424). These practices are not common outside reference laboratories (241). To circumvent these biosafety requirements, pseudovirus-based neutralization assays (PBNAs) have been developed, where SARS-CoV-2 proteins are expressed on a surrogate virus backbone such

as a lentivirus, retrovirus, or vesicular stomatitis virus (VSV) (516, 518, 519). Other alternatives include the use of a protein-based surrogate neutralization ELISA (snELISA), which is based on the competition between ACE2 and nAbs for binding to recombinant antigens (520–526).

Few studies have looked at nAbs, and data on the extent and duration of nAbs over the course of SARS-CoV-2 infection are scarce (508, 527–530). Suthar et al. used an FRNT to demonstrate that nAb binding to the SARS-CoV-2 S protein RBD is detectable within 6 days after PCR confirmation (480). While days postonset would have better defined the antibody profiles over time, these authors showed that there is rapid isotype switching in nAbs from IgA and IgM to IgG1 and IgG3. In a limited data set from Long et al., it was noted that there was a decline in nAbs over time in both asymptomatic and symptomatic individuals (239). Similarly, Seow et al. performed a longitudinal study using sequential serum sampling and demonstrated that seroconversion was observed in 95% of cases, with nAbs present 8 days after the onset of symptoms (531). They also noticed that the magnitude of nAb responses depended on disease severity and waned over time, which was consistent with the results of others (206, 239, 532–535). In some cases, nAbs persisted up to 60 days, while others approached the limit of detection in this period (531). In a more recent study by Isho et al., the duration of antibody responses was evaluated in both serum and saliva (242). Antibodies to S protein were detected in 90% of cases approximately 10 days after symptom onset, and longitudinal studies showed the persistence of nAbs up to 105 days. Similarly, nAbs (defined using snELISAs) reached a maximum from days 30 to 45. Interestingly, the sensitivities of anti-S or anti-RBD IgG in saliva were 89% and 85%, showing promise for noninvasive methods for seroepidemiological studies and vaccine trials. The sensitivities of IgA, on the other hand, were 51% and 30%, and those for IgM were 57% and 33%, respectively. It should be noted that the limited number of longitudinal studies seem to suggest that SARS-CoV-2-specific antibodies decrease over a 2- or 3-month period; however, the longevity of humoral immunity is not yet fully understood for SARS-CoV-2. It is possible that memory T cells may still be able to mount effective responses upon reexposure to SARS-CoV-2 (509, 536–538). Research into the role of cell-mediated immune responses is needed to help unravel knowledge gaps for SARS-CoV-2 immune responses (508, 509).

Overall, whether derived from vaccines or natural infection, quantitative analyses of nAbs and establishing a correlate of protection would help inform public health and health care policies. Using neutralization assays with targets outside those used in vaccines could still be of benefit to understand seroepidemiology to help better define populations at risk, which would be important for vaccine trials or evaluations of novel SARS-CoV-2-specific therapies like the use of hyper-IgG preparations or convalescent-phase sera (520, 523, 539–541). Like any other method for SARS-CoV-2 detection, serology research should consider antibody and cellular immune responses over time, have a population- and individual-level testing perspective, as well as account for factors like the presence or absence of symptoms, the timing from symptom onset (if present), the severity of illness, host factors (e.g., age and medical comorbidities), and any collection, transport, or processing steps that may affect the reliability of the analyte profiles over time. Additional research is still needed to meet these goals.

CONCLUSIONS AND OUTLOOK

Despite the recent availability of vaccines, with the ongoing and rapid spread of SARS-CoV-2 worldwide, laboratory testing remains the cornerstone of public health containment and mitigation strategies. Given the thoroughness of the data on methodologies in the body of this review, only key findings, some considerations for testing, and areas for improvement and successes are discussed below; however, a summary of testing modalities is presented in Fig. 13.

While compatible signs and symptoms, routine laboratory testing for biomarkers of health or disease, and diagnostic imaging have roles to play in diagnostic investigations,

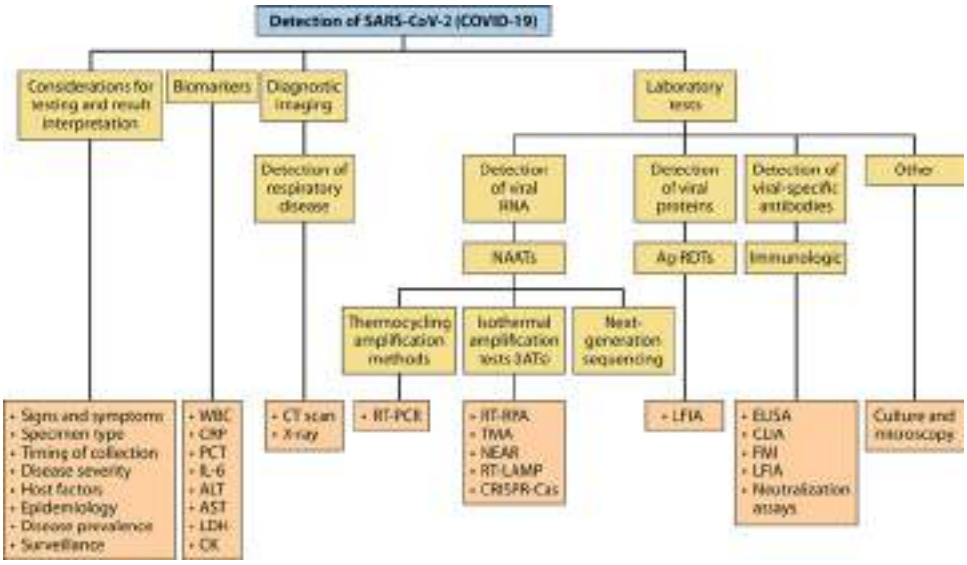

FIG 13 Methods used for SARS CoV 2 detection or identification of COVID 19. Of note, cell culture and microscopy are not used for clinical diagnosis but are used for research purposes. Abbreviations: WBC, white blood cell; CRP, C reactive protein; PCT, procalcitonin; IL 6, interleukin 6; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; NAAT, nucleic acid amplification test; RT PCR, reverse transcription PCR; TMA, transcription mediated amplification; RT LAMP, reverse transcription loop mediated isothermal amplification; RT RPA, reverse transcription recombinase polymerase amplification; CRISPR Cas, clustered regularly interspaced short palindromic repeat (CRISPR) CRISPR associated (Cas); NEAR, nicking enzyme assisted reaction; Ag RDT, antigen rapid diagnostic test; LFIA, lateral flow immunoassay; ELISA, enzyme linked immunosorbent assay; CLIA, chemiluminescence immunoassay; FMI, fluorescent microparticle immunoassay; CT scan, computed tomography scan.

none alone are sufficient for diagnosing SARS-CoV-2, and the reliance on specific laboratory testing is paramount. Many technological advances have been made to detect SARS-CoV-2, which include NAATs to detect viral RNA and immunoassays to detect viral antigens or virus-specific antibodies generated by the immune system in response to SARS-CoV-2. There is a growing list of commercially available methods for testing for SARS-CoV-2 (29, 30), and while many have been validated, the results of any test should be interpreted with consideration of the context in which they are used and based on the sum of all diagnostic evidence. When using any method to rule in or out SARS-CoV-2 infection, many factors should be considered, such as the timing and type of specimen collection, the anatomical site of sampling, the method and its expected performance characteristics, host factors like compatible signs and symptoms (versus asymptomatic testing), risk factors for serious outcomes, and disease prevalence in the population (82, 542–544).

NAATs like real-time RT-PCR quickly became the gold standard for diagnostic testing. However, apart from those listed above, other considerations for NAATs are inherent to the methodologies that are all based on the detection of SARS-CoV-2 RNA. For example, it is important to recognize that the performance of any molecular diagnostic method can be influenced by sequence mismatches between the method's targets and the different genome permutations of circulating SARS-CoV-2 lineages and variants. A possible strategy to reduce the chance of false-negative results that could occur by target mismatches is the simultaneous use of molecular methods targeting more than one gene, as failure to detect a signal in one target gene may not preclude detection in another (40, 164, 443). Alternative strategies could include the use of degenerate primers and probes, a strategy used with other RNA viruses that are prone to mutation (443, 545, 546). Ongoing molecular surveillance using sequencing technologies should also be encouraged to monitor changes in SARS-CoV-2 genome sequences and COVID-19 epidemiology, particularly with an emphasis on variants linked to

failures in diagnostic testing, with increased transmissibility, increased severity, or decreased susceptibility to convalescent-phase sera or responses to vaccines.

The primary reliance on NAATs for SARS-CoV-2 detection during the pandemic came with many challenges globally. With human resource strains and supply chain shortages, providing NAATs during the pandemic was challenged by factors such as PPE, human resource strains for sample collection and testing, swabs, and test reagent availability for NAATs. From a clinical perspective, alternatives to NP swabs traditionally used for respiratory specimens were rapidly validated, as was the use of various transport media or swab-free options that are amenable to self-collection (e.g., saliva or saline gargles). The application of these specimens in the laboratory added complexity to the laboratory workflow and required rapid validations to ensure compatibility with new or existing instrumentation.

To help meet capacity demands in the laboratory, laboratories were faced with the need to rapidly procure large quantities of supplies, acquire instrumentation, train additional personnel, and validate specimens, reagents, and equipment. Despite this, supply chain challenges and rapid escalation of testing demands led to the need for resource-sparing strategies for NAATs, including specimen pooling and extraction-free NAAT protocols. Such strategies come at the cost of a relatively reduced sensitivity, which is associated with the potential risk of missing detection of SARS-CoV-2 in specimens with low viral loads. It could be argued that small reductions in sensitivity may have little impact on the detection of most cases. Remnant SARS-CoV-2 at the outset of illness can persist for weeks and is unlikely to represent a period of communicability. On the other hand, missing detection of SARS-CoV-2 in a specimen with a low viral load at the early stages of illness may potentially lead to further virus spread. These testing strategies should be carefully considered prior to implementation.

SARS-CoV-2-specific NAATs evolved over time to facilitate testing and streamline the laboratory workflow. For example, to further streamline testing for respiratory viruses, some methods have now been multiplexed to simultaneously detect SARS-CoV-2, influenza A and B viruses, and other respiratory viruses like respiratory syncytial virus (RSV). In nonpandemic years, influenza and other viral etiologies of respiratory tract infections represented a leading cause of death in North America, particularly among hospitalized patients with community-acquired pneumonia (547–553). Interestingly, while cocirculation and coinfection with other respiratory viruses were reported, there was little activity for non-SARS-CoV-2 respiratory viruses (554). It is unclear whether public health interventions (e.g., travel restrictions, social distancing, handwashing, or PPE like masks) resulted in this decline or whether other factors inadvertently contributed to biases in data, such as fewer individuals seeking routine medical attention or the lack of testing for influenza and other respiratory viruses due to competition for resources used for SARS-CoV-2 testing (554–558). Concomitant diagnostic testing using multiplex technologies could provide an option for syndromic testing that would ensure surveillance for SARS-CoV-2 and other important respiratory viruses like influenza virus and appropriate interventions as needed (e.g., antivirals).

The public and political pressure for laboratory testing evolved with public health indications, and laboratory testing continues to guide public health policies as restrictions ease or escalate throughout the ongoing pandemic (47, 484). One area of significant advancement in NAAT methodologies includes the use of automation to minimize hands-on processing time and increase specimen throughput. With the high demand for laboratory testing, automation is an important consideration to avoid the possibility of staff repetitive-stress injuries. Over the course of the COVID-19 pandemic, the scale and demand for laboratory testing have been unmatched by other pandemics. Concerns over SARS-CoV-2 prompted the testing of both symptomatic and asymptomatic individuals, in the context of public health case contact tracing and surveillance purposes. This includes testing for SARS-CoV-2 in both health care settings where patients are at increased risk (e.g., hospitals and long-term-care facilities) and situations where testing would not otherwise have been performed (i.e., professional sports teams, public events, prior to or after travel, and various workplaces). Thus, innovative,

dynamic, and adaptable approaches were required to meet the testing demands, which are covered extensively in this review.

Other areas are recognized as being crucial to increase laboratory testing capacity but are not covered in this review, such as supply procurement, distribution, and management and the coordination of training or recruitment of increased human resources for specimen collection, testing, processing, and registration. Also, rapid validation of laboratory tests and collection devices to meet regulatory requirements despite availability through EUA from regulatory bodies as well as the development of an information technology infrastructure to continuously improve the laboratory information management system (LIMS) in the laboratory testing workflow and dissemination of near-real-time laboratory data to various stakeholders from local to national levels and dissemination to the public through various media formats are of great value. While digitization was not an absolute requirement, the interconnectivity of data ensured transparency and up-to-date information as decision support tools for recommendations, policies, and guidelines (53, 559–561). All of these have been identified by the WHO as key factors to control the COVID-19 pandemic (562).

To further enhance testing capacity and provide access for rapid SARS-CoV-2 testing options, both antigen- and NAAT-based RDTs have been developed and are now readily available (29, 30). These can support rapid laboratory and POC applications, screening of large patient populations, or rapid deployment for assessments of target areas. NAAT-based RDTs rely on real-time RT-PCR or isothermal amplification methods (e.g., RT-RPA, RT-LAMP, and NEAR) and, like antigen-based RDTs, can provide rapid results without complex instrumentation. The ease of use of these portable devices allows access to SARS-CoV-2 diagnostics in settings that may have been prohibitive for traditional laboratory NAATs. Throughout the literature, the main limitation noted for RDTs is their reduced sensitivity compared to traditional NAATs, but the evaluations of their performance do not always reflect conditions in which the RDT was licensed under EUA, and the comparator method and distribution of expected specimen results can have a large impact on assay performance (274, 290, 341, 342, 457). Even if these issues are not considered, and all SARS-CoV-2 detection results were considered of value, a possible strategy to mitigate the relatively reduced sensitivity of antigen- or NAAT-based RDTs is to increase the frequency of testing in the patient population over time, to increase the chances of identifying individuals who fall in a period of high viral shedding (which would be less likely to be impacted by reduced sensitivity) (288, 299, 301, 467, 468). On the other hand, the implementation of such strategies has challenges of its own due to the limited scalability of RDTs, and the balance between sensitivity and testing frequency to achieve optimal SARS-CoV-2 detection in the target population would need to be defined (288). Moreover, if, for example, EUA defined the use of RDTs as within 7 days of symptom onset, this excluded their use for testing of asymptomatic individuals. While much development is ongoing to enhance existing RDT technologies or explore novel methodologies (53, 465, 466, 563–565), how RDTs can effectively be used in practice is the subject of ongoing debate, and further research is needed to understand what setting they would best be of benefit.

For serology, currently available commercial assays are based on ELISAs, CLIAs, and LFIAs and are designed to detect SARS-CoV-2 antibodies. However, the performance of serological assays varies across the different technologies, the timing from disease onset, and comparator methods. Clinical validation of serological methods is ongoing, but recent meta-analyses and systematic reviews so far have shown high levels of heterogeneity and a risk of bias and applicability (472, 502, 503). For example, with the time required to mount anti-SARS-CoV-2 antibodies during seroconversion (or possibly the absence of seroconversion in mild disease), serology has limited value in identifying SARS-CoV-2 in the early stages of illness. Serology has value for seroepidemiological studies to help with ongoing outbreak investigations, can aid in the diagnosis of suspect cases for whom NAATs were persistently negative or not performed, or can help with conditions in children and adolescents like multisystem inflammatory

syndrome where NAAT results may be negative (102, 133, 241, 566–570). Much research is needed to expand the knowledge on the use of immunological methods, particularly in the context of the recent availability of vaccines.

Key areas of research interest for serology should include the relevance, magnitude, and duration of protective antibody responses, particularly faced with a population that may have been exposed to SARS-CoV-2 or other human coronaviruses or vaccinated against SARS-CoV-2. Detection of different antibody isotypes is possible with commercial or laboratory-developed serological assays, and recent quantitative methods have now become commercially available; however, much is yet to be learned on how these methods correlate with protective immune responses. Establishing correlates of protection will require longitudinal studies with parallel assessments of quantitative levels of nAbs and cell-mediated immune responses. Various neutralization assays have been established to assess and quantify antibodies against SARS-CoV-2 in serum or plasma (e.g., PRNTs, MN tests, or surrogate assays like PBNAs and snELISAs), but data are scarce when it comes to longitudinal studies undertaken to fully understand the differences or similarities between commercial assays for the qualitative detection of antibodies, quantitative antibody analyses over time, and relevance to the level and duration of protective nAb titers. While the longevity of humoral immunity is not yet fully understood for SARS-CoV-2, some data suggest that antibody levels against SARS-CoV-2 wane over 3 months. Notwithstanding these observations, it is possible that memory T cells may still be able to mount effective responses upon reexposure to SARS-CoV-2, and the role of cell-mediated immune responses may also provide additional benefits (508, 509). Further research is needed, as a greater understanding of the immune response to SARS-CoV-2 is fundamental in making informed recommendations for the use of immunological methods to assess current or future protection against the virus, to determine meaningful endpoints in the development and evaluation of effective vaccines, or to assess effectiveness following immunization with existing vaccines.

Overall, methods based on RNA, antigen, or antibody detection as well as diagnostic imaging all have a place in our response to SARS-CoV-2, but ongoing research is crucial to further optimize and apply all these testing modalities. The emergence of the SARS-CoV-2 pandemic has created a wave of innovative and creative thinking, and more and more creative methods and platforms are being introduced with goals to increase the armamentarium of diagnostic methods for SARS-CoV-2 detection. An understanding of the advantages and limitations of each method used for SARS-CoV-2 detection as well as the development of novel methods will help us unravel the unknowns of disease pathogenesis, epidemiology, and transmissibility and help us develop interventions to mitigate and contain its spread. There will always be a need for laboratory testing and collaboration between clinical laboratories, public health, infection prevention and control, and many others who contribute to the efforts to contain the spread of COVID-19. On the other hand, it is also recognized that maintaining large investments in the rapid deployment of translational research and such a high degree of laboratory testing for COVID-19 will likely not be sustainable from an economic perspective, and justifications for such investments will be more difficult if cases decline significantly with vaccines. However, the lessons learned from SARS-CoV-2 could potentially be used in the preparedness for potential future pandemic threats, thus strengthening global health and surveillance systems.

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Seyed Hamid Safiabadi Tali is a Ph.D. candidate in the Anbuhi Research Group in the Chemical and Materials Engineering Department at Concordia University, which he joined in June 2019. He obtained his B.Sc. and M.Sc. in chemical engineering with a specialty in biotechnology from the University of Tehran, Iran, in 2015 and 2018, respectively. His main area of research is the development of low cost and portable sensor and biosensor devices for the detection of pathogens and biomarkers for different applications, from food and environmental monitoring to disease diagnostics.

Zubi Sadiq, Ph.D., is a researcher at Concordia University, Canada, and is interested in the detection of pathogens in food, water, and the environment. She has received her B.S. (Hons) and Ph.D. in Chemistry from Lahore College for Women University, Pakistan. She received a gold medal and academic roll of honor in her M.S. studies. She served as lecturer at the Preparatory Year Deanship, King Faisal University, Saudi Arabia. Her area of expertise also includes the development of sustainable protocols for heterocyclic molecules and evaluation of different bioactivities against infectious microbes.

Jason J. LeBlanc, Ph.D., FCCM, d(ABMM), is a Professor in the Department of Pathology, Faculty of Medicine, at Dalhousie University, with cross appointments in Medicine (infectious diseases) and the Department of Microbiology and Immunology in the same institution. He is the Director of Virology, Immunology, and Molecular Microbiology in the Division of Microbiology, Department of Pathology and Laboratory Medicine, Nova Scotia Health, Halifax, Nova Scotia, Canada, and holds credentials as a Fellow of the Canadian College of Microbiologists (FCCM) and Diplomat of the American Board of Medical Microbiologists [d(ABMM)]. Dr. LeBlanc has a long standing research interest in molecular diagnostics, molecular epidemiology, and molecular pathogenesis, with application to the fields of vaccine preventable diseases and emerging respiratory pathogens like SARS CoV 2.

Oyejide Damilola Oyewunmi obtained his B.Sc. in Chemical Engineering at the University of Lagos, Nigeria. He is currently a graduate student at the Department of Chemical and Materials Engineering at Concordia University, Montreal, Canada. His primary research field is the investigation into paper based sensors and biosensors for environmental monitoring and biological diagnostics at the Anbuhi Research Group.

Carolina Camargo, Ph.D., is a postdoctoral fellow in the Sagan laboratory in the Department of Microbiology and Immunology at McGill University. Dr. Camargo received her Ph.D. from the University of Missouri Columbia. Dr. Camargo has been working in virology since her graduate studies using pseudoviruses to study different envelope glycoproteins such as those of HIV, Ebola virus, and Marburg virus. Currently, she is working on negative strand RNA viruses, mainly focusing on respiratory syncytial virus.

Bahareh Nikpour received her B.Sc. and M.Sc. in Electrical and Computer Engineering from Shahid Bahonar University of Kerman in 2010 and 2016, respectively. She is currently a Ph.D. student at the Department of Electrical and Computer Engineering, McGill University, Montreal, Canada. Her current research interests include machine learning, reinforce ment learning, and their applications.

Narges Armanfard received her Ph.D. in Electrical and Computer Engineering from McMaster University, Hamilton, ON, Canada, in 2016. She completed her postdoctoral studies at the University of Toronto in 2018. She is currently an Assistant Professor at the Department of Electrical and Computer Engineering, McGill University, and Mila Quebec AI Institute, Montreal, QC, Canada. She performs fundamental and applied research in machine learning.

Selena M. Sagan, Ph.D., is an Associate Professor in the Department of Microbiology and Immunology and the Department of Biochemistry, McGill University. Dr. Sagan received her Ph.D. from the University of Ottawa and completed her postdoctoral fellowship training in the Department of Microbiology and Immunology at Stanford University. Dr. Sagan is a Canada Research Chair in RNA Biology and Viral Infections, and her laboratory studies positive strand RNA viruses of the *Flaviviridae* family (including hepatitis C virus, dengue virus, Zika virus, and coronaviruses) as well as negative strand RNA viruses (including respiratory syncytial virus). The main focus of her research program is RNA RNA and protein RNA interactions at the host virus interface.

Sana Jahanshahi-Anbuhi, Ph.D., is currently an Assistant Professor in the Chemical and Materials Engineering Department at Concordia University, which she joined in summer 2018. She earned her Ph.D. in 2015, after which she stayed on at McMaster University and continued her research as a postdoctoral research fellow until joining Concordia University. Her primary field of research focuses on developing diagnostic tools, bioactive analytical devices, microfluidic chips, and paper based sensors for the detection of biomarkers, point of care testing, and environmental monitoring. She has been the principal investigator of many research projects on thermal stabilization of viral vaccines as well as the development of ultrastable and low cost biosensors and monitoring tools.

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The Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19: Molecular Diagnostic Testing

Authors

Kimberly E. Hanson,[1] Angela M. Caliendo,[2] Cesar A. Arias,[3] Mary K. Hayden,[4] Janet A. Englund,[5] Mark J. Lee,[6] Mark Loeb,[7] Robin Patel,[8] Abdallah El Alayli,[9] Osama Altayar,[10] Payal Patel,[11] Yngve Falck-Ytter,[12] Valery Lavergne,[13] Rebecca L. Morgan,[14] M. Hassan Murad,[15] Shahnaz Sultan,[16] Adarsh Bhimraj,[17] Reem A. Mustafa[18]

Affiliations

[1]Department of Internal Medicine and Pathology, University of Utah, Salt Lake City, Utah

[2]Department of Medicine, Warren Alpert Medical School of Brown University, Providence, Rhode Island

[3]Division of Infectious Diseases, Center for Antimicrobial Resistance and Microbial Genomics, University of Texas Health McGovern Medical School, Center for Infectious Diseases, University of Texas Health School of Public Health, Houston, TX

[4]Division of Infectious Diseases, Department of Medicine, Rush University Medical Center, Chicago, Illinois; Department of Pathology, Rush University Medical Center, Chicago, Illinois

[5]Department of Pediatrics, University of Washington, Seattle Children's Research Institute, Seattle, Washington

[6]Department of Pathology and Clinical Microbiology Laboratory, Duke University School of Medicine, Durham, North Carolina

[7]Divinsion of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario

[8]Division of Clinical Microbiology, Mayo Clinic, Rochester, Minnesota

[9]Outcomes and Implementation Research Unit, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, Kansas

[10]Department of Medicine, Washington University School of Medicine, St. Louis, Missouri.

[11]Department of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Department of Medicine, Emory University, Atlanta, Georgia

[12]VA Northeast Ohio Healthcare System, Case Western Reserve University School of Medicine, Cleveland, Ohio

[13]Department of Pathology and Laboratory Medicine, Vancouver General Hospital, Vancouver, British Columbia, Canada

[14]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario

[15]Division of Preventive Medicine, Mayo Clinic, Rochester, Minnesota

[16]Division of Gastroenterology, Hepatology, and Nutrition, University of Minnesota, Minneapolis VA Healthcare System, Minneapolis, Minnesota

[17]Department of Infectious Diseases, Cleveland Clinic, Cleveland, Ohio

[18]Division of Nephrology and Hypertension, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, Kansas

Corresponding Author: Kimberly E. Hanson

Panel Members: Kimberly E. Hanson (lead), Angela M. Caliendo, Cesar A. Arias, Mary K. Hayden, Janet A. Englund (PIDS representative), Mark J. Lee, Mark Loeb (SHEA representative), Robin Patel (ASM representative), Adarsh Bhimraj

Methodologists: Reem A. Mustafa (lead), Abdallah El Alayli, Osama Altayar, Payal Patel, Yngve Falck-Ytter, Valery Lavergne, Rebecca L. Morgan, M. Hassan Murad, Shahnaz Sultan

Abstract

Background: Accurate molecular diagnostic tests are necessary for confirming a diagnosis of coronavirus disease 2019 (COVID-19). Direct detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleic acids in respiratory tract specimens informs patient, healthcare institution and public health level decision-making. The numbers of available SARS-CoV-2 nucleic acid detection tests are rapidly increasing, as is the COVID-19 diagnostic literature. Thus, the Infectious Diseases Society of America (IDSA) recognized a significant need for frequently updated systematic reviews of the literature to inform evidence-based best practice guidance.

Objective: The IDSA's goal was to develop an evidence-based diagnostic guideline to assist clinicians, clinical laboratorians, patients and policymakers in decisions related to the optimal use of SARS-CoV-2 nucleic acid amplification tests. In addition, we provide a conceptual framework for understanding molecular diagnostic test performance, discuss the nuance of test result interpretation in a variety of practice settings and highlight important unmet research needs in the COVID-19 diagnostic testing space.

Methods: IDSA convened a multidisciplinary panel of infectious diseases clinicians, clinical microbiologists, and experts in systematic literature review to identify and prioritize clinical questions and outcomes related to the use of SARS-CoV-2 molecular diagnostics. Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to assess the certainty of evidence and make testing recommendations.

Results: The panel agreed on 17 diagnostic recommendations.

Conclusions: Universal access to accurate SARS-CoV-2 nucleic acid testing is critical for patient care, hospital infection prevention and the public response to the COVID-19 pandemic. Information on the clinical performance of available tests is rapidly emerging, but the quality of evidence of the current literature is considered moderate to very low. Recognizing these limitations, the IDSA panel weighed available diagnostic evidence and recommends nucleic acid testing for all symptomatic individuals suspected of having COVID-19. In addition, testing is recommended for asymptomatic individuals with known or suspected contact with a COVID-19 case. Testing asymptomatic individuals without known exposure is suggested when the results will impact isolation/quarantine/personal protective equipment (PPE) usage decisions, dictate eligibility for surgery, or inform solid organ or hematopoietic stem cell transplantation timing. Ultimately, prioritization of testing will depend on institutional-specific resources and the needs of different patient populations.

IDSA Disclaimer

It is important to realize that guidelines cannot always account for individual variation among patients. They are assessments of current scientific and clinical information provided as an educational service; are not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is developed and when it is published or read); should not be considered inclusive of all proper treatments methods of care, or as a statement of the standard of care; do not mandate any particular course of medical care; and are not intended to supplant physician judgment with respect to particular patients or special clinical situations. Whether and the extent to which to follow guidelines is voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances. While IDSA makes every effort to present accurate, complete, and reliable information, these guidelines are presented "as is" without any warranty, either express or implied. IDSA (and its officers, directors, members, employees, and agents) assume no responsibility for any loss, damage, or claim with respect to

any liabilities, including direct, special, indirect, or consequential damages, incurred in connection with these guidelines or reliance on the information presented.

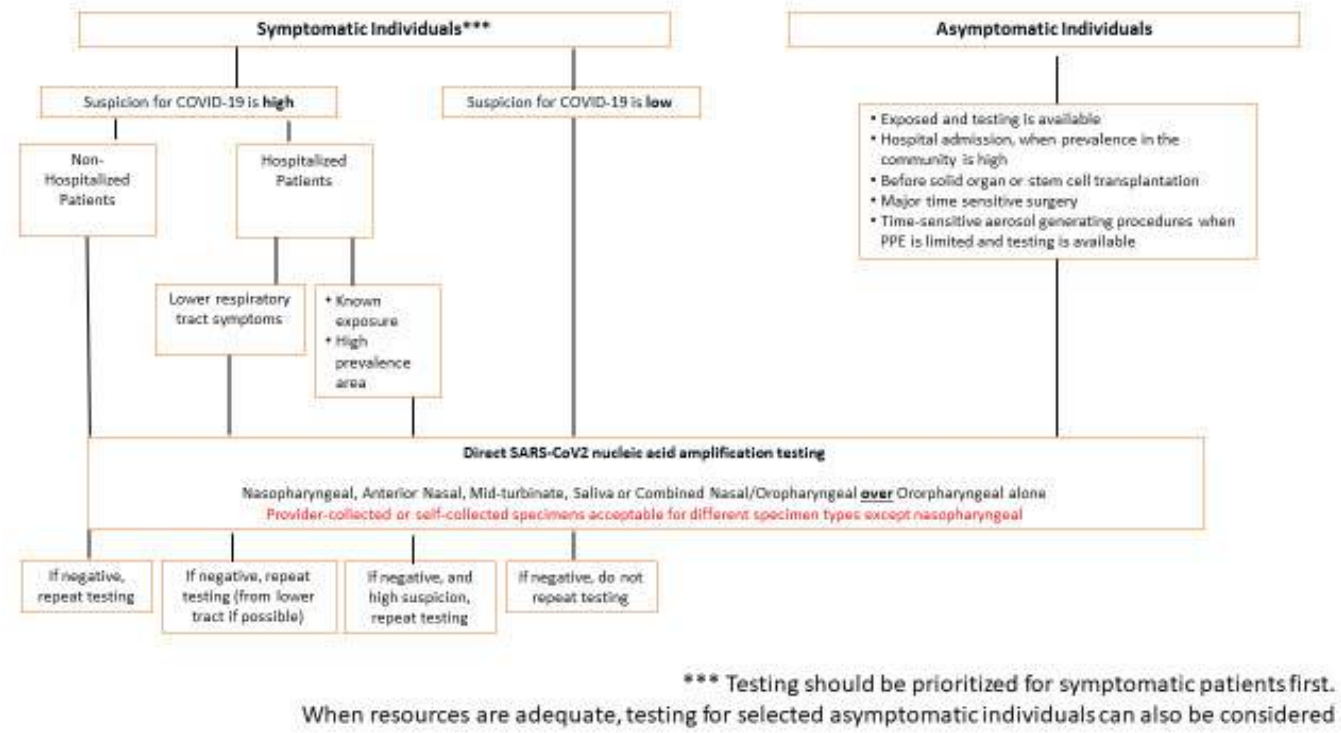
Executive Summary

Molecular diagnostic testing has played a critical role in the global response to the COVID-19 pandemic. Accurate SARS-CoV-2 nucleic acid amplification tests (NAATs) are needed to inform patient management decisions, hospital infection prevention practices, and public health responses. Additionally, detection and quantification of SARS-CoV-2 RNA over the course of infection is also essential for understanding biology of disease. Given the rapid expansion of the COVID-19 molecular diagnostic literature along with increasing test availability, the IDSA recognized the need for frequently updated, evidence-based guidelines to support clinicians, clinical microbiologists, patients and policy makers in decisions related to the use of SARS-CoV-2 diagnostics.

Summarized below are 17 recommendations for SARS-CoV-2 nucleic acid testing based on systematic reviews of the diagnostic literature. An algorithm based on these recommendations is provided as well to aid in decision-making (see **Figure 1**). Primary recommendations assumed availability of diagnostic tests and specimen collection devices. Contingency recommendations were crafted for situations where testing supplies or personal protective equipment (PPE) are limited. Based on reviews of baseline risk, assumptions were made about COVID-19 disease prevalence in the community and/or pretest probabilities in individual patients, both of which influenced testing recommendations.

A detailed description of background, methods, evidence summary and rationale that support each recommendation, and research needs can be found online in the full text. Briefly, an expert panel consisting of clinicians, medical microbiologists, and methodologists critically appraised the COVID-19 diagnostic literature using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to assess the certainty of evidence. Per GRADE, recommendations are categorized as “strong” or “conditional.” The word “recommend” indicates strong recommendations and “suggest” implies conditional recommendations.

Figure 1. IDSA Algorithm for SARS-CoV-2 Nucleic Acid Testing



Recommendation 1: The IDSA panel recommends a SARS-CoV-2 NAAT in symptomatic individuals in the community suspected of having COVID-19, even when the clinical suspicion for COVID-19 is low *(strong recommendation, very low certainty of evidence)*.

- **Remarks**:
  - The panel considered symptomatic patients to have at least one of the most common symptoms compatible with COVID-19 (**Table 1**).
  - Clinical assessment alone is not accurate in predicting COVID-19 diagnosis.
  - The panel considered timeliness of SARS-CoV-2 NAAT results essential to impact individual care, healthcare institution, and public health decisions. In the outpatient setting, results within 48 hours of collection is preferable.

Recommendation 2: The IDSA panel suggests collecting a nasopharyngeal swab, mid-turbinate swab, anterior nasal swab, saliva or a combined anterior nasal/oropharyngeal swab rather than

an oropharyngeal swab alone for SARS-CoV-2 RNA testing in symptomatic individuals suspected of having COVID-19 *(conditional recommendation, very low certainty of evidence)*.

- **Remark**: The panel considered symptomatic patients to have at least one of the most common symptoms compatible with COVID-19 (**Table 1**)

Recommendation 3: The IDSA panel suggests that anterior nasal and mid-turbinate (MT) swab specimens may be collected for SARS-CoV-2 RNA testing by either patients or healthcare providers, in symptomatic individuals with upper respiratory tract infection (URTI) or influenza-like illness suspected of having COVID-19 *(conditional recommendation, low certainty of evidence)*.

- **Remarks:**
  - Appropriate specimen collection and transport to the laboratory is critical. General instructions for swab-based SARS-CoV-2 testing are shown in **Table 3**. Additional resources are available on the IDSA website.
  - A clear, step-by-step protocol needs to be presented to patients attempting self-collection. This could be in the form of a short video or printed pamphlet with illustrations.
  - The majority of self-collection studies were performed in the presence of a healthcare worker.
  - The available evidence for nasal and MT swabs as alternatives to healthcare personnel collection is based on assessment of symptomatic patients. Data on self-collection in asymptomatic individuals is currently unavailable.
  - The panel considered symptomatic patients to have at least one of the most common symptoms compatible with COVID-19 (**Table 1**).

Recommendation 4: The IDSA panel suggests a strategy of initially obtaining an upper respiratory tract sample (e.g., nasopharyngeal swab) rather than a lower respiratory sample for SARS-CoV-2 RNA testing in hospitalized patients with suspected COVID-19 lower respiratory

tract infection. If the initial upper respiratory sample result is negative, and the suspicion for disease remains high, the IDSA panel suggests collecting a lower respiratory tract sample (e.g., sputum, bronchoalveolar lavage fluid, tracheal aspirate) rather than collecting another upper respiratory sample *(conditional recommendations, very low certainty of evidence)*.

- **Remark**: The panel considered timeliness of SARS-CoV-2 NAAT results essential to impact individual care and isolation decisions. In the hospital setting, results within 24 hours of collection is preferable.

Recommendation 5: The IDSA panel suggests performing a single viral RNA test and not repeating testing in symptomatic individuals with a low clinical suspicion of COVID-19 *(conditional recommendation, low certainty of evidence)*.

- **Remarks**:
  - A low clinical suspicion should be informed by epidemiological information available for the region coupled with clinical judgment.
  - The panel considered symptomatic patients to have at least one of the most common symptoms compatible with COVID-19 (**Table 1**).

Recommendation 6: The IDSA panel suggests repeating viral RNA testing when the initial test is negative (*versus* performing a single test) in symptomatic individuals with an intermediate or high clinical suspicion of COVID-19 *(conditional recommendation, low certainty of evidence)*.

- **Remarks**:
  - Intermediate/high clinical suspicion typically applies to the hospital setting and is based on the severity, numbers and timing of compatible clinical signs/symptoms.
  - Repeat testing should generally occur 24-48 hours after initial testing and once the initial NAAT result has returned as negative.
  - Another specimen type, preferably a lower respiratory tract specimen if the patient has signs/symptoms of LRTI, should be considered for repeat testing.

- The panel considered symptomatic patients to have at least one of the most common symptoms compatible with COVID-19 (**Table 1**).

Recommendation 7: The IDSA panel suggests using either rapid RT-PCR or standard laboratory-based NAATs over rapid isothermal NAATs in symptomatic individuals suspected of having COVID-19 *(conditional recommendation, low certainty of evidence).*

- **Remarks**:
  - Rapid NAAT was defined as assays generating results in approximately one hour or less of instrument run time (inclusive of nucleic acid extraction).
  - This recommendation only applies to the tests evaluated in the included studies (**Table s4f**).
  - Standard laboratory-based NAAT methods evaluated included RT-PCR and transcription mediated amplification (TMA).
  - Studies of rapid isothermal NAAT primarily used the Abbott ID NOW test
  - Rapid isothermal NAAT is an acceptable testing option when rapid RT-PCR or standard laboratory-based NAAT is not readily available.
  - A negative rapid isothermal test result from an individual with a high clinical suspicion for SARS-CoV-2 infection, or anyone in a moderate (10%) or high prevalence (40%) population, should be confirmed by standard NAAT or a rapid RT-PCR test when testing is available and the results will affect patient management.

Recommendation 8: The IDSA panel suggests SARS-CoV-2 RNA testing in asymptomatic individuals who are either known or suspected to have been exposed to COVID-19 *(conditional recommendation, very low certainty of evidence)*.

- **Remarks**:
  - Known exposure was defined as direct contact with a laboratory confirmed case of COVID-19.

- Suspected exposure was defined as working or residing in a congregate setting (e.g., long-term care, correctional facility, cruise ship, factory, among others) experiencing a COVID-19 outbreak.
- The risk of contracting SARS-CoV-2 may vary under different exposure conditions.
- This recommendation assumes the exposed individual was not wearing appropriate PPE.
- The decision to test asymptomatic patients will be dependent on the availability of testing resources.

Recommendation 9: The IDSA panel suggests against SARS-CoV-2 RNA testing in asymptomatic individuals with no known contact with COVID-19 who are being hospitalized in areas with a low prevalence of COVID-19 in the community (conditional recommendation, very low certainty of evidence).

- **Remarks**:
  - Asymptomatic individuals are defined as those with no symptoms or signs of COVID-19.
  - A low prevalence of COVID-19 in the community was considered communities with a prevalence of <2%.
  - This recommendation does not apply to immunocompromised individuals.
  - This recommendation does not apply to individuals undergoing time-sensitive major surgery or aerosol generating procedures.

Recommendation 10: The IDSA panel suggests direct SARS-CoV-2 RNA testing in asymptomatic individuals with no known contact with COVID-19 who are being hospitalized in areas with a high prevalence of COVID-19 in the community (i.e., hotspots) *(conditional recommendation, very low certainty of evidence)*.

- **Remarks**:

- Asymptomatic individuals are defined as those with no symptoms or signs of COVID-19.
- A high prevalence of COVID-19 in the community was considered communities with a prevalence of ³10%.
- The decision to test asymptomatic patients (including when the prevalence is between 2 and 9%) will be dependent on the availability of testing resources.

Recommendation 11: The IDSA panel recommends for SARS-CoV-2 RNA testing in immunocompromised asymptomatic individuals who are being admitted to the hospital regardless of exposure to COVID-19 *(strong recommendation, very low certainty of evidence)*.

- **Remark**: This recommendation defines immunosuppressive procedures as cytotoxic chemotherapy, solid organ or stem cell transplantation, biologic therapy, cellular immunotherapy, or high-dose corticosteroids.

Recommendation 12: The IDSA panel recommends SARS-CoV-2 RNA testing (*versus* no testing) in asymptomatic individuals before hematopoietic stem cell (HSCT) or solid organ transplantation (SOT) regardless of a known exposure to COVID-19 *(strong recommendation, very low certainty of evidence)*.

- **Remark:** Testing should ideally be performed as close to the planned treatment/procedure as possible (e.g., within 48-72 hours).

Recommendation 13: The IDSA panel makes no recommendations for or against SARS-CoV-2 RNA testing before initiating immunosuppressive therapy in asymptomatic individuals with cancer *(evidence gap)*.

- **Remarks**:
  - The decision to pursue testing should be individualized. Factors to consider include the type of cancer, the need for induction *versus* maintenance immunosuppressive

therapy, the type of immunosuppressive therapy, patient comorbidities and the availability of testing.

- This recommendation does not apply to hematopoietic stem cell transplant candidates or recipients.

Recommendation 14: The IDSA panel makes no recommendations for or against SARS-CoV-2 RNA testing before the initiation of immunosuppressive therapy in asymptomatic individuals with autoimmune disease *(evidence gap)*.

- **Remark**: The decision to pursue testing should be individualized. Factors that may affect the decision to test include the type and severity of autoimmune disease, the type of immunosuppressive therapy, the need for induction *versus* maintenance immunosuppressive therapy, patient comorbidities and the feasibility of testing.

Recommendation 15: The IDSA panel suggests SARS-CoV-2 RNA testing in asymptomatic individuals (without known exposure to COVID-19) who are undergoing major time-sensitive surgeries *(conditional recommendation, very low certainty of evidence)*.

- **Remarks**:
  - The panel defined time-sensitive surgery as medically necessary surgeries that need to be done within three months**.**
  - Testing should ideally be performed as close to the planned surgery as possible (e.g., within 48-72 hours).
  - To limit potential poor outcomes, deferring non-emergent surgeries should be considered for patients testing positive for SARS-CoV-2.
  - Decisions about PPE use for the aerosol generating portions of these procedures may be dependent on test results when there is limited availability of PPE. However, there is a risk for false negative test results, so caution should be exercised by those who will be in close contact with/exposed to the upper respiratory tract (e.g., anesthesia personnel, ENT procedures).

- The decision to test asymptomatic patients will be dependent on the availability of testing resources.
- This recommendation does not address the need for repeat testing if patients are required to undergo multiple surgeries over time.

Recommendation 16: The IDSA panel suggests against SARS-CoV-2 RNA testing in asymptomatic individuals without a known exposure to COVID-19 who are undergoing a time-sensitive aerosol generating procedure (e.g., bronchoscopy) when PPE is available *(conditional recommendation, very low certainty of evidence)*.

- **Remarks**:
  - The panel defined time-sensitive procedures as medically necessary procedures that need to be done within three months**.**
  - Procedures considered to be aerosol-generating are listed in **Table 11**.

Recommendation 17: The IDSA panel suggests SARS-CoV-2 RNA testing in asymptomatic individuals without a known exposure to COVID-19 who are undergoing a time-sensitive aerosol generating procedure (e.g., bronchoscopy) when PPE is limited, and testing is available *(conditional recommendation, very low certainty of evidence)*.

- **Remarks**:
  - The panel defined time-sensitive procedures as medically necessary procedures that need to be done within three months**.**
  - Testing should be performed as close to the planned procedure as possible (e.g., within 48-72 hours).
  - Decisions about PPE will be dependent on test results because of limited availability of PPE. However, there is a risk for false negative test results, so caution should be exercised for those who will be in close contact with/exposed to the patient's airways.
  - Procedures considered to be aerosol-generating are listed in **Table 11**.

- The decision to test asymptomatic patients will be dependent on the availability of testing resources.
- This recommendation does not address the need for repeat testing if patients are required to undergo multiple procedures over time.

Background

In late December 2019, an outbreak of pneumonia cases of unclear etiology was reported in Wuhan City, Hubei Province, China [1]. Unbiased next generation sequencing (NGS) using lower respiratory tract (LRT) specimens collected from affected patients subsequently identified a novel coronavirus as the cause of illness now known as Coronavirus Disease 2019 (COVID-19). The entire viral genome was shared online within days and phylogenetic analyses established close relationship to human severe acute respiratory syndrome coronavirus (SARS-CoV) as well as several other SARS-like bat coronaviruses [1, 2]. Based on genetic similarities, the novel coronavirus was officially named SARS-CoV-2 [3]. By March 11th, 2020, the virus had spread to at least 114 countries and killed more than 4,000 people, prompting the World Health Organization (WHO) to officially declare a global pandemic [4].

Public availability of the SARS-CoV-2 genome was an essential first step enabling development of accurate molecular diagnostic assays. Nucleic acid amplification tests designed to detect one or more gene sequences specific to SARS-CoV-2 are essential for confirming COVID-19 diagnoses. On February 4, 2020, the United States (U.S.) Secretary of Health and Human Services announced that circumstances existed justifying authorization of the emergency use of SARS-CoV-2 molecular tests. This declaration meant that commercial manufacturers and clinical laboratories were required to submit details about their SARS-CoV-2 assays to the U.S. Food and Drug Administration (FDA) for review and emergency use authorization (EUA).

To date, multiple commercial test manufacturers and clinical laboratories, including academic medical centers, have received EUA for a SARS-CoV-2-specific molecular diagnostic test. The first home-based test collection kit was also recently granted an EUA [5]. It is important to recognize, however, that EUA guidance differs substantially from the standard FDA approval process. In the setting of a public health emergency, the FDA only requires test developers to establish acceptable analytical accuracy. Clinical test performance (i.e., sensitivity and specificity) has yet to be determined or comprehensively compared across EUA platforms. As a result, most of the NAAT performance data used to inform this guideline was derived from

studies evaluating assays not widely used in the U.S. We assumed, therefore, that performance of standard NAAT methods to be comparable across countries (which may or may not be correct).

Given increasing test availability combined with a rapidly growing number of NAAT-focused studies published online or in academic journals, the Infectious Diseases Society of America (IDSA) formed a multidisciplinary panel to critically appraise the existing literature and develop evidence-based diagnostic test recommendations. The panel identified and prioritized practical diagnostic questions pertaining to symptomatic patients and asymptomatic individuals to drive the literature review. The symptoms considered compatible with COVID-19 are listed in **Table 1**.

It is anticipated that these guidelines will continue to be updated as substantive new information becomes available.

Table 1. Symptoms Compatible with COVID-19 [1,2]

Symptoms may appear **2-14 days after exposure to the virus.** People with these symptoms or combinations of symptoms may have COVID-19*	Most common symptoms* • Cough • Shortness of breath or difficulty breathing • Fever Additional reported symptoms • Chills • Fatigue • Muscle pain • Headache • Sore throat • New loss of taste or smell • Congestion or runny nose • Nausea or vomiting • Diarrhea

*This list is not all inclusive. Fever, cough or shortness of breath were the most common symptoms reported among a convenience sample of U.S. COVID-19 patients

References

1. Centers for Disease Control and Prevention. Symptoms of Coronavirus. Available at: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. Accessed 3 May 2020.
2. Burke RM, Killerby ME, Newton S, et al. Symptom Profiles of a Convenience Sample of Patients with COVID-19 — United States, January–April 2020. Morbidity and Mortality Weekly Report - CDC **2020**; 69(28): 904-8.

Methods

The guideline was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for evidence assessment. In addition, given the need for rapid response to an urgent public health crisis, the methodological approach was modified according to the Guidelines International Network/McMaster checklist for development of rapid recommendations [6]. This guideline serves as an update to the original IDSA Guidelines on the Diagnosis of COVID-19 [7], and focuses on the performance of different specimen types for the detection of SARS-CoV-2 RNA (recommendation 2), the accuracy of rapid versus standard laboratory-based nucleic acid amplification tests (recommendation 7) as well as molecular diagnostic testing before immunosuppressive therapy in selected groups of patients (recommendations 12, 13 and 14).

Panel Composition

The panel was composed of eight members including frontline clinicians, infectious diseases specialists, and clinical microbiologists who were members of IDSA, American Society for Microbiology (ASM), Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS). They represented the disciplines of adult and pediatric infectious diseases, medical microbiology, as well as nephrology and gastroenterology. The Evidence Foundation provided technical support and guideline methodologists for the development of this guideline.

Disclosure and Management of Potential Conflict of Interest (COI)

The conflict of interest (COI) review group included two representatives from IDSA who were responsible for reviewing, evaluating and approving all disclosures. All members of the

expert panel complied with the COI process for reviewing and managing conflicts of interest, which required disclosure of any financial, intellectual, or other interest that might be construed as constituting an actual, potential, or apparent conflict, regardless of relevancy to the guideline topic. The assessment of disclosed relationships for possible COI was based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The COI review group ensured that the majority of the panel and chair was without potential relevant (related to the topic) conflicts. The chair and all members of the technical team were determined to be unconflicted.

Question Generation

For the original guideline, clinical questions were developed into a Population, Intervention, Comparison, Outcomes (PICO) format [8] prior to the first panel meeting (**Table s1**). IDSA panel members prioritized questions with available evidence that met the minimum acceptable criteria (i.e., the body of evidence reported on at least test accuracy results can be applied to the population of interest). Panel members prioritized patient-oriented outcomes related to SARS-CoV-2 testing such as requirement for self-quarantine, eligibility for investigational COVID-19 treatment, timing of elective surgery or procedures, and management of immunosuppressive therapy. We also considered the impact of SARS-CoV-2 results on infection prevention and public health practices, including the use of personal protective equipment (PPE) and contact tracing. In this update, the panel focused on the questions addressing rapid tests and different sample types for the diagnosis of COVID-19 as well as testing before immunosuppressive therapy for the treatment of cancer or autoimmune disease.

Search Strategy

The National Institute of Health and Care Excellence (NICE) and the Center for Disease Control and Prevention (CDC) highly sensitive search was reviewed by the methodologist in

consultation with the technical team information specialist and was determined to have high sensitivity. An additional term, COVID, was added to the search strategy used in addition to the terms identified in the PICO questions (**Table s2**). Ovid Medline and Embase databases were searched for studies from 2019 through October 3, 2020. Horizon scans were performed during the evidence assessment and recommendation process to locate additional grey literature, manuscript preprints, and published literature from 2019 to August 20, 2020 from the following sources: LitCovid, medRxiv, SSRN, and Trip databases. The preprints were followed for final publication. In this update, the panel decided not to include studies that are solely published in preprint format due to the sufficient number of published studies identified. Reference lists and literature suggested by panelists were reviewed for inclusion. No restrictions were placed on language or study type.

Screening and Study Selection

Two reviewers independently screened titles and abstracts, as well as eligible full-text studies. We included studies reporting data on diagnostic test accuracy (cohort studies, cross sectional studies and case-control studies). When questions compared the performance of different tests (e.g., different testing or sampling methods) or testing strategies, we included studies that provided direct test accuracy data about all tests in the same population, referred to as direct comparative test accuracy studies. For this analysis, studies were excluded if all patients did not receive all tests. When these direct studies where lacking, we included studies that assessed a single test and compared its results to a reference standard. We did not limit our inclusion to a specific reference standard due to sparsity of data. We also included studies that assessed the prevalence of COVID-19 in different populations. Reviewers extracted relevant information into a standardized data extraction form.

Exclusion criteria for studies that assessed rapid testing were studies evaluating an index test that was not a rapid molecular test (sample to result was >1 hour turnaround time), studies focused on a specific population rather than general diagnostic data (i.e., focused on test accuracy in patients with specific cycle thresholds), studies with incomplete test accuracy information (i.e., reported sensitivity without specificity), and studies where the endpoint of

the rapid test was based on visual inspection of result. Patients that were known COVID-19 positive but were tested in the recovery phase of illness and patients with invalid or inconclusive results were also excluded from the analysis. In addition, patients were presumed positive if an assay provided a positive result for at least one gene. For example, if two genes are tested on a single assay, a minimum of one gene needed to be positive to presume the patient as a positive result for that test.

For the direct comparative test accuracy studies (including rapid versus standard tests), data was abstracted with each test as the index test and the combination of tests as a reference standard. The panel determined the combination of tests reference standard would be a minimum of at least two positive tests. For example, if one out of four tests were positive, this patient would be considered negative. If two out of four tests were positive, this patient would be considered positive. In addition, when the same population received more than one standard test, the panel determined which test to use for the direct comparative analysis, as pooling all of the standard tests from a single study would duplicate the same population.

Exclusion criteria for studies that assessed test accuracy based on sample type were studies with fewer than 10 patients, studies with incomplete test accuracy information (i.e., reported sensitivity without specificity), studies that did not report synchronous collection of different sample, studies that reported test accuracy results in recovering patients or with samples collected ≥7 days since symptom onset, and studies that reported results as a number of samples and not as a number of patients.

For patients with autoimmune conditions or cancer, studies assessing the outcomes of COVID-19 if a pre-testing strategy before the initiation of immunosuppressive therapy was utilized could not be identified. Thus, studies that indirectly informed the PICO questions were included. Those included studies of the outcome of COVID-19 in patients with autoimmune conditions or cancer, and the outcomes of COVID-19 in patients receiving treatments for autoimmune conditions or cancer. The role of testing in transplant patients was not prioritized in this update.

Data Collection and Analysis

Two reviewers completed data extraction independently and in duplicate. Reviewers extracted relevant information into a standardized data extraction form. Disagreements were resolved by discussion to reach consensus and in consultation with expert clinician scientists. Data extracted included general study characteristics (authors, publication year, country, study design), diagnostic index test and reference standard, prevalence of COVID-19, and parameters to determine test accuracy (i.e., sensitivity and specificity of the index test). Accuracy estimates from individual studies were pooled quantitatively using the logit transformation and the bivariate random effects model, when there were enough studies, which accounts for between study variation as well as the correlation between sensitivity and specificity. We used the random effects generalized linear mixed models to pool the sensitivity and specificity separately when it was not possible to conduct the bivariate model, and as a sensitivity analysis when the bivariate model was conducted. The Freeman-Tukey double arcsine transformation was used when there were no false negatives or false positives [9, 10]. The between study heterogeneity was assessed by examining the forest plots. When the analysis included studies that used different sample types and/or transport media for the index and reference tests, we conducted sensitivity analyses that excluded those studies to assess the robustness of our findings. The analyses were performed using the packages mada 0.5.10 and meta 4.11.0 in R 3.6.3 [11-13].

To calculate the absolute differences in effects for different testing or sampling strategies, we applied the results of the sensitivity and specificity to a range of plausible prevalence in the population. We then calculated true positives, true negatives, false positives, and false negatives. To determine the prevalence for each question, we considered the published literature in consultation with the clinical experts. Prevalence, as defined by the results of surveillance testing in a given community, has been shown to change overtime. For the purposes of the guideline, we used a prevalence of <2% to represent asymptomatic individuals in a community with ongoing SARS-CoV-2 transmission, 10% to represent symptomatic outpatients (although this may be much higher in some locations), 40% for

patients with compatible signs and symptoms being admitted to the hospital and as high as 80% for those admitted to the ICU.

Risk of Bias and Certainty of Evidence

We conducted the risk of bias assessment for diagnostic test accuracy studies using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 revised tool (**Table s3**) [14]. GRADE framework was used to assess overall certainty by evaluating the evidence for each outcome on the following domains: risk of bias, imprecision, inconsistency, indirectness, and publication bias [15, 16]. GRADE summary of findings tables were developed in GRADEpro Guideline Development Tool [17].

Evidence to Recommendations

The panel considered core elements of the GRADE evidence in the decision process, including certainty of evidence and balance between desirable and undesirable effects. Additional domains were acknowledged where applicable (e.g., feasibility, resource use, acceptability). For all recommendations, the expert panelists reached consensus. Voting rules were agreed on prior to the panel meetings for situations when consensus could not be reached.

As per GRADE methodology, recommendations are labeled as "strong" or "conditional". The words "we recommend" indicate strong recommendations and "we suggest" indicate conditional recommendations. **Figure 2** provides the suggested interpretation of strong and weak recommendations for patients, clinicians, and healthcare policymakers. Rarely, low certainty evidence may lead to strong recommendations. In those instances, we followed generally recommended approaches by the GRADE working group, which are outlined in five paradigmatic situations (e.g., avoiding a catastrophic harm) [18]. For recommendations pertaining to good practice statements, appropriate identification and wording choices were followed according to the GRADE working group [19]. A "good practice statement" represents a message perceived by the guideline panel as necessary to health care practice, that is

supported by a large body of indirect evidence difficult to summarize and indicates that implementing this recommendation would clearly result in large net positive consequences. For recommendations where the comparators are not formally stated, the comparison of interest was implicitly referred to as "not using the test". Some recommendations acknowledge the current "knowledge gap" and aim at avoiding premature favorable recommendations for test use and to avoid encouraging the rapid diffusion of potentially inaccurate tests.

Revision Process

The draft guideline underwent rapid review for approval by IDSA Board of Directors Executive Committee external to the guideline development panel. The guideline was reviewed by ASM, SHEA and PIDS, and endorsed by ASM and PIDS. The IDSA Board of Directors Executive Committee reviewed and approved the guideline prior to dissemination.

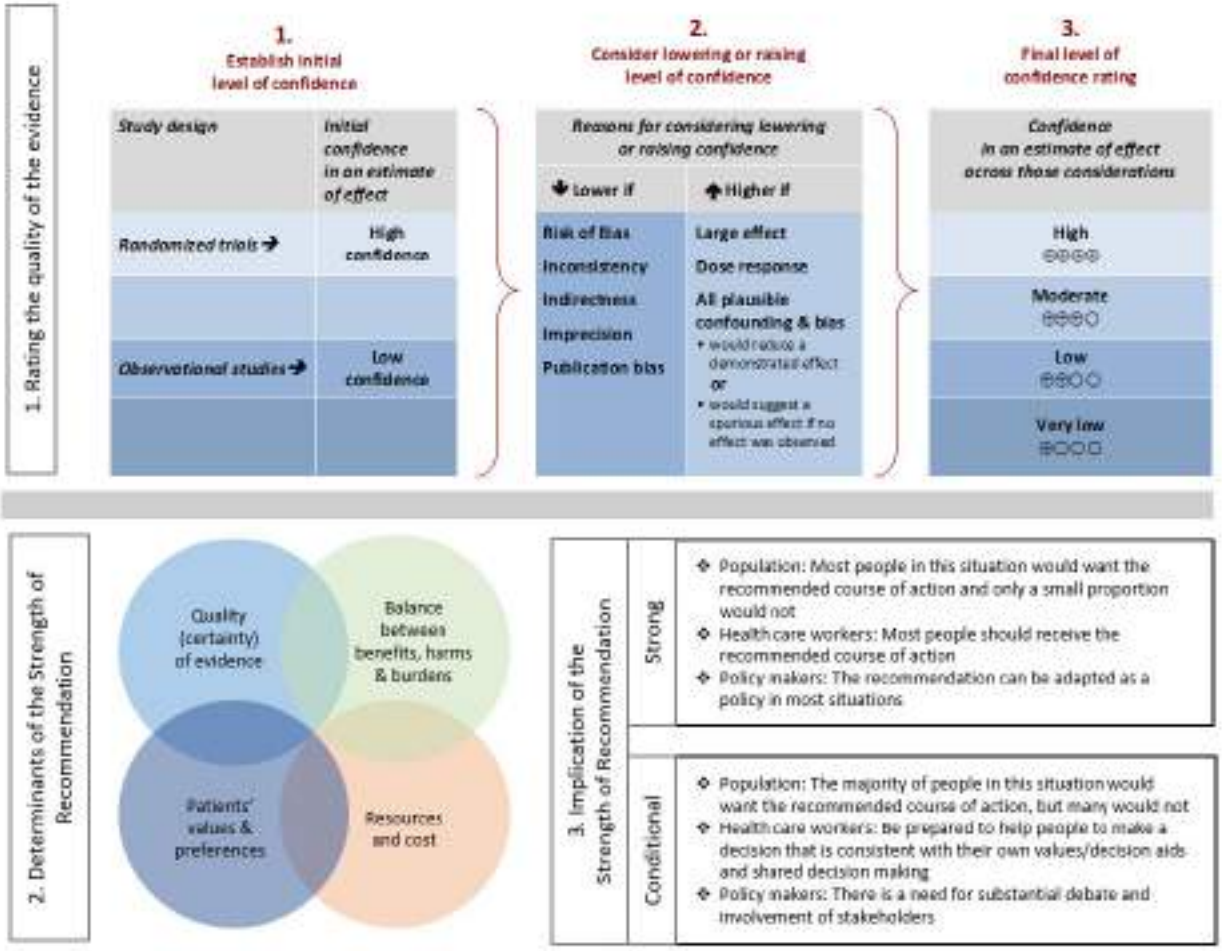
Updating Process

Regular, frequent screening of the literature will take place to determine the need for revisions based on the likelihood that new data will have an impact on the recommendations. If necessary, the expert panel will be reconvened to discuss potential changes.

Search Results

Systematic review and horizon scan of the literature identified 26,536 references, of which 560 full texts and 12 systematic reviews were reviewed. Nineteen studies informed the evidence base for the rapid testing recommendations, 26 studies informed the evidence base for the sample type recommendations and 66 manuscripts focused on patients with cancer (excluding transplant recipients) or autoimmune disease were also reviewed (**Figure s1**). Characteristics of the included studies can be found in **Tables s4a-s4m**.

Figure 2. Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE methodology (unrestricted use of the figure granted by the U.S. GRADE Network)



Recommendations

NAAT in Symptomatic Individuals

Recommendation 1: The IDSA panel recommends a SARS-CoV-2 NAAT in symptomatic individuals in the community suspected of having COVID-19, even when the clinical suspicion for COVID-19 is low (strong recommendation, very low certainty of evidence).

- **Remarks**:
  - The panel considered symptomatic patients to have at least one of the most common symptoms compatible with COVID-19 (**Table 1**).
  - Clinical assessment alone is not accurate in predicting COVID-19 diagnosis.
  - The panel considered timeliness of SARS-CoV-2 NAAT results essential to impact individual care, healthcare institution, and public health decisions. In the outpatient setting, results within 48 hours of collection is preferable.

Summary of the evidence

Direct evidence comparing the effects of NAAT testing *versus* no testing in symptomatic individuals in the community suspected of having COVID-19 was lacking. We identified eight studies that provided indirect information about rates of false positive results in populations identified as potentially having COVID-19 based on various clinical symptoms and signs [17, 20-26] (**Supplement B**). Clinical diagnostic scenarios were variable and included respiratory symptoms such as cough, shortness of breath, fever, alongside radiologic and biomarker indicators of having the disease. These studies included hospitalized and non-hospitalized patients. Four of the studies included in the analysis involved patients presenting to the hospital, potentially with pneumonia, which is different from a community-based symptomatic population [17, 21, 24, 26]. Due to the mentioned concerns with the studies and the inconsistency among them, the panel assessed the overall certainty of evidence as very low. However, over the last few months there is an overwhelming indirect evidence documenting

the benefits of testing. Additionally, we have indirect evidence documenting higher certainty about the harms of no testing in populations with widespread community transmission. This recommendation falls under one of the paradigmatic situations for a strong recommendation despite certainty evidence.

Benefits and harms

The panel considered minimizing the number of the false positive COVID-19 diagnoses to be a priority. Relying solely on clinical judgment to make a diagnosis of COVID-19 led to a large proportion of patients being diagnosed with COVID-19 when they did not have the disease (over diagnosis ranged between 62 and 98%). Even in hospitalized patients with pneumonia, the proportion of false positive diagnoses reached 62% in some studies. The harmful consequences of over diagnosis (i.e., false positive results) are unnecessary isolation/quarantine and possible exposure to treatment. Additionally, people may believe incorrectly that they have already been infected with SARS-CoV-2 and stop taking the appropriate precautions which could lead to additional harms of further spreading the disease in the future. Based on the available evidence, and despite its limitations, there is high certainty that testing will decrease the number of false positives considerably. The panel considered this as a critical benefit of using testing compared to no testing. One can speculate that considering the high proportion of asymptomatic individuals who have the disease, relying solely on clinical presentation is likely to also lead to a high number of false negatives. The panel also considered false negatives to be a potential harm of testing. False negative test results could cause symptomatic individuals to ignore isolation/quarantine directives.

Additional considerations

SARS-CoV-2 testing is acceptable to patients and providers. However, testing may not be readily available in some areas.

Conclusions and research needs for this recommendation

SARS-CoV-2 testing is recommended for all symptomatic patients in the community. However, the availability of test reagents, specimen collection devices, and PPE shortages may influence who can realistically be tested. When resources are limited, prioritizing testing to high-risk groups may be necessary. The CDC, IDSA, and other agencies have published priorities for testing patients with suspected COVID-19 infection [27, 28]. Future studies are needed to assess the frequency of false negative NAAT results in community-based settings, where patients are more likely to present with mild or moderate symptoms.

Nasopharyngeal, Mid-Turbinate, Anterior Nasal, Saliva, and Oropharyngeal Swabs

Recommendation 2: The IDSA panel suggests collecting a nasopharyngeal swab, mid-turbinate swab, anterior nasal swab, saliva or a combined anterior nasal/oropharyngeal swab rather than an oropharyngeal swab alone for SARS-CoV-2 RNA testing in symptomatic individuals suspected of having COVID-19 *(conditional recommendation, very low certainty of evidence)*.

- **Remark**: The panel considered symptomatic patients to have at least one of the most common symptoms compatible with COVID-19 (**Table 1**).

Summary of the evidence

We reviewed the published literature to identify studies assessing the performance of different specimen types relative to nasopharyngeal (NP) swabs for the detection of SARS-CoV-2 RNA. Specimen types were grouped into NP swabs, mid-turbinate (MT) swabs (also referred to as "deep nasal" swabs in some studies), anterior nasal (AN) swabs, oropharyngeal (OP) swabs (also referred to as "throat" swabs in some studies), saliva or a combined swab sampling of AN and OP. A swab insertion cutoff of 0.5 inch was used to differentiate between AN and MT

swabs. Due to variability in collection methods, saliva specimens were further subdivided into saliva with coughing, if the study reported asking individuals to cough or clear their throat prior to saliva specimen collection, and saliva without coughing if the study did not report asking individuals to cough prior to the saliva specimen collection. Analyses of "tongue" or "mouth" swabs were excluded due to inadequate study numbers.

Twenty studies [29-48] reported the test accuracy of different sample types using a NP swab as a reference test. Random effects generalized linear mixed model was used to pool the sensitivity and specificity, separately, of alternative sample types *versus* NP swabs as the reference standard. Findings are displayed in **Supplement C**. For the sample types that had enough studies, the random effects bivariate model was conducted and showed comparable pooled estimates. An additional eight studies [49-56] did not use NP swabs as a reference standard and were assessed separately. Summary statistics of the different specimen type are shown in **Table 2**. The overall quality of the evidence was deemed to be low due to a risk of bias introduced by using NP swabs as the reference standard and to be very low when imprecision and/or inconsistency were also present.

Benefits and harms

There are multiple potential benefits of using specimen types other than a NP swab for the molecular diagnosis of SARS CoV-2 infection. Collection of nasal swabs (either AN or MT) and saliva is less invasive than NP sampling and may be more comfortable for patients. In addition, these sample types are amendable to patient self-collection, either at home or in a healthcare setting. This provides flexibility and reduces strain on trained healthcare staff. Compared to NP swab collection, nasal swabs or saliva (collected without coughing) also have less potential to generate infectious aerosols, thus reducing transmission risk to healthcare workers involved in specimen collection. Saliva has the added benefit of being a "swab-free" sample type. Swab supply shortages have been problematic in many locations. In addition, saliva collection vials can be made directly compatible with laboratory robotics, allowing facile processing.

The potential harms of alternative specimen types include false negative and false positive results relative to NP sampling. False negative results may lead to additional transmission events, because infected individuals incorrectly believe there are not infectious to others and therefore do not self-isolate. Or they may lead to patients not receiving appropriate care. False positive results can cause anxiety, have the potential for lost work or school productivity, may lead to the unnecessary use of contact tracing resources and may lead to a missed diagnosis of the true cause of symptoms and possibly administration of unnecessary treatment for COVID-19. NP swabs, however, are an imperfect standard due to potential variability in collection techniques leading to sampling error. Apparent "false positive" saliva or non-NP swab results may actually be true positives, given that these specimens were mostly obtained from symptomatic patients in settings with a moderate prevalence of COVID-19.

Saliva testing requires clinical laboratories to validate this specimen type on their test platforms. Saliva is a complex sample matrix, especially if sputum or mucus is mixed with the sample. Including coughing may theoretically improve specimen quality by sampling the posterior nasopharynx and/or the lower respiratory tract. However, coughing may create exposure risks to those in the vicinity of specimen collection. Coughing may also add more mucus to saliva that can interfere with test performance and negatively affect test results. As a result, saliva testing typically produces a higher number of invalid results compared to swabs in transport media [7] . Such results may cause provider and patient frustration and can be associated with increased cost if repeat testing or sample recollection using an alternative method is required. The need for repeat testing delays reporting of true positive or negative results, which in turn delays isolation decisions, clinical management, and contact tracing around true positive cases.

Additional considerations

COVID-19 testing is performed on both symptomatic and asymptomatic individuals. The majority of studies addressed herein assessed symptomatic subjects. Whether or not these findings are generalizable to asymptomatic individuals is unknown. We note, however, that NP swab viral loads have been shown to be similar in symptomatic and asymptomatic individuals

[25] Additionally, a majority of included studies focused on adult subjects; generalizability of results to children is unknown.

Although the actual types of swabs used were not considered separately in this analysis, there could be performance differences among swab-types (e.g., flocked *versus* non-flocked swabs or natural *versus* synthetic swab tip material) not accounted for in this analysis. Likewise, the process of swab collection may be variable and that inconsistency could have affected results. Some studies sampled unilateral and others bilateral nasal passages. Sampling the nares and throat together may be done with two swabs placed in the same tube or a single swab. The nature and volume of media the swabs were placed into (e.g., type and amount of specific transport media) also varied. Furthermore, different nucleic acid amplification assays, gene targets and interpretive criteria were applied across studies. We only assessed assay results as positive or negative (as defined in the studies analyzed) and did not include signal strength of nucleic acid amplification (e.g., Ct value for real-time PCR assays), which could differ between the sample-types analyzed.

Saliva has not been a common specimen type used for infectious diseases diagnostics and limited data on saliva performance was available for the first version of the IDSA diagnostic guidelines. There is now enough published literature to be able to address saliva testing, but heterogeneity in specimen collection processes used may have affected downstream test performance. In general, saliva collection requires that the patient is able to follow and cooperate with the collection instructions, which may be difficult for individuals with severe symptoms, young children or those with cognitive impairment. As noted, some studies collected saliva with coughing (also referred to as "deep throat saliva" in some studies) and some without coughing using dribbling, drooling or spitting. Some groups have described the use of specimen containers including a short straw, with subjects asked to collect saliva in their mouth and run it down the straw into the tube. The use of a straw avoids aerosolization from spitting and may reduce potential for contaminating the outside of the container but requires active cooperation with the subject. Contamination of the outside of the container is a concern and is possibly mitigated by wiping the container with a virucidal agent or placing the collection

container in another larger one. There were also differences across studies related to use of dilution steps prior to saliva testing or use of collection kits with stabilizing agents, which may impact sensitivity. Lastly, many saliva studies asked subjects to refrain from eating, drinking, chewing gum or tobacco, or smoking for 30 minutes prior to collection, which may not always be feasible in walk-up or "on demand" testing locations.

Conclusions and research needs for this recommendation

Specimen types, including AN swabs, MT swabs, saliva, and a combination of AN/OP, sampling have comparable performance to NP swabs for the detection of SARS-CoV-2 RNA. Saliva with coughing, MT swabs or combined AN/OP samples were the most similar to NP swabs. In contrast, OP swabs alone were the least sensitive sampling modality. Given that NP swabs are an imperfect standard, future studies might consider using a composite gold standard consisting of multiple site sampling to try to improve the reference standard. Studies in pediatric patients (particularly addressing non-invasive specimen-types such as saliva and anterior nares swabs) are needed as are studies in asymptomatic individuals of all ages. Lastly, additional studies of novel oral fluid sampling approaches are needed. Some examples of methods currently under evaluation include collection devices that "wick up" saliva and use colorimetric indicators to tell the subject when enough specimen has been obtained, as well as various 'swish, gargle, and spit' approaches.

Table 2. GRADE Summary of Findings of Test Accuracy Results for Prevalence/Pre-Test Probability of 10% for different Specimen Types

Sample site	Saliva without coughing	Saliva with coughing	OP swab	AN swab	MT swab	Combined AN/OP swab
Sensitivity	0.90 (95% CI: 0.85 to 0.93)	0.99 (95% CI: 0.94 to 1.00)	0.76 (95% CI: 0.58 to 0.88)	0.89 (95% CI: 0.83 to 0.94)	0.95 (95% CI: 0.83 to 0.99)	0.95 (95% CI: 0.69 to 0.99)
Specificity	0.98 (95% CI: 0.93 to 1.00)	0.96 (95% CI: 0.83 to 0.99)	0.98 (95% CI: 0.96 to 0.99)	1.00 (95% CI: 0.99 to 1.00)	1.00 (95% CI: 0.89 to 1.00)	0.99 (95% CI: 0.92 to 1.00)
Outcome	**Effect per 1,000 patients tested**					
	Pre-test probability of 10% [a,f]					
True positives (patients with COVID-19)	90 (85 to 93)	99 (94 to 100)	76 (58 to 88)	89 (83 to 94)	95 (83 to 99)	95 (69 to 99)
False negatives (patients incorrectly classified as not having COVID-19)	10 (7 to 15)	1 (0 to 6)	24 (12 to 42)	11 (6 to 17)	5 (1 to 17)	5 (1 to 31)
Quality of the evidence [b,c,d]	9 studies 387 patients ⊕⊕◯◯ LOW[b]	3 studies 137 patients ⊕⊕◯◯ LOW[b]	4 studies 64 patients ⊕◯◯◯ Very LOW[b,d,e]	2 studies 130 patients ⊕⊕◯◯ LOW[b]	5 studies 855 patients ⊕⊕◯◯ LOW[b]	2 studies 61 patients ⊕◯◯◯ Very LOW[b,d,e]
True negatives (patients without COVID-19)	882 (837 to 900)	864 (747 to 891)	882 (864 to 891)	900 (891 to 900)	900 (801 to 900)	891 (828 to 900)

False positives (patients incorrectly classified as having COVID-19)	18 (0 to 63)	36 (9 to 153)	18 (9 to 36)	0 (0 to 9)	0 (0 to 99)	9 (0 to 72)
Quality of Evidence	9 studies 2662 patients ⊕⊕◯◯ LOW[b,c]	3 studies 316 patients ⊕◯◯◯ Very LOW[b,d]	4 studies 368 patients ⊕⊕◯◯ LOW[b]	2 studies 722 patients ⊕⊕◯◯ LOW[b]	5 studies 682 patients ⊕◯◯◯ Very LOW[b,d]	2 studies 237 patients ⊕⊕◯◯ LOW[b]

Explanations: This table is based on applying the sensitivity and specificity estimates to calculate true and false positives and negatives in a hypothetical population of 1000 individuals

a. Typically seen in general population in an at-risk population
b. Using the NP swab as a reference standard increases the risk of bias for all the studies.
c. One study with unexplained inconsistent results noted. However, a sensitivity analysis without this study showed robustness of the overall pooled estimate of specificity.
d. Considering the upper and lower limits of the confidence interval might lead to different clinical decisions.
e. The test of interest was conducted in a small number of patients which might lead to imprecise results.
f. The different sample types were not assessed directly in the same studies.

Swab Collection by Patients or Healthcare Providers (Symptomatic)

Recommendation 3: The IDSA panel suggests that anterior nasal and mid-turbinate swab specimens may be collected for SARS-CoV-2 RNA testing by either patients or healthcare providers, in symptomatic individuals with upper respiratory tract infection (URTI) or influenza-like illness suspected of having COVID-19 *(conditional recommendation, low certainty of evidence)*.

- **Remarks:**
  - Appropriate specimen collection and transport to the laboratory is critical. General instructions for swab-based SARS-CoV-2 testing are shown in **Table 3**. Additional resources are available on the IDSA website.
  - A clear, step-by-step protocol needs to be presented to patients attempting self-collection. This could be in the form of a short video or printed pamphlet with illustrations.
  - The majority of self-collection studies were performed in the presence of a healthcare worker.
  - The available evidence for nasal and MT swabs as alternatives to healthcare personnel collection is based on assessment of symptomatic patients. Data on self-collection in asymptomatic individuals is currently unavailable.
  - The panel considered symptomatic patients to have at least one of the most common symptoms compatible with COVID-19 (**Table 1**).

Summary of the evidence

This recommendation is based on three cohort studies (**Supplement D**). In the first study, test accuracy results were provided for self-collected non-invasive specimens compared to healthcare-collected NP swabs as the standard [57]. For self-collection, participants were provided with instructions and asked to self-collect tongue, nasal, and MT swabs, in that order.

Tongue samples were collected with a nylon flocked swab. Nasal samples were collected with a foam swab bilaterally. Mid-turbinate samples were collected with a nylon flocked swab bilaterally. After patient sampling was completed, NP samples were collected by a healthcare worker using a polyester tipped swab on a skinny wire. In the second study, patients attending dedicated COVID-19 collection clinics were offered the option to first self-collect nasal and throat swabs followed by healthcare provider collection of nasal, throat or oropharyngeal swabs [58]; concordance of results were presented. The third study compared positivity for supervised oral fluid sampling, supervised self-collected deep nasal swabs, unsupervised oral fluid sampling and provider collected NP swabs [59]. In this analysis, any positive test, obtained from any of the reported sampling methods including the index test, was considered to be a true positive. Although the study reported the results for "oral fluid," it is likely these samples were mixed with sputum. Lastly, the panel considered unpublished data submitted to the FDA on home collection, which demonstrated good stability of specimens stored in universal transport media (UTM) during transport from homes to laboratories and comparable quantities of virus in self-collected compared to healthcare provider collected swabs. Summary statistics for self-collected versus health-care worker collected nasal swabs are shown in **Table 4**.

The studies used to inform the recommendation were small and heterogeneous. Sources of heterogeneity included variable swab and transport media types as well as use of unilateral *versus* bilateral nares self-collection. The timing of collection relative to symptom onset is also important but was not well documented in available data. Due to the mentioned concerns with the studies and the lack of direct comparisons between different specimen types in the same patient population, the panel agreed that overall certainty of evidence was low.

Benefits and harms

The panel placed a high value on avoiding the close exposure of healthcare providers to patient droplets and possible droplet nuclei generated during specimen collection. We assumed that self-collected specimens including anterior nasal swabs, MT swabs and saliva (without cough) would reduce provider exposure and could reduce mask or respirator use. The overall

sensitivity of testing when samples were collected by patients was comparable to those collected by healthcare providers.

Additional considerations

Other potential benefits of self-collection include increasing the availability of testing outside the healthcare system and increased patient satisfaction with self-collection. Concerns with self-collection include lack of experience or documentation for actual collection methods by patients; inappropriate sample collection and/or handling could then lead to inaccurate results.

Conclusions and research needs for this recommendation

Although data is limited, both healthcare provider collected, and self-collected nasal or MT swabs appear to result in similar rates of detection of SARS-CoV-2. Self-collection of NP swabs is unlikely to be an option as a self-collection method. There are advantages of having multiple strategies to collect clinical specimens, particularly in times of PPE shortages when limiting exposure to healthcare personnel or other patients is important, or when testing in specific populations without access to the healthcare system is required. Further comparative studies of self-collected non-invasive specimens (i.e., nasal, mid-turbinate, and throat swabs, as well as saliva) compared with healthcare provider-collected NP swabs is warranted. Research is needed comparing sample collection at various intervals from time of onset of symptoms, evaluation of single *versus* two-sided sampling, and quantitation of virus recovery from samples obtained via different collection methods. Studies comparing collection methods in symptomatic and asymptomatic individuals are also needed. Lastly, studies of home-collection in asymptomatic individuals and parental swab collection in children with COVID-19 are needed.

Table 3. General Instructions for Swab-based SARS-CoV-2 Testing

	Nasopharyngeal*	Oropharyngeal	Mid-Turbinate	Nasal/Anterior Nares
Who Collects	Healthcare professional	• Healthcare professional • Medical-supervised on-site self-collection	• Healthcare professional • Medical-supervised on-site self-collection	• Healthcare professional • Medical-supervised on-site self-collection
Tools/ Equipment^	Flocked, synthetic fiber mini-tip swabs with plastic or wire shafts	Synthetic fiber swabs with plastic shafts only	Flocked tapered swab	Flocked, synthetic fiber or foam swab with plastic shaft
How to Collect	1. Tilt patient's head back 70° 2. Insert flexible shaft mini-tip swab through nares parallel to palate (not upwards) until: a. Resistance is met, **OR** b. Distance is equivalent to the distance from the patient's ear to their nostril 3. Gently rub and roll swab 4. Leave swab in place for several seconds to absorb secretions 5. Slowly remove swab while rotating it 6. Immediately place swab in sterile tubes containing transport media If collected with OP, combine in single tube → limit use of testing resources	1. Insert swab in posterior pharynx and tonsillar areas 2. Rub swab over posterior pharynx and bilateral tonsillar pillars; avoid tongue, teeth, and gums 3. Immediately place swab in sterile tubes containing transport media If collected with NP, combine in single tube → limit use of testing resources	1. Tilt patient's head back 70° 2. While gently rotating swab, insert swab about 2.5 cm (~1 in.)# straight back (not up) into nostril until the collar/safety stopping point touches the outside of the nose 3. Rotate swab several times against wall 4. Leave swab in place for several seconds to absorb secretions 5. Repeat for both nostrils using same swab# 6. Immediately place in sterile tube containing transport media	1. Insert swab about 1 cm (0.5 in) inside nares# 2. Rotate swab and leave in place for 10-15 seconds 3. Using same swab, repeat for other nostril 4. Immediately place in sterile tube containing transport media

NP: nasopharyngeal; **OP**: oropharyngeal; **MT**: nasal mid-turbinate; **NS**: anterior nares swab.

^**Cautions:** Do NOT use calcium alginate swabs or swabs with wooden shafts, which may contain substances that interfere with nucleic acid amplification. Rayon swabs may not be compatible with all molecular platforms. Clinical laboratories should confirm compatibility of collection devices during assay validation.

#**Pediatrics**: Swab insertion distance will differ for pediatric patients. Swabs with stoppers make estimating distance easier for MT self-collection. Two-sided MT sampling not always performed.

References

1. Centers for Disease Control and Prevention. Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens for COVID-19. COVID-19 (Coronavirus Disease) 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html. Accessed 22 April 2020.
2. U.S. Food and Drug Administration. FAQs on Testing for SARS-CoV-2. 2020. Available at: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/faqs-diagnostic-testing-sars-cov-2. Accessed 29 April 2020.

Table 4. GRADE Summary of Findings of Test Accuracy Results for Prevalence/Pre-Test Probability of 10% for Self-Collected versus Healthcare-Collected Samples

Self-collected nasal	**Sensitivity**: 0.95 (95% CI: 0.88 to 1.00) **Specificity**: 1.00 (95% CI: 0.99 to 1.00)			
Health care worker collected	**Sensitivity**: 0.94 (95% CI: 0.86 to 1.00) **Specificity**: 1.00 (95% CI: 0.99 to 1.00)			
Outcome	**Effect per 1,000 patients tested** **pre-test probability of 10%** [c]		**№ of patients (studies)**	**Test accuracy CoE**
	Self-collected nasal	**Health care worker collected**		
True positives (patients with COVID-19)	95 (88 to 100)	94 (86 to 100)	200 (3)	⊕⊕◯◯ LOW [a,b]
	1 more TP in Self-collected Nasal			
False negatives (patients incorrectly classified as not having COVID-19)	5 (0 to 12)	6 (0 to 14)		
	1 fewer FN in Self-collected Nasal			
True negatives (patients without COVID-19)	900 (891 to 900)	900 (891 to 900)	600 (3)	⊕⊕◯◯ LOW [a,b]
	0 fewer TN in Self-collected Nasal			
False positives (patients incorrectly classified as having COVID-19)	0 (0 to 9)	0 (0 to 9)		
	0 fewer FP in Self-collected Nasal			

CoE: Certainty of evidence

Explanations: This table is based on applying the sensitivity and specificity estimates to calculate True and false positives and negatives in a hypothetical population of 1000 individuals

a. There is a high risk of bias in regard to the reference test that is considered to be the healthcare provider collected swab result.

b. The studies provide test accuracy results or concordance results but do not provide patient-important outcomes based on those results.

c. Typically seen in symptomatic outpatients who have not reached a hospital facility

Upper vs. Lower Respiratory Tract Samples

Recommendation 4: The IDSA panel suggests a strategy of initially obtaining an upper respiratory tract sample (e.g., nasopharyngeal swab) rather than a lower respiratory sample for SARS-CoV-2 RNA testing in hospitalized patients with suspected COVID-19 lower respiratory tract infection. If the initial upper respiratory sample result is negative, and the suspicion for disease remains high, the IDSA panel suggests collecting a lower respiratory tract sample (e.g., sputum, bronchoalveolar lavage fluid, tracheal aspirate) rather than collecting another upper respiratory sample *(conditional recommendations, very low certainty of evidence)*.

- **Remark**: The panel considered timeliness of SARS-CoV-2 NAAT results essential to impact individual care and isolation decisions. In the hospital setting, results within 24 hours of collection is preferable.

Summary of the Evidence

We identified nine studies that performed both an upper respiratory tract (URT) swab and lower respiratory tract (LRT) sample collection consecutively on the same patient (**Supplement E**). Two reported on viral load and did not report on sensitivity [60, 61]. Seven studies reported on sensitivity, of which three had a case control design [62-64] and one reported results per sample and not per patient [65]. The three cohort studies [59, 66, 67] were used to inform the panel's decision-making process. The sample type varied by study and included throat and nasal swabs for URT sampling and sputum and bronchoalveolar lavage (BAL) fluid specimens for LRT sampling. Summary statistics for URT versus LRT sampling in three cohort studies are shown in **Table 5**. The timing of specimen collection with regards to clinical course was not reported for all these studies and different diagnostic reference standards were used. These issues led to very low certainty about test accuracy results comparing URT *versus* LRT samples.

Benefits and harms

The evidence suggests that testing LRT specimens increases sensitivity of testing for SARS-CoV-2 RNA, reducing the number of false negative results. The panel considered minimizing the number of false negatives to be the most important priority when analyzing the data. This approach was taken to strengthen both the individual and population impact of the tests evaluated. The obvious benefit of LRT testing is to reduce the numbers of patients whose infection is missed and pose a risk to others. There are also risks to collecting LRT samples in infected patients, including the possibility of aerosolization and increased PPE requirement, which may be in short supply.

Additional considerations

It was assumed that patients fulfilling clinical criteria for COVID-19 pneumonia, in a hospital setting, would exhibit a high or very high likelihood of true infection. The use of a LRT sample would therefore only apply to patients ill enough to be hospitalized including those likely to be in intensive care units. The panel also considered the feasibility concerns with suggesting lower sampling for all patients with signs/symptoms of lower respiratory tract infection (LRTI). These included that not all patients may be able to produce sputum, PPE shortages may impact the availability of more invasive sampling, and not all laboratories may have validated testing using LRT samples. The panel agreed that a tracheal aspirate, as opposed to BAL, may be the most feasible specimen in intubated patients. In some situations, obtaining a lower sample first may be easier such that an NP sample is not required. Induced sputum should be avoided due to risk for aerosol generation. Regardless of the LRT sample used, assay validation for these specimen types might remain an issue. Additionally, it is important to note that confirmation of infection is also typically required for enrollment in clinical trials of investigational agents.

Conclusions and research needs for this recommendation

Considering the upper and lower limits of the confidence intervals in the sensitivity value, the panel believes the increased sensitivity of the LRT sample would lead to more

appropriate clinical and infection control decisions. However, feasibility concerns with LRT sampling prompted the panel to suggest a diagnostic strategy that incorporated both upper and lower sampling to minimize the amount of lower sampling needed. Large (multicenter) comparative studies are needed to assess the accuracy of upper and lower respiratory tract samples collected from the same patient for the diagnosis of COVID-19 pneumonia. Simultaneous collection of NP swabs and sputum are of particular interest. Studies should include assessment of the timing of specimen collection in relationship to the onset of symptoms and use widely available, validated tests in combination with a standardized definition of COVID-19 LRTI.

Table 5. GRADE Summary of Findings of Test Accuracy Results for Prevalence/Pre-Test Probability of 40% and 80% for upper respiratory tract (URT) vs lower respiratory tract (LRT) Sampling (three studies)

URT sampling	**Sensitivity**: 0.76 (95% CI: 0.51 to 1.00 **Specificity**: 1.00 (95% CI: 0.99 to 1.00)					
LRT sampling	**Sensitivity**: 0.89 (95% CI: 0.84 to 0.94) **Specificity**: 1.00 (95% CI: 0.99 to 1.00)					
Outcome	**Effect per 1,000 patients tested**				**No patients (studies)**	**Test accuracy CoE**
	pre-test probability of 40% [d]		**pre-test probability of 80%** [e]			
	URT sampling	**LRT sampling**	**URT sampling**	**LRT sampling**		
True positives (patients with COVID-19)	304 (204 to 400)	356 (336 to 376)	608 (408 to 800)	712 (672 to 752)	280 (3)	⊕◯◯◯ VERY LOW [a,b,c]
	52 fewer TP in URT sampling		104 fewer TP in URT sampling			
False negatives (patients incorrectly classified as not having COVID-19)	96 (0 to 196)	44 (24 to 64)	192 (0 to 392)	88 (48 to 128)		
	52 more FN in URT sampling		104 more FN in URT sampling			
True negatives (patients without COVID-19)	600 (594 to 600)	600 (594 to 600)	200 (198 to 200)	200 (198 to 200)	8 (1)	⊕◯◯◯ VERY LOW [a,c]
	0 fewer TN in URT sampling		0 fewer TN in URT sampling			

False positives (patients incorrectly classified as having COVID-19)	0 (0 to 6)	0 (0 to 6)	0 (0 to 2)	0 (0 to 2)		
	0 fewer FP in URT sampling		0 fewer FP in URT sampling			

CoE: Certainty of evidence

Explanations: This table is based on applying the sensitivity and specificity estimates to calculate True and false positives and negatives in a hypothetical population of 1000 individuals

a. There was no direct evidence comparing the accuracy of a strategy with starting with upper sample and then conducting a lower sample if the upper sample is negative. Additionally, studies reported test accuracy results but did not report on patient-important and population-important outcomes based on the results.
b. There is serious unexplained heterogeneity.
c. Considering the upper vs lower limits of the sensitivity's confidence interval would lead to different clinical decisions. Also, only one study informed specificity with only 8 patients.
d. Typically seen in patients meeting clinical definition for COVID-19 who were hospitalized.
e. Typically seen in patients meeting clinical definition for COVID-19 who were admitted to intensive care units.

Single vs. Repeating RNA Test (Symptomatic)

Recommendation 5: The IDSA panel suggests performing a single viral RNA test and not repeating testing in symptomatic individuals with a low clinical suspicion of COVID-19 *(conditional recommendation, low certainty of evidence)*.

- **Remarks**:
  - A low clinical suspicion should be informed by epidemiological information available for the region coupled with clinical judgment.
  - The panel considered symptomatic patients to have at least one of the most common symptoms compatible with COVID-19 (**Table 1**).

Recommendation 6: The IDSA panel suggests repeating viral RNA testing when the initial test is negative (*versus* performing a single test) in symptomatic individuals with an intermediate or high clinical suspicion of COVID-19 *(conditional recommendation, low certainty of evidence)*.

- **Remarks**:
  - Intermediate/high clinical suspicion typically applies to the hospital setting and is based on the severity, numbers and timing of compatible clinical signs/symptoms.
  - Repeat testing should generally occur 24-48 hours after initial testing and once the initial NAAT result has returned as negative.
  - Another specimen type, preferably a lower respiratory tract specimen if the patient has signs/symptoms of LRTI, should be considered for repeat testing.
  - The panel considered symptomatic patients to have at least one of the most common symptoms compatible with COVID-19 (**Table 1**).

Summary of the evidence

These recommendations are based on a three cohort studies [17, 68, 69] (**Supplement F**). In these reports, targeted NAAT testing was performed using a NP swab collected from symptomatic patients with signs of LRTI. The diagnostic reference standard was detection of SARS-CoV-2 by metagenomics sequencing. If the first NAAT result was negative, a second NP sample was collected two or three days later for repeat testing. Summary statistics for single versus repeated testing are shown in **Table 6**. We did not identify any studies that assessed the benefits and harms of repeat testing on patient or population outcomes. Given the lack of direct assessment of the implications of single *versus* repeat testing and the small number of patients included in the identified studies, the panel agreed that the overall certainty of evidence was low.

Benefits and harms

The panel placed a high value on avoiding a missed diagnosis in patients who have COVID-19 (i.e., false negatives) in the inpatient setting. Patients who are inappropriately labeled as not having COVID-19 pose a risk of transmitting the virus to others in the community, to healthcare providers and staff as well as other patients in the hospital. The panel determined that a false negative (FN) rate of <2% would be acceptable. Single testing compared to repeat testing will lead to a FN rate of about 10-20 cases out of 1000 in the low clinical suspicion group and to higher rates (FN of >60 cases out of 1000) in the intermediate and high clinical suspicion groups.

Additional considerations

Multiple factors affect the generalizability of available evidence for or against repeat testing. First, the selected studies included subjects with a high likelihood of COVID-19 based on epidemiology and clinical symptoms. Consideration of disease prevalence is important given that the negative predictive value (NPV) of a diagnostic test increases as the disease prevalence decreases. Thus, a single negative COVID-19 test result in areas of low disease prevalence is more predictive than in areas of high disease prevalence. We also assumed that the performance of the assays studied was comparable to commercial NAAT platforms currently

available in the United States. Other studies evaluating repeat testing have utilized different gold standards, such as chest CT findings, and relied on throat swabs, which may not be as sensitive as NP specimens. In addition, the diagnostic yield of a second test may be impacted by the duration of symptoms and the clinical site sampled. Depending on the clinical situation (e.g., whether pneumonia is present or not) and disease progression, alternative specimen types such as a lower respiratory collection should be considered. Evidence suggests that viral distribution in different anatomical sites can impact detection and virus loads may be higher in lower respiratory tract symptoms. Clinicians are advised to contact their local laboratory to determine locally acceptable specimen types for SARS-CoV-2 RNA testing.

Conclusions and research needs for this recommendation

High-quality evidence addressing the predictive value of a single negative SARS-CoV-2 test result compared to repeat testing for clinical diagnosis is lacking. Based on current available evidence, clinical practice, and availability of testing resources, the panel recommends use of clinical judgment combined with knowledge of local epidemiology in considering repeat molecular testing of respiratory tract samples. In settings with lower rates of SARS-CoV-2 circulation in the community, or in persons with symptoms not typical of COVID-19, benefits of repeat testing may be lower. When repeat testing is warranted, the site of specimen collection should be carefully assessed. Further studies evaluating the potential benefit and timing of repeat testing relative to symptom onset in both inpatient and outpatient settings are warranted.

Table 6. GRADE Summary of Findings of Test Accuracy Results for Prevalence/Pre-Test Probability of 10% and 40% for single versus repeat PCR testing

Single testing	**Sensitivity**: 0.71 (95% CI: 0.65 to 0.77) **Specificity**: 1.00 (95% CI: 0.99 to 1.00)					
Repeat testing	**Sensitivity**: 0.88 (95% CI: 0.80 to 0.96) **Specificity**: 1.00 (95% CI: 0.99 to 1.00)					
Outcome	**Effect per 1,000 patients tested**				**№ of patients (studies)**	**Test accuracy CoE**
	pre-test probability of 10% [c]		**pre-test probability of 40%** [d]			
	RT-PCR Single testing	**RT-PCR Repeat testing**	**RT-PCR single testing**	**RT-PCR Repeat testing**		
True positives (TP) (patients with COVID 19)	71 (65 to 77)	88 (80 to 96)	284 (260 to 308)	352 (320 to 384)	253 (3)	⨁⨁◯◯ LOW [a,b]
	17 fewer TP in RT-PCR rapid testing		**68 fewer TP in RT-PCR rapid testing**			
False negatives (FN) (patients incorrectly classified as not having COVID 19)	29 (23 to 35)	12 (4 to 20)	116 (92 to 140)	48 (16 to 80)		
	17 more FN in RT-PCR rapid testing		**68 more FN in RT-PCR rapid testing**			
True negatives (TN) (patients without COVID 19)	900 (891 to 900)	900 (891 to 900)	600 (594 to 600)	600 (594 to 600)	105 (2)	⨁⨁◯◯ LOW [a,b]
	0 fewer TN in RT-PCR rapid testing		**0 fewer TN in RT-PCR rapid testing**			

False positives (FP) (patients incorrectly classified as having COVID 19)	0 (0 to 9)	0 (0 to 9)	0 (0 to 6)	0 (0 to 6)		
	0 fewer FP in RT-PCR rapid testing		**0 fewer FP in RT-PCR rapid testing**			

CoE: Certainty of evidence

Explanations: This table is based on applying the sensitivity and specificity estimates to calculate True and false positives and negatives in a hypothetical population of 1000 individuals

a. Studies reported test accuracy results but did not report on patient-important and population-important outcomes based on the results.
b. Considering the lower vs upper limit of the sensitivity confidence interval may lead to different clinical decision, and the low number of patients lead to very serious imprecision
c. Typically seen in symptomatic outpatients who have not reached a hospital facility
d. d. Typically seen in patients meeting clinical definition for COVID-19 who were hospitalized

Rapid vs. Standard Laboratory-based NAAT (Symptomatic)

Recommendation 7: The IDSA panel suggests using either rapid RT-PCR or standard laboratory-based NAATs over rapid isothermal NAAT in symptomatic individuals suspected of having COVID-19 *(conditional recommendation, low certainty of evidence).*

- **Remarks**:
  - Rapid NAAT was defined as assays generating results in approximately one hour or less of instrument run time (inclusive of nucleic acid extraction).
  - This recommendation only applies to the tests evaluated in the included studies (**Table s4f**).
  - Standard laboratory-based NAAT methods evaluated included RT-PCR and transcription mediated amplification (TMA).
  - Studies of rapid isothermal NAAT primarily used the Abbott ID NOW test
  - Rapid isothermal NAAT is an acceptable testing option when rapid RT-PCR or standard laboratory-based NAAT is not readily available.
  - A negative rapid isothermal test result from an individual with a high clinical suspicion for SARS-CoV-2 infection, or anyone in a moderate (10%) or high prevalence (40%) population, should be confirmed by standard NAAT or a rapid RT-PCR test when testing is available and the results will affect patient management.

Summary of the evidence

We systematically identified and reviewed published studies evaluating the diagnostic test accuracy of "rapid" *versus* "standard" SARS-CoV-2 NAAT technologies. Rapid tests were defined as those that generate results in approximately one hour or less of instrument run time, exclusive of the time it takes to collect the specimen and transport it to the testing location, but inclusive of any processing and/or extraction required. Rapid tests typically have

few operator steps and are amendable to testing at the point-of-care by non-laboratory staff. Rapid test methodologies include rapid RT-PCR and rapid isothermal NAAT. Standard tests require instrumentation and/or processing that must be performed in a clinical laboratory by trained laboratory staff. Assay run times generally require more than an hour and use RT-PCR or transcription mediated amplification (TMA). **Table s4f** displays the various assays and methodologies that were included in our review.

In all, we identified 19 studies [70-88] that assessed diagnostic test accuracy of rapid RT-PCR or rapid isothermal NAAT *versus* standard methods in symptomatic patients (**Supplement G**). A subset of studies involved a multi-way comparison between three or more SARS-CoV-2 molecular diagnostic tests (i.e., a single rapid test and multiple standard laboratory-based NAATs). The reference standard in these studies was labeled a "composite reference standard," that defined a "positive case" or a "negative case" of SARS CoV-2 infection using a combination of multiple tests. The definition of a "positive case" was set to require at least two out of the total number of tests performed to be positive. These studies allowed a direct comparison of the performance of a rapid test and a standard NAAT against a "composite reference standard" that combined the results of multiple tests. Twelve studies [73-77, 81-84, 86-88] assessed the test accuracy of rapid RT-PCR compared to standard NAAT or a composite reference standard when available and nine studies [70-72, 78-80, 83, 85, 88] assessed the diagnostic test accuracy of rapid isothermal NAAT compared to standard NAAT or a composite reference standard when available. There were four studies comparing rapid RT-PCR and a standard test to a composite reference standard [70, 75, 82, 83, 88] and four studies comparing a rapid isothermal NAAT and a standard test versus a composite reference standard [80, 83, 88].

Rapid RT-PCR tests had a pooled sensitivity of 97% (95% CI: 94-99) with specificity 96% (95% CI: 94-98; **Figure s7a-s7b** and **Table s13**) compared to a single standard NAAT or composite reference standard when available. In the subgroup of studies that allowed direct comparison of the diagnostic accuracy of rapid RT-PCR and standard laboratory-based NAAT using a composite reference standard, the sensitivity and specificity of rapid RT-PCR were comparable to standard laboratory-based tests (98% [95% CI: 95-100] vs. 98% [95% CI: 95-99]

and 97% [95% CI: 89-99] vs. 97% [95% CI: 92-99], respectively; **Table 7** and **Figures s9a-s9b**). Rapid isothermal NAAT had a sensitivity of 70% (95% CI: 56-81) with specificity 99% (95% CI, 97-99; **Figures s8a-s8b and Table s14**) compared to a single standard NAAT or composite reference standard when available. In the subgroup of studies that allowed direct comparison of rapid isothermal tests and standard laboratory-based NAAT using a composite reference standard, rapid isothermal tests had lower sensitivity than standard laboratory-based tests (81% [95% CI: 75-86] vs. 99% [95% CI: 97-100]) but comparable specificity (99% [95% CI: 96-100] vs 97% [95% CI: 93-99]; **Table 8** and **Figure s10**). We explored inconsistency in a sensitivity analysis including only studies that used the same sampling method and transport conditions for both the rapid isothermal test and standard laboratory-based NAAT. Sampling method did not affect the results (**Figures s8c-s8d**). All NAAT methods showed high specificity (i.e., ≥97%).

All the analyses were conducted using the bivariate model, thus we performed sensitivity analyses using the random-effects generalized linear mixed models and the results were comparable. Overall quality of evidence ranged from low to moderate. Quality was downgraded for risk of bias (concerns about different sample sources and transport media, and/or using a single test as a reference standard), inconsistency (variable levels of heterogeneity across the comparisons), and/or imprecision (due to small sample sizes and/or wide confidence interval that may lead to different conclusions).

Benefits and harms

The benefits and harms of SARS-CoV-2 testing need to balance the value of a rapid result against the test performance characteristics of rapid NAAT, which may not be as sensitive as a standard laboratory-based test. The value of obtaining a test result rapidly (within one hour), while the patient is still present, is that it allows patients to be put into isolation and management decisions to be made quickly. A rapid result also decreases concerns of losing patients to follow up and generally makes follow up easier. However, a less sensitive test increases the number of false negative results, which could delay a diagnosis of COVID-19 infection and lead to spread of the disease and miss a management opportunity for infected individuals.

Using rapid RT-PCR and standard laboratory-based tests will minimize false negative results, due to their high sensitivity. The rapid isothermal tests evaluated here had a reduced sensitivity compared to rapid RT-PCR and standard laboratory-based NAAT tests, leading to an increased number of false negative results. Individuals with COVID-19 will test negative and not be isolated as a result of false negative results, thus increasing the potential for spread of the disease. In addition, false negatives may delay opportunities for treatment. The degree of harm is related to the number of false negative isothermal NAAT results, which will vary depending on the prevalence of disease. All rapid and non-rapid molecular tests had a very high specificity, thus minimizing false positive results. The harm of false positive results includes isolating individuals who do not have COVID-19 infection, causing unnecessary anxiety, delaying additional evaluation looking for the cause of symptoms, potentially administering unnecessary therapeutics for COVID-19, and increasing days out of work and contact tracing.

Additional considerations

The vast majority of the studies included in our analysis were conducted on symptomatic individuals, with limited information provided regarding the timing of specimen collection in relationship to the onset of symptoms. Timing of testing relative to symptom onset may have a significant impact on the sensitivity of the test. In addition, there is very limited data on the performance of rapid tests in asymptomatic individuals and in children. Whether our findings are generalizable to these groups is unknown. However, we do note that asymptomatic patients appear to have viral load levels in their respiratory secretions similar to symptomatic individuals [25]

An additional factor that complicated the assessment of the performance of the rapid tests was differences in specimen type and the use of viral transport media (VTM). Some rapid isothermal NAAT studies tested a NP swab sample in VTM, which dilutes the specimen and may reduce the sensitivity of some rapid isothermal tests. In other studies, a dry anterior nasal swab was collected for the rapid isothermal test, while a NP swab in VTM was used as the standard laboratory-based comparator test. These differences in specimen type and dilution of specimens may impact the sensitivity of the rapid isothermal tests. Lastly, there were no

studies directly comparing rapid isothermal NAAT and rapid RT-PCR tests to one another, which precludes the direct comparisons of different rapid test performance.

Conclusions and research needs for this this recommendation

The sensitivity of rapid RT-PCR and standard laboratory-based NAAT appear to be essentially equivalent. In contrast, the rapid isothermal NAATs evaluated were less sensitive than either rapid RT-PCR or standard laboratory based NAATs. We believe the 81% sensitivity estimate for rapid isothermal NAAT best reflects test performance because the composite reference standard used for this calculation is a higher quality of evidence. Regardless of the sensitivity differences across methodologies, rapid isothermal NAAT will likely continue to be used due to test kit supply shortages affecting a variety of different test manufacturers. Also, compared to rapid RT-PCR which usually takes 45-60 minutes, rapid isothermal NAAT can generate results within 5-15 minutes, which is advantageous in many clinical settings. When using rapid isothermal tests, false negative results are reduced when testing is performed in low prevalence populations (1%). Conversely, a negative rapid isothermal test result in an individual with a high clinical suspicion of SARS-CoV-2 infection in a low prevalence area or anyone in a moderate (10%) or high prevalence (40%) population should be confirmed with a standard NAAT or rapid RT-PCR test when testing is available and the results will affect patient management.

Future research should include rigorously designed studies in symptomatic patients using specimen types that optimize the performance of the tests studied, with particular attention to time of testing in relationship to symptom onset. Studies of rapid isothermal methods other than Abbot ID NOW are also needed, as are comparative studies on the test performance of rapid and standard NAAT in asymptomatic individuals and children.

Table 7. GRADE Summary of Findings of Test Accuracy Results for Prevalence/Pre-Test Probability of 1%, 10%, and 40% for rapid RT-PCR and standard non-rapid laboratory-based NAAT vs. composite reference standard

	Rapid RT-PCR	Standard laboratory based NAAT
Sensitivity	0.98 (95% CI: 0.95 to 1.00)	0.98 (95% CI: 0.95 to 0.99)
Specificity	0.97 (95% CI: 0.89 to 0.99)	0.97 (95% CI: 0.92 to 0.99)

Outcome	No of patients (studies)	Effect per 1,000 patients tested						Test accuracy CoE
		Pre-test probability of 1%		Pre-test probability of 10%		Pre-test probability of 40%		
		Rapid RT-PCR	Standard NAAT	Rapid RT-PCR	Standard NAAT	Rapid RT-PCR	Standard NAAT	
True positives (patients with SARS-CoV2 infection)	460 (4)	10 (10 to 10)	10 (10 to 10)	98 (95 to 100)	98 (95 to 99)	392 (380 to 400)	392 (380 to 396)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having SARS-CoV2 infection)		0 (0 to 0)	0 (0 to 0)	2 (0 to 5)	2 (1 to 5)	8 (0 to 20)	8 (4 to 20)	
True negatives (patients without SARS-CoV2 infection)	329 (4)	960 (881 to 980)	960 (911 to 980)	873 (801 to 891)	873 (828 to 891)	582 (534 to 594)	582 (552 to 594)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly classified as having SARS-CoV2 infection)		30 (10 to 109)	30 (10 to 79)	27 (9 to 99)	27 (9 to 72)	18 (6 to 66)	18 (6 to 48)	

CoE: Certainty of evidence

Table 8. GRADE Summary of Findings of Test Accuracy Results for Prevalence/Pre-Test Probability of 1%, 10%, and 40% for rapid isothermal NAAT and standard non-rapid laboratory-based NAAT vs. composite reference standard

	Rapid isothermal NAAT	Standard laboratory based NAAT
Sensitivity	0.81 (95% CI: 0.75 to 0.86)	0.99 (95% CI: 0.97 to 1.00)
Specificity	0.99.(95% CI: 0.96 to 1.00)	0.97 (95% CI: 0.93 to 0.99)

Outcome	No of patients (studies)	Effect per 1,000 patients tested						Test accuracy CoE
		Pre-test probability of 1%		Pre-test probability of 10%		Pre-test probability of 40%		
		Rapid isothermal NAAT	Standard NAAT	Rapid isothermal NAAT	Standard NAAT	Rapid isothermal NAAT	Standard NAAT	
True positives (patients with SARS-CoV-2 infection)	576 (4)	8 (8 to 9)	10 (10 to 10)	81 (75 to 86)	99 (97 to 100)	324 (300 to 344)	8 (8 to 9)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having SARS-CoV-2 infection)		2 (1 to 2)	0 (0 to 0)	19 (14 to 25)	1 (0 to 3)	76 (56 to 100)	2 (1 to 2)	
True negatives (patients without SARS-CoV-2 infection)	418 (4)	980 (950 to 990)	960 (921 to 980)	891 (864 to 900)	873 (837 to 891)	594 (576 to 600)	980 (950 to 990)	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly		10 (0 to 40)	30 (10 to 69)	9 (0 to 36)	27 (9 to 63)	6 (0 to 24)	10 (0 to 40)	

classified as having SARS-CoV-2 infection)								
False positives (patients incorrectly classified as having SARS-CoV-2 infection)		10 (0 to 40)	30 (10 to 69)	9 (0 to 36)	27 (9 to 63)	6 (0 to 24)	10 (0 to 40)	

CoE: Certainty of evidence

RNA Testing in Exposed Individuals (Asymptomatic)

Recommendation 8: The IDSA panel suggests SARS-CoV-2 RNA testing in asymptomatic individuals who are either known or suspected to have been exposed to COVID-19 *(conditional recommendation, very low certainty of evidence)*.

- **Remarks**:
  - Known exposure was defined as direct contact with a laboratory confirmed case of COVID-19.
  - Suspected exposure was defined as working or residing in a congregate setting (e.g., long-term care, correctional facility, cruise ship, factory, among others) experiencing a COVID-19 outbreak.
  - The risk of contracting SARS-CoV-2 may vary under different exposure conditions.
  - This recommendation assumes the exposed individual was not wearing appropriate PPE.
  - The decision to test asymptomatic patients will be dependent on the availability of testing resources.

Summary of the evidence

We did not identify any studies that directly assessed a strategy of testing *versus* no testing of asymptomatic individuals exposed to SARS-CoV-2. Therefore, the effect of testing on the pre-specified outcomes could not be directly assessed. We also did not identify test accuracy studies directly assessing the performance of SARS-CoV-2 NAATs in asymptomatic individuals. However, based on evidence that asymptomatic or pre-symptomatic patients may have similar viral loads and shedding compared to those who are symptomatic [89-91], the panel agreed that it is reasonable to apply test accuracy data based on symptomatic patients to

the asymptomatic populations. Hence, it was essential to determine the pre-test probability or prevalence of COVID-19 in the asymptomatic groups.

We assessed studies that reported the prevalence of COVID-19 among asymptomatic individuals in household clusters [89, 92, 93], a nursing home outbreak [94], active surveillance of passengers quarantined on a cruise ship or passengers of repatriation flights [95], hospital employees with close contact to COVID-19 positive patients [96], and customers and employees of a restaurant that had a COVID-19 outbreak [97]. Overall, prevalence ranged from 10% to 50% in settings where substantial transmission was suspected prior to testing. Summary statistics for single versus repeated testing are shown in **Table 9** and **Supplement H**. We acknowledge that information on individual exposure was limited in the evidence base. All these limitations led to very low certainty in the evidence overall.

Benefits and harms

Testing asymptomatic individuals who have been exposed, or suspected to have been exposed, allows for isolation for those who are positive. Whether in an institutional cluster or a wider community outbreak, isolation will help reduce further transmission. In addition, the CDC has recently updated their guidance to allow for a reduced duration of post-exposure quarantine. Shorter quarantine can help reduce economic hardship and lessen stress on the public health system but may not capture the incubation period for all individuals. Per CDC guidance, quarantine can now end on day seven after last exposure when an individual remains asymptomatic and has a negative test [98]. There is potential harm in a false negative NAAT result collected from an exposed individual who is actually infected; these individuals may incorrectly consider themselves non-infected, and unknowingly expose others to SARS-CoV-2 as a result. Some individuals may still be in the incubation phase, subsequently develop active viral shedding, and incorrectly consider themselves non-infected. A positive result, however, would reinforce the importance of isolation as well as inform contact tracing, cohorting, or other mitigation strategies.

Additional considerations

Diagnostic test performance in asymptomatic individuals has not been established. Assuming an overall test sensitivity between 75% and 95% [57, 58, 62, 64, 65, 99], false negative test results are expected. There is also cost to testing asymptomatic exposed individuals; since quarantine may still be indicated regardless of test results, such testing may add cost without changing practice. Data are limited to define definitions of close contact. Risk stratification of a given exposure can be made in consultation with public health authorities. In addition, the CDC has published guidance on defining healthcare exposures and categorizing exposure risks [100]. The ideal time to test an asymptomatic contact of a known or suspected COVID-19 case is also unknown. Timing also becomes complicated for household contacts with ongoing exposure. The average incubation period for SARS-CoV-2 has been determined to be five days [101]. Thus, testing five days following exposure may be a reasonable time frame to consider post-exposure testing and would allow time to obtain test results for discontinuation of quarantine as early as day seven post-exposure. In addition, data to inform the definition of a significant exposure or close contact are limited. Considerations when assessing the risk of a known contact include the duration of exposure and the clinical symptoms (e.g., cough) of the person with COVID-19.

Conclusions and research needs for this recommendation

Testing in asymptomatic subjects with known or suspected exposures should be coordinated with local public health officials. This indication for testing is especially important in situations where knowledge of asymptomatic or pre-symptomatic infection is essential for determining medical follow-up, defining risks for other vulnerable individuals in the household, congregate setting or hospital. Special consideration should also be given to healthcare personnel exposed without appropriate PPE in healthcare settings. Definitions of appropriate PPE can be found on the CDC website [102].

Comparative studies (preferably randomized controlled trials) along with cost-effectiveness analyses of testing strategies in asymptomatic populations are needed. Studies on the ideal time and collection method to test asymptomatic individuals who have been exposed to COVID-19 should be performed. In addition, what constitutes an exposure that would justify

testing requires further research. Whether early diagnosis of COVID-19 might provide an opportunity to intervene therapeutically and change the ultimate course of infection (i.e., prevent severe pneumonia) is unknown. If this is shown to be the case, the opportunity for therapeutic intervention might justify screening exposed individuals.

Table 9. GRADE Summary Table of Test Accuracy Results for Prevalence/Pre-Test Probability of 10% 25% and 50% for SARS CoV-2 NAAT

Sensitivity	0.75 (95% CI: 0.55 to 0.95)				
Specificity	0.99 (95% CI: 0.99 to 1.00)				
Outcome	**Effect per 1,000 patients tested** [d]			**№ of patients (studies)**	**Test accuracy CoE**
	Pre-test probability of 10%	**Pre-test probability of 25%**	**Pre-test probability of 50%**		
True positives (patients with COVID-19)	75 (55 to 95)	188 (138 to 238)	375 (275 to 475)	385 (6)	⊕◯◯◯ VERY LOW [a,b,c]
False negatives (patients incorrectly classified as not having COVID-19)	25 (5 to 45)	62 (12 to 112)	125 (25 to 225)		
True negatives (patients without COVID-19)	900 (891 to 900)	750 (742 to 750)	500 (495 to 500)	457 (2)	⊕◯◯◯ VERY LOW [a,b,c]
False positives (patients incorrectly classified as having COVID-19)	0 (0 to 9)	0 (0 to 8)	0 (0 to 5)		

CoE: Certainty of evidence

Explanations: This table is based on applying the sensitivity and specificity estimates to calculate True and false positives and negatives in a hypothetical population of 1000 individuals

a. Reference standard considered to be nasopharyngeal specimen RT-PCR.
b. Studies report test accuracy results but do not report on patient-important outcomes based on these results.
c. A small number of patients included.
d. We assessed studies that reported the prevalence of COVID-19 among asymptomatic individuals who were exposed to COVID-19 and determined that the prevalence may range from 10% to 50% based on household clusters, nursing home outbreak, active surveillance of passengers quarantined on a cruise ship or passengers of repatriation flights, hospital employees with close contact with COVID-19 positive patients and customers and employees of a restaurant that had a COVID-19 outbreak.

RNA Testing in Unexposed, Hospitalized Individuals (Asymptomatic)

Recommendation 9: The IDSA panel suggests against SARS-CoV-2 RNA testing in asymptomatic individuals with no known contact with COVID-19 who are being hospitalized in areas with a low prevalence of COVID-19 in the community *(conditional recommendation, very low certainty of evidence)*.

- **Remarks**:
  - Asymptomatic individuals are defined as those with no symptoms or signs of COVID-19.
  - A low prevalence of COVID-19 in the community was considered communities with a prevalence of <2%.
  - This recommendation does not apply to immunocompromised individuals.
  - This recommendation does not apply to individuals undergoing time-sensitive major surgery or aerosol generating procedures.

Recommendation 10: The IDSA panel suggests direct SARS-CoV-2 RNA testing in asymptomatic individuals with no known contact with COVID-19 who are being hospitalized in areas with a high prevalence of COVID-19 in the community (i.e., hotspots) *(conditional recommendation, very low certainty of evidence)*.

- **Remarks**:
  - Asymptomatic individuals are defined as those with no symptoms or signs of COVID-19.
  - A high prevalence of COVID-19 in the community was considered communities with a prevalence of ³10%.
  - The decision to test asymptomatic patients (including when the prevalence is between 2 and 9%) will be dependent on the availability of testing resources.

Summary of evidence

We did not identify any studies that directly assessed a strategy of nucleic acid testing for SARS-CoV-2 *versus* no testing before hospitalization for non-COVID-19 related reasons. We also did not identify test accuracy studies directly assessing the performance of SARS-CoV-2 viral RNA tests in asymptomatic individuals. However, based on existing evidence suggesting that asymptomatic or pre-symptomatic patients may have similar virus loads and shedding as those who are symptomatic [90, 91], the panel agreed to infer test accuracy for asymptomatic populations before being hospitalized.

It was also essential to determine the pre-test probability or prevalence of the disease in asymptomatic patients admitted to the hospital. We assessed studies that reported prevalence of COVID-19 among asymptomatic individuals in the community and determined that the prevalence may range from <1 to 10% [25, 103, 104]. This range pertains to communities where there is low levels or high levels (i.e., "hot spots") of transmission of COVID-19. Significant limitations with the available evidence led to very low certainty in the effect of testing overall.

After considering consequences of missing a diagnosis of COVID-19 both on the individual- and population-level, and considering the sensitivity of the available tests, the panel determined that a maximum threshold of <10-20 missed cases per 1,000 would be acceptable. Not testing individuals in low prevalence areas (<2%) met that threshold. However, in intermediate to high prevalence areas (>2%), not testing would lead to higher numbers of missed cases which the panel considered to exceed the acceptable threshold.

Benefits and harms

The panel considered the benefit of screening asymptomatic patients on admission to hospital in those areas where SARS-CoV-2 transmission is widespread ("hotspots"). The ability to identify positive patients and isolate them would help reduce the risk of nosocomial outbreaks. However, there is potential harm in missing infected individuals (i.e., false negative NAAT results). False negatives could ultimately result in transmission to healthcare workers or other patients. Assuming an overall test sensitivity between 75% - 95% [57, 58, 62, 64, 65, 99],

false negative test results are expected, and repeat testing may be necessary. Alternatively, false positive results would lead to unnecessary isolation, PPE usage and potentially cohorting with other positive patients.

Additional considerations

Determining the true prevalence of COVID-19 in the community is difficult, is changing over time, and may be underestimated, especially when test availability is limited. In addition, the panel's acceptable threshold for missed cases is expert opinion only and not based on cost-effectiveness data. There are costs and logistical challenges involved SARS-CoV-2 screening on admission. Ideally, test results should be available rapidly (i.e., results in an hour) to optimally inform bed management and need for isolation. However, not all hospitals may have access to rapid tests. In addition, when testing supplies are limited, prioritization of symptomatic patients may be required.

Conclusions and research needs for this recommendation

The panel's recommendations for testing asymptomatic patients on admission to the hospital do not address areas with intermediate prevalence (i.e., 2-9%). Individual institutions should base their testing strategies on available resources. Comparative studies (preferably randomized controlled trials) along with cost-effectiveness analyses of testing strategies in asymptomatic populations are needed. Well-designed point prevalence studies are also needed to better inform local and regional prevalence estimates. Shortages of PPE and/or testing for SARS-CoV-2 in some healthcare facilities may affect practicality of following the recommendation. Definitions as to what constitutes a hotspot or "high"-prevalence are needed. This recommendation may also need to be revisited over the course of the pandemic as rates of previously infected patients and healthcare workers, who may have protective immunity, change.

RNA Testing in Immunocompromised Individuals (Asymptomatic)

Recommendation 11: The IDSA panel recommends SARS-CoV-2 RNA testing in immunocompromised asymptomatic individuals who are being admitted to the hospital regardless of exposure to COVID-19 *(strong recommendation, very low certainty of evidence)*.

- **Remark**: This recommendation defines immunosuppressive procedures as cytotoxic chemotherapy, solid organ or stem cell transplantation, biologic therapy, cellular immunotherapy, or high-dose corticosteroids.

Recommendation 12: The IDSA panel recommends SARS-CoV-2 RNA testing (*versus* no testing) in asymptomatic individuals before hematopoietic stem cell (HSCT) or solid organ transplantation (SOT) regardless of a known exposure to COVID-19 *(strong recommendation, very low certainty of evidence)*.

- **Remark:** Testing should ideally be performed as close to the planned treatment/procedure as possible (e.g., within 48-72 hours).

Summary of evidence

We did not identify any studies that directly assessed a strategy of testing for SARS-CoV-2 *versus* no testing of asymptomatic individuals before transplantation or admission to the hospital. In addition, we were unable to evaluate the risks of delaying necessary transplants if testing was positive or not available and quarantine/delay of treatment was then required. A number of other professional societies have issued guidelines for HSCT or SOT candidates [105-108]. All current guidance recommends molecular diagnostic testing for SARS-CoV-2 shortly before transplantation [105-108]. If the results are positive, deferral is generally recommended. Recommendations 11 and 12 are paradigmatic situations for a strong recommendation, based on low certainty evidence, in order to avoid a potentially catastrophic event.

Benefits and harms

The panel considered that patients who will receive a transplant could suffer catastrophic outcomes if they have undiagnosed SARS-CoV-2 infection; hence, the strong recommendation in the setting of very low certainty evidence. The potential of nosocomial transmission of disease from an asymptomatic individual admitted to an inpatient ward of high-risk patients could also result in serious disease with poor outcomes. Although data are limited, there are reports documenting outbreaks of respiratory viruses in hospitalized immunocompromised hosts [109]. In addition, increased risks of severe adverse respiratory virus-related outcomes in this population are documented [110].

Additional considerations

While the panel recognized that testing capacity may be limited in some settings, the risk of not testing patients in this population and subsequent potential for nosocomial transmission and/or rapid progression of infection resulting in death would outweigh the benefits of not testing. We did not identify any test accuracy studies directly assessing the performance of NAAT in asymptomatic individuals or immunocompromised hosts. However, based on existing evidence supporting that asymptomatic or pre-symptomatic patients may have similar virus loads and shedding as those who are symptomatic [90, 91], the panel agreed that test accuracy data from symptomatic patients would apply to asymptomatic transplant candidates being hospitalized.

Conclusions and research needs for this recommendation

The limited data available indicates that heavily immunocompromised patients have increased risk of severe outcomes from COVID-19 disease. Therefore, testing asymptomatic patients at the time of hospital admission and/or before transplantation is warranted (e.g., testing within 48 hours). In addition, transplant candidates should be screened with a standardized questionnaire for symptoms and known exposures in between visits as well as before transplant.

Although case reports of COVID-19 disease in transplant recipients are accumulating, more information is needed. One important question to address is the safety of transplantation in COVID-19 recovered patients. This group of patients includes individuals whose symptoms have resolved, are typically more than 21 days post-SARS-CoV-2 diagnosis [111], but continue to have RNA detected in respiratory secretions by sensitive NAAT methods. Research on alternative methods of viral detection (e.g., subgenomic RNA) as a predictor of ongoing viral replication, longitudinal follow-up of RNA shedding, assessments of the potential for relapsed infection and general clinical outcomes in transplant patients due to multiple underlying conditions are necessary. Definition of the impact of antiviral therapy in this high-risk population is also needed, particularly as many of these patients may have not meet enrollment criteria for treatment trials.

RNA Testing Before Immunosuppressive Therapy for Cancer (Asymptomatic)

Recommendation 13: The IDSA panel makes no recommendations for or against SARS-CoV-2 RNA testing before initiating immunosuppressive therapy in asymptomatic individuals with cancer *(evidence gap)*.

- **Remarks**:
  - The decision to pursue testing should be individualized. Factors to consider include the type of cancer, the need for induction *versus* maintenance immunosuppressive therapy, the type of immunosuppressive therapy, patient comorbidities and the availability of testing.
  - This recommendation does not apply to hematopoietic stem cell transplant candidates or recipients.

Summary of methods and results

This literature review focused on patients with hematologic or solid tumor malignancies and excluded studies specifically focused on hematopoietic transplant candidates/recipients. We did not identify any study that assessed the impact of SARS-CoV-2 NAAT prior to starting cancer treatment. There were also no studies directly comparing COVID-19 outcomes in cancer patients receiving treatment to cancer patients not receiving treatment. We identified 11 studies that compared the outcomes of COVID-19 between cancer patients and patients without cancer [112-122] and 22 studies that reported the outcomes of COVID-19 in cancer patients [43, 123-143] (**Tables s4i and s4j**). Fourteen [123, 124, 128-133, 135-137, 141-143] of the outcome studies included regression analyses to look for predictors of mortality and poor outcomes among cancer patients; however, they were not consistent in terms of the variables adjusted for in the models. Additionally, cancer treatment status, cancer stage, and comorbidities were not included in the final multivariable analysis in many of the models.

Overall, the evidence identified was of very low quality. Important limitations in the published literature include the observational nature of the studies, risk of bias due to selection bias and confounding, inconsistency in results and indirectness. Indirectness was due to lack of direct assessments of the effect of SARS-CoV-2 testing before initiation of immunosuppressive therapy and absence of comparisons of COVID-19 outcomes in cancer patients who either were or were not receiving immunosuppressive treatment.

Studies comparing COVID-19 outcomes in patients with cancer to those without cancer

Of the 11 studies that reported COVID-19 related outcomes in patients with cancer compared to those without cancer, four were focused on hematological malignancies [114, 118, 119, 122], one on solid malignancy [116] and six did not specify the type of malignancy [112, 113, 115, 117, 120, 121]. The studies of patient with hematological malignancies showed a possible increase in the risk of poor outcomes, such as death and ICU admission, when compared to patients without cancer. The single study that focused specifically on solid

malignancies showed a comparable mortality rate across groups; but when patients were stratified based on age, outcomes of COVID-19 cancer patients younger than 50 were worse than age-matched controls without cancer. Of note, the number of patients and events was small, raising concerns regarding imprecision as well as risk of bias. The studies that did not specify the type of malignancy showed variable results, with some observing comparable outcomes and others showing worse outcomes in cancer patients compared to patients without cancer. Some of the studies in this group conducted regression models to assess predictors of poor outcomes, but these methods were not consistent in terms of variables included in the models. When the presence of cancer was included in the multivariable models, many studies showed a trend toward worse outcomes, although the confidence intervals crossed the line of no difference in most of models [113, 115, 119].

Studies evaluating COVID-19 outcomes among patients with cancer

Of the 22 studies that reported outcomes of COVID-19 in cancer patients, seven focused on hematological malignancies [43, 123, 125, 126, 128, 132, 135], three on solid malignancy [127, 139, 143] and 12 did not specify the type of malignancy [124, 129-131, 133, 134, 136-138, 140-142]. The seven studies of hematological malignancy included three that were focused on plasma cell disorders [43, 125, 126] and four that did not specify the type of hematological malignancy [123, 128, 132, 135]. Study sample sizes and all-cause mortality rates varied across studies, as shown in **Table 10**. A single study evaluated the outcomes of hospitalized cancer patients who presented with symptoms suspicious of COVID-19 found that a positive SARS-CoV-2 PCR was associated with increased risk of mortality (OR 1.92) compared to a negative SARS-CoV-2 PCR in univariable analysis; however, it did not meet the threshold of statistical significance to be included in the multivariable model [124].

Table 10. Summary of Studies assessing all-cause Mortality in Cancer Patients with COVID-19

Malignancy	Study size Total number of subjects (N) (Range; median)	All-cause Mortality % Range (median)
Plasma cell disorders (3 studies)	N= 99 (20-56; 21)	0-35% (12%)
Non-specified heme malignancy (4 studies)	N= 232 (35-536; 134)	36-40% (37%)
Solid malignancy (3 studies)	N= 839 (4-200; 28)	25-33% (29%)
Malignancy type not specified (12 studies)	N= 4,315 (18-928; 211)	10-34% (23%)

Studies assessing the effect of cancer type, disease stage and treatment type on outcomes in patients with COVID-19

We identified 14 studies that reported multivariable regression models assessing the effect of cancer and its treatment on COVID-19 outcomes [123, 124, 128-133, 135-137, 141-143]. Two studies limited to COVID-19 patients with hematological malignancies reported results of multivariable regression models assessing predictors of mortality. One showed increased mortality in patients receiving chemotherapy [132], while the other showed an increased risk of death in patients with progressive malignancy and different types of hematological malignancies, but no association with time since cancer diagnosis or last treatment [135]. An additional study limited to solid malignancies showed an association between severe events and receipt of antitumor therapy within 14 days in a multivariable model [143]. The remaining 11 studies included cancer patients regardless of the type of cancer. Of these, four studies assessed the association between anti-cancer treatment (not otherwise specified) and mortality; three showed an increased risk of death [130, 136, 142] while the fourth study showed a decreased risk [137].

Six additional studies assessed the association between chemotherapy and outcomes. Four of the chemotherapy-focused studies observed an increased risk of death in patients

receiving treatment [121, 130, 131, 141]. The remaining two studies had conflicting results with one showing increased risk of poor outcomes [133] and other one showing decreased risk of poor outcomes [129]. Hormonal therapy, immunotherapy and targeted therapy were associated with lower risk of death in one study [131], while two others showed increased risk of mortality in patients receiving immune therapy and/or targeted therapy [121, 138]. Patients with a recent diagnosis of malignancy tended to have a lower risk of mortality in one study [117]. Having active malignancy was associated with higher mortality in one study [137] and remission was associated with less poor outcomes in another study [129]. Similarly, risk of mortality was increased in patients with progressing malignancy as well as stable/responding malignancy compared to patients who were in remission [130]. As for the disease stage and the presence of metastases, they were associated with increased mortality and poor outcomes in three studies [117, 121, 136]; however, one showed less poor outcomes in patients with metastatic disease [138]. Patients with hematological malignancies tended to have a higher risk of mortality and poor outcomes [129, 130, 138]. Finally, having intrathoracic or pulmonary malignancies was associated with increased risk of mortality in one study [129] but decreased mortality in another study [117].

Benefits and harms

The potential benefits of SARS CoV-2 testing before initiation of cancer treatment include the ability to identify patients with asymptomatic or pre-symptomatic infection and then potentially delaying or adjusting treatment depending on an individual's risk for a poor outcome from COVID-19 weighed against the deleterious effect of delayed or interrupted cancer treatment. This may be particularly important when cytotoxic chemotherapy or other treatments that have major effects on protective immunity are planned. However, depending on the type and stage of the underlying malignancy, delaying cancer therapy may not be possible even if SARS-CoV-2 infection is detected. In this case, identification of asymptomatic or pre-symptomatic infection may still be useful because it has potential implications for SARS-CoV-2 treatment and infection control practices as well as for anticipation of potential complications and patient education.

The potential harms of testing include obtaining false positives results, especially when the prevalence of SARS-CoV-2 infection in the community is low. False positives may unnecessarily delay critical treatment of the underlying malignancy. False positives may also promote anxiety, and result in unneeded treatment for COVID-19 as well as unnecessary contact tracing related to the inaccurate diagnosis. True positive results may also lead to unnecessarily delayed or altered treatment, which may be harmful if certain cancer treatments (i.e., non-cytotoxic or less immunosuppressive therapies) do not substantially increase the risk of poor COVID-19 related outcomes.

Additional considerations

Hematologic and solid tumor malignancies are a diverse group of complex diseases. Current chemotherapeutic agents and biologic response modifiers used to treat cancer have variable effects on the immune system. Some, but not all, cancer treatment regimens are associated with an increased risk for developing infection, while other drugs might actually have protective effects. In the case of SARS-CoV-2 infection, limited data in the form of case reports suggests that receipt of Bruton tyrosine kinase inhibitors might be associated with less severe SARS-CoV-2 infection [144, 145]. It has also been speculated that immune checkpoint inhibitors could reduce the severity of COVID-19 complications. A single population-based study reported that receipt of androgen receptor signaling antagonists for prostate cancer was associated with a lower risk for acquiring SARS-CoV-2 infection [146]. Additional considerations related to the decision to perform nucleic acid amplification testing in asymptomatic cancer patients are the prevalence of infection in the community, the availability of testing and turn-around-time to test results.

Conclusions and research needs for this recommendation

In summary, most cancer studies reported poor outcomes in COVID-19 patients receiving cytotoxic chemotherapy as well as in those with active or progressive disease and/or hematological malignancies. Evidence linking recent oncologic therapy to COVID-19 complications was, however, mixed. Significant heterogeneity across study populations and

statistical analyses precluded making generalized conclusions about the impact of cancer type, disease stage and treatment type on patient outcomes. The number of patients and/or events was small in many of the models, which also raises concerns about imprecision. Most confidence intervals crossed the threshold of no difference. Furthermore, the factors adjusted for in different models varied widely and the selection for inclusion of variables in the models was dependent on findings of univariable analyses, which raise additional concerns about over-fitting combined with the effect of unknown confounders and excluded variables.

Going forward, interventional studies comparing testing *versus* no testing before initiation or continuation of immunosuppressive treatment are unlikely to be feasible. Thus, decisions about testing before initiation of oncologic treatment should be individualized and consider the availability of testing and whether the results would affect patient management decisions. Factors to consider include the urgency and type of treatment, underlying medical conditions and turn-around-time to SARS-CoV-2 NAAT results. Standardized symptom screens and queries regarding known contacts with laboratory confirmed cases are also useful to help guide targeted testing. To understand the potential impact of immunosuppressive therapies on COVID-19 outcomes, observational registries should ideally be prospective and enroll patients across a spectrum of infection severity and treatment modalities. Case-control studies that include well-matched controls could also be valuable for assessing the impact of different cancer therapies or diagnoses on patient outcomes.

RNA Testing Before Immunosuppressive Therapy in Individuals with Autoimmune Disease (Asymptomatic)

Recommendation 14: The IDSA panel makes no recommendations for or against SARS-CoV-2 RNA testing before the initiation of immunosuppressive therapy in asymptomatic individuals with autoimmune disease *(evidence gap)*.

- **Remark**: The decision to pursue testing should be individualized. Factors that may affect the decision to test include the type and severity of autoimmune disease, the type of immunosuppressive therapy, the need for induction *versus* maintenance immunosuppressive therapy, patient comorbidities and the feasibility of testing.

Summary of methods and results

We could not identify any studies that assessed the impact of SARS-CoV-2 nucleic acid amplification testing before initiation of immunosuppressive therapy for autoimmune disease on patient outcomes. Specifically, we searched for studies in which testing was performed prior to starting immunosuppressive therapy as treatment for rheumatologic, inflammatory bowel, dermatologic or neurologic autoimmune conditions. There was also a lack of studies directly comparing COVID-19 outcomes in patients with autoimmune disease on immunosuppressive therapy versus not receiving immunosuppressive therapy.

We did identify 33 studies (**Tables s4k and s4l**) that assessed the prevalence and outcomes of COVID-19 in patients with autoimmune conditions, including 15 studies of patients with rheumatologic disease [147-161], five studies of patients with dermatologic disease [162-166], two studies of patients with neurologic disease [167, 168], and 11 studies of patients with inflammatory bowel disease [169-179]. Some conducted regression analyses to assess the association between immunosuppressive therapy and COVID-19 outcomes, but reports were not consistent in terms of adjusting for other confounding variables [160, 161, 166, 172, 179]. The overall quality of the evidence was very low due to the observational nature of the identified studies, high risk of bias (mostly due to high risk of selection bias), inconsistent results among different studies and indirect comparisons.

Rheumatologic disease review

The prevalence of SARS-CoV-2 infection in the seven studies of patients with rheumatologic disease ranged from 0.2 to 47.2% (median 0.8%). The rate of hospitalization

ranged from 58.5-70.0% (median 68.8%, four studies), with an intensive care admission rate of 3.4-9.8% (median 5.9%, three studies), and a death rate of 0.0-26.3% (median 9.8%, seven studies). We identified three retrospective cohort studies that compared outcomes of COVID-19 in patients with and without rheumatologic diseases, and in patients on and off treatment for rheumatologic diseases [150, 160, 161]. Overall, there was no association between the presence of rheumatologic diseases, or their treatments, and poor outcomes in patients with COVID-19.

Inflammatory bowel disease review

The prevalence of SARS-CoV-2 infection in seven studies of patients with inflammatory bowel disease ranged from 0.0 to 3.0% (median 0.3%). The rate of hospitalization ranged from 26.6-66% (median 33.3%, seven studies), with an intensive care admission rate of 0.0-8.3% (median 3.6%, seven studies), and a death rate of 0.0-20.0% (median 5.0%, seven studies). We identified one retrospective cohort study that compared outcomes of COVID-19 in patients with and without inflammatory bowel disease [179]. It showed no association between the presence of inflammatory bowel disease and poor outcomes in patients with COVID-19. However, the correlation with specific treatment options or immunosuppression was unclear.

Dermatologic disease review

The prevalence of SARS-CoV-2 infection in the three studies of patients with autoimmune dermatologic disease ranged from 0.8 to 3.6% (median 1.1%). The hospitalization rate ranged from 20.0-66.7% (median 41.7%, three studies), with an intensive care admission rate of 16.7-33.3% (two studies), and a death rate of 0.0% (95% CI 0.0-26.5%; one study including 12 patients). We identified one retrospective cohort study that compared the prevalence and outcomes of COVID-19 in patients with plaque psoriasis on biologics to the population of the Lombardi region in Italy. Although univariable analysis showed an increased risk of COVID-19 in patients on biologics compared to the population, there was no association with intensive care admission or death [166].

Neurologic disease review

The prevalence of SARS-CoV-2 infection in the one study of patients with autoimmune neurologic disease was 0.04% (95% CI 0.0-0.15%; 4,864 patients). The hospitalization rate was 23.7% (95% CI 14.7-34.8; one study including 76 patients), and the death rate ranged from 0.0-7.8% (two studies). We could not identify any studies that reported intensive care admission rates or compared outcomes COVID-19 in patients with and without autoimmune neurologic disease.

Benefits and harms

The potential benefits of SARS CoV-2 testing before initiation of biologic therapy is the ability to identify asymptomatic or pre-symptomatic infection. Knowing a patient's SARS-CoV-2 infection status could inform treatment delay or adjustments depending on an individual's risk for poor outcomes from COVID-19 (particularly when medications that have major effects on cell immunity are planned) *versus* the deleterious effect of delayed or interrupted therapy for autoimmune disease. Identification of asymptomatic or pre-symptomatic infections also has potential implications for patient self-isolation recommendations, contact tracing and treatment. The potential harms of testing include obtaining false positives results, especially when the prevalence of SARS-CoV-2 infection in the community is low. False positives may lead to unnecessary delays in treatment, unnecessary treatment for SARS-CoV-2, and anxiety related to an (inaccurate) diagnosis of SARS-CoV-2. True positive results may also lead to unnecessarily delayed or altered anti-inflammatory therapy, if it turns out that treatment of infected patients does not increase risk of adverse COVID-19 outcomes.

Additional considerations

Biologic response modifiers are a diverse group of drugs with different mechanisms of action and variable effects on the immune system. Some, but not all, have been associated with an increased risk for developing infection including respiratory virus infections [180]. In contrast, several biologic agents including IL-6 and IL-1 inhibitors, as well as various Janus kinase (JAK) inhibitors, are currently being studied as treatments for the inflammatory response associated with COVID-19. Questions have been raised about whether these drugs may actually

reduce the risk for severe SARS-CoV-2 inflammatory effects in patients who are already receiving them for treatment of autoimmune disease. Additional considerations related to the decision to perform NAAT in asymptomatic patients is the prevalence of infection in the community, the availability of testing and turn-around-time to test results.

Conclusions and research needs for this recommendation

Currently, there is no evidence that patients with autoimmune disease or those receiving immunosuppressive biologic drugs are at an increased risk for becoming infected with SARS-CoV-2. However, there is theoretical concern that patients with SARS-CoV-2 infection who receive immunosuppressive treatment will be at increased risk of more severe COVID-19 disease, especially if they also have other underlying comorbidities and/or older age which predispose to worse outcomes. Concomitant chronic steroid use ($\geq$10 mg a day) may be a risk for poor COVID-19 outcomes, but this was not reproducibly observed across all studies. Interventional studies comparing nucleic acid amplification testing *versus* no testing before initiation or continuation of biologic therapy are unlikely to be feasible. Therefore, decisions as to whether to test before initiation of immunosuppressive therapy should be individualized and include an assessment of whether or not the results would change patient management decisions. Factors to consider include the urgency and type of treatment, underlying medical conditions and availability of SARS-CoV-2 NAATs. Standardized symptom screens and queries regarding known contacts with laboratory confirmed cases are also useful to help guide targeted testing. To understand the potential impact of immunosuppressive drugs on COVID-19 outcomes, observational registries should ideally be prospective, include larger numbers of patients across a spectrum of infection severity and evaluate clinically important outcomes. Case-control designs could include well-matched controls without autoimmune disease as well as studies evaluating specific groups of patients who are either receiving or not receiving common treatments for autoimmune disease.

RNA Testing in Unexposed Individuals Undergoing Major Time-Sensitive Surgeries or Aerosol-Generating Procedures (Asymptomatic)

Recommendation 15: The IDSA panel suggests SARS-CoV-2 RNA testing in asymptomatic individuals (without known exposure to COVID-19) who are undergoing major time-sensitive surgeries *(conditional recommendation, very low certainty of evidence)*.

- **Remarks**:
  - The panel defined time-sensitive surgery as medically necessary surgeries that need to be done within three months**.**
  - Testing should ideally be performed as close to the planned surgery as possible (e.g., within 48-72 hours).
  - To limit potential poor outcomes, deferring non-emergent surgeries should be considered for patients testing positive for SARS-CoV-2.
  - Decisions about PPE use for the aerosol generating portions of these procedures may be dependent on test results when there is limited availability of PPE. However, there is a risk for false negative test results, so caution should be exercised by those who will be in close contact with/exposed to the upper respiratory tract (e.g., anesthesia personnel, ENT procedures).
  - The decision to test asymptomatic patients will be dependent on the availability of testing resources.
  - This recommendation does not address the need for repeat testing if patients are required to undergo multiple surgeries over time.

Recommendation 16: The IDSA panel suggests against SARS-CoV-2 RNA testing in asymptomatic individuals without a known exposure to COVID-19 who are undergoing a time-sensitive aerosol generating procedure (e.g., bronchoscopy) when PPE is available *(conditional recommendation, very low certainty of evidence)*.

- **Remarks**:
  - The panel defined time-sensitive procedures as medically necessary procedures that need to be done within three months**.**
  - Procedures considered to be aerosol-generating are listed in **Table 11**.

Recommendation 17: The IDSA panel suggests SARS-CoV-2 RNA testing in asymptomatic individuals without a known exposure to COVID-19 who are undergoing a time-sensitive aerosol generating procedure (e.g., bronchoscopy) when PPE is limited, and testing is available *(conditional recommendation, very low certainty of evidence)*.

- **Remarks**:
  - The panel defined time-sensitive procedures as medically necessary procedures that need to be done within three months**.**
  - Testing should be performed as close to the planned procedure as possible (e.g., within 48-72 hours).
  - Decisions about PPE will be dependent on test results because of limited availability of PPE. However, there is a risk for false negative test results, so caution should be exercised for those who will be in close contact with/exposed to the patient's airways.
  - Procedures considered to be aerosol-generating are listed in **Table 11**.
  - The decision to test asymptomatic patients will be dependent on the availability of testing resources.
  - This recommendation does not address the need for repeat testing if patients are required to undergo multiple procedures over time.

Summary of evidence

The panel did not identify any studies that directly assessed a strategy of testing for SARS-CoV-2 *versus* no testing of asymptomatic individuals before undergoing major surgery or aerosol generating procedures (AGPs). The panel also did not identify test accuracy studies directly assessing the performance of SARS-CoV-2 NAATs in asymptomatic individuals. However, based on existing evidence supporting that asymptomatic or pre-symptomatic patients may have similar viral loads and shedding as those who are symptomatic, the panel agreed that test accuracy data from symptomatic patients could be applied to asymptomatic populations before surgery.

It was essential to determine the pre-test probability or prevalence of disease in the asymptomatic patients who will undergo surgery. We assessed studies that evaluated the prevalence of COVID-19 among asymptomatic individuals and determined that the range of prevalence would be between <1 to 10% based on assessing rates of infection in asymptomatic individuals in the general population in low prevalence and in "hotspot" areas [25, 103, 104]. The panel recommendation was based on emphasizing the importance of preventing infection in healthcare providers during major time-sensitive surgeries and AGPs. In addition, the very limited data showing poor outcomes in COVID-19 positive patients undergoing a major surgical procedure requiring intubation informed decisions to reduce this risk for asymptomatic patients [181]. There are no data that assess the outcome of AGPs in SARS-CoV-2 positive patients.

Benefits and harms

The benefit of suggesting testing for SARS-CoV-2 in asymptomatic patients undergoing major time-sensitive surgery is that it allows for the identification of infected patients before the procedure; thus allowing surgery to delayed based on the limited data suggesting that patients testing positive may have poor outcomes [181]. This approach also has the potential to inform healthcare workers in terms of PPE use, particularly in areas where PPE is limited. Of note, there is very low certainty evidence from retrospective case series suggesting poor outcomes of time-sensitive surgeries for those with COVID-19. The surgeries included were variable in complexity and it was not clear if the poor outcomes came mostly from major or

minor surgeries. However, it is plausible that poor outcomes were driven by the major surgeries.

A potential harm of testing of immunocompetent, asymptomatic patients before a major surgery or AGP is depletion of testing supplies and the diversion of all associated resources away from symptomatic patients. An additional harm of testing is related to the sensitivity of the NAATs for SARS-CoV-2, which will not detect all asymptomatic patients with COVID-19 infection. Therefore, some patients may be missed and healthcare workers at high risk could be exposed. Thus, the panel suggests that healthcare workers at the highest risk during surgical procedures (e.g., those performing intubation or ENT procedures) consider wearing PPE at all times, regardless of test results. This would be especially important in high prevalence areas (i.e., "hotspots"). An additional harm is that false positive tests for SARS-CoV-2 may unnecessarily delay a major time-sensitive surgery.

Additional considerations

There is no standard definition of what constitutes a major surgery. In general, the panel in consultation with surgical colleagues, agreed that major surgeries would be defined as more complicated and/or prolonged surgeries that require general anesthesia and intubation (which is an AGP). Additionally, time-sensitive surgeries/procedures were defined as those for which a delay greater than three months would negatively affect outcomes.

The panel prioritized two factors concerning these recommendations, namely avoidance of spread of COVID-19 to healthcare workers during AGPs as well as minimizing the risk of poor outcomes in patients undergoing major time-sensitive surgery when infected with SARS-CoV-2. There is no evidence of poor outcomes for patients with COVID-19 after AGPs. In these cases, testing could be considered to aid in decisions when PPE is limited. It should also be noted that the CDC does not prioritize asymptomatic patients undergoing procedures or surgeries for testing [182]. However, the panel felt that it is reasonable to consider these patients in local or state plans based on the availability of testing. Ideally, if PPE availability were unlimited, all healthcare workers should wear PPE for all AGPs and major time-sensitive surgeries. The

strategy of no testing eliminates the risk of false negative test results missing asymptomatic patients with COVID-19 infection but would increase use of PPE. In contrast, without testing, it would not be possible to identify asymptomatic patients with SARS-CoV-2 undergoing major time-sensitive surgery who might be at risk of poor outcomes. The feasibility of performing NAAT for SARS-CoV-2 for all asymptomatic patients undergoing AGPs and major time-sensitive surgeries will be impacted by the availability of testing as well as the turnaround time of the test results to providers. Logistically, individual institutions will need to decide whether a strategy of test and triage PPE or just use PPE matches available resources. An additional complexity is the need for repeated procedures or surgeries over time. Whether, and when, to retest should be considered on a case by case basis based on the potential risk for exposure in between procedures/surgeries.

Conclusions and research needs for this recommendation

Emergency surgeries and procedures should not be delayed for testing. Decisions around SARS-CoV-2 RNA testing before non-emergency, time-sensitive major surgeries and AGPs hinges on whether results will be used to inform optimal timing of the surgery and/or PPE requirements. The timing of testing should generally be within the 48 hours before the procedure. There are several important areas for future research, including assessing COVID-19 attributable outcomes after surgical procedures performed in the setting of an active infection and determining the risk of AGPs in asymptomatic individuals.

Table 11. Various Organizations' Lists of Aerosol-Generating Procedures*

	CDC (COVID-19 guidance)[1]	CDC (Seasonal influenza guidance)[2]	WHO (COVID-19 guidance)[3]	WHO (Epidemic and pandemic - prone acute respiratory diseases)[4]
Procedures listed	• Open suctioning of airways • Sputum induction • Cardiopulmonary resuscitation • Endotracheal intubation and extubation • Non-invasive ventilation (e.g., BiPAP, CPAP) • Bronchoscopy • Manual ventilation	• Bronchoscopy • Sputum induction • Elective intubation and extubation • Autopsies • Cardiopulmonary resuscitation • Emergent intubation and open suctioning of airways	• Tracheal intubation • Non-invasive ventilation • Tracheotomy • Cardiopulmonary resuscitation • Manual ventilation before intubation • Bronchoscopy	• Aspiration of respiratory tract • Intubation • Resuscitation • Bronchoscopy • Autopsy

CDC: Centers for Disease Control and Prevention; **WHO**: World Health Organization; **BiPAP**: bilevel positive airway pressure; **CPAP**: continuous positive airway pressure

*Accessed April 16, 2020

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Narrative Summaries of Diagnostics Undergoing Evaluation

SARS-CoV-2 antigen detection tests have recently become available. We anticipate systematically reviewing the clinical utility of these tests as data accumulates on their performance in comparison to NAAT. In addition, current NAATs detect genomic viral RNA but cannot distinguish infectious from non-infectious virus. This determination typically requires viral culture, which is not routinely performed in clinical laboratories for biosafety reasons and is likely less sensitive than NAAT. A number of investigators have described the use of assays designed to detect subgenomic RNA (sgRNA), which may be used in addition to standard NAATs targeting genomic RNA [183, 184]. The detection of sgRNA is thought to represent active viral replication and could be a surrogate for culture positivity. However, additional studies are required to determine the correlation between sgRNA detection and culture. Whether individuals who remain sgRNA positive after symptom resolution, and potentially seroconversion, remain infectious to others also is not known. Lastly, mRNA vaccines designed that encode the SARS-CoV-2 spike protein have received emergency use authorization. There is currently no evidence that receipt of the vaccine would interfere with SARS-CoV-2 molecular diagnostic testing.

Discussion

Molecular tests designed to detect SARS-CoV-2 nucleic acids are essential both for confirming COVID-19 diagnosis and for public health responses aimed at curbing the pandemic. Several countries have deployed NAAT on a massive scale as the cornerstone of a successful containment strategy. Although the United States was hampered by limited test availability early in the outbreak, there are now more than 180 different commercially available SARS-CoV-2 assays and multiple clinical laboratories have developed their own laboratory-developed

tests. Aggressive efforts are underway to assure access to testing, but regional differences in availability persist. Individual medical centers and clinics are likely to have different testing capacity as well. Furthermore, which test a laboratory or facility chooses to perform will vary based on the resources of a given setting (e.g., near-patient *versus* high complexity laboratory) and turn-around-time to result requirements (i.e., rapid *versus* standard).

The primary recommendations set forth in this guideline assume that SARS-CoV-2 testing is available to healthcare providers on the front lines. However, the panel also recognized that resources may vary, and contingency recommendations were developed for situations where NAAT supplies or PPE are limited. Individual institutions will need to prioritize testing based on available resources and unique patient populations. Testing for symptomatic patients should be prioritized. When testing capacity for symptomatic individuals is considered sufficiently robust, testing for asymptomatic individuals should be considered. There will undoubtedly be challenges prioritizing and implementing testing strategies for asymptomatic groups. The strongest recommendation for testing in asymptomatic individuals in this guideline pertains to immunocompromised patients being admitted to the hospital or in advance of transplantation.

Molecular tests have been central to our understanding of SARS-CoV-2. However, much about the biology of SARS-CoV-2 remains unknown. Early experience suggests that SARS-CoV-2 is detectable in the upper respiratory tract, with peak levels typically measurable during the first week of symptoms [61, 90, 185]. RNA detection rates, however, appear to vary from patient to patient and change over time. Some patients with pneumonia, for example, have negative upper respiratory tract samples but positive lower airway samples [64, 186]. Much less it known about the frequency of viral detection in asymptomatic individuals, although the concentration of detectable virus in some people with infection may be quite high [90, 91]. A better understanding of the spectrum of viral load kinetics over time at different anatomic sites is needed to inform decisions about the optimal testing strategies, including when and how to repeat if the first test is negative. Like other respiratory viruses, shedding of viral RNA in respiratory secretions may persist beyond resolution of symptoms and seroconversion [187].

Whether such patients remain infectious to others is uncertain and this is an important area for future study.

The clinical performance of commercially available SARS-CoV-2 molecular diagnostic tests depends in large part on the biology of the virus. Typically, when tests for the detection of viral respiratory pathogens are submitted to the FDA, both analytical and clinical performance data are provided. Under EUA, however, only analytical data are required. Diagnostic developers may test contrived specimens, by spiking viral RNA or inactivated virus into the desired matrix, rather than using real clinical specimens collected from patients with COVID-19. Thirty contrived positive and 30 negative specimens tested, with 95% sensitivity and 100% specificity required for EUA. Therefore, while we have information regarding the limit of detection of the test and evidence (both *in vitro* and *in silico* studies) that the primer design is specific for SARS-CoV-2, there is no information on how each test performs clinically at the time the EUA is issued. Clinical laboratories using commercial EUA tests must verify analytic test performance at some level in their own hands, including evaluation of different specimen types and collection methods (e.g., swab types and transport media).

Clinical performance metrics include sensitivity, which is the ability of the test to correctly identify those with infection, and specificity, the ability of the test to correctly identify those without the disease. In practice, the positive and negative predictive values of the test are also essential for interpreting test results. Estimations of community prevalence and patient pre-test probability combined with knowledge of test sensitivity and specificity are essential for determining the likelihood that an individual has COVID-19. In practice, however, the true prevalence of COVID-19 in the community may not be well-defined and may be underestimated when test availability is limited. In addition, while SARS-CoV-2 RNA tests are highly specific, their respective sensitivities are likely to vary. Recognizing these complexities, estimates of prevalence/pre-test probability and assay sensitivity were varied in our analyses based on the available literature in an attempt to mirror what may be encountered in clinical practice. Clinical test performance should also ideally be determined in prospective multicenter studies using a well-defined reference standard as the benchmark for test comparisons. **Table 12**

outlines the type of clinical studies needed to address the most pressing COVID-19 diagnostic knowledge gaps.

One of the most important problems with current COVID-19 diagnostic literature is the lack of a standard definition to define COVID-19. The studies included in the systematic reviews that informed this guideline used variable case definitions and many classified diseases based in part on the results of the index test under investigation. Incorporation of the investigational index test into the diagnostic "gold" standard falsely inflates sensitivity and specificity estimates (i.e., incorporation bias). **Table 13** outlines options for defining a confirmed COVID-19 case in diagnostic trials. It is recognized that not all individuals with COVID-19 will have detectable SARS-CoV-2 nucleic acid. Therefore, a "probable" case definition is also proposed. False negative NAAT results may be due to a variety of factors, including assay limit of detection, anatomic location and adequacy of specimen collection, timing of sampling relative to symptom onset, and underlying biology of disease. To fully understand SARS-CoV-2 viral dynamics, studies need to be designed to obtain specimens from multiple sites, ideally from the same patient at the same time. In addition, information on the duration of symptoms (if present), assessment of potential exposures and longitudinal follow-up of outcomes will be essential to define optimal diagnostic test strategies across a variety of patient populations.

Table 12. Suggested Diagnostic Studies

	Diagnostic Research Needs Addressing Symptomatic Patients	Diagnostic Research Needs Addressing Asymptomatic Individuals Known to Have Been Exposed to a Laboratory-Confirmed COVID-19 Case
Research Needs	1. Measurements of clinical test performance (assay sensitivity and specificity) 2. Specimen type and/or collection methods comparisons	1. Measurements of clinical test performance (assay sensitivity and specificity) 2. Percent test positive 3. Specimen type comparisons 4. Post-exposure outcomes including timing of positive test results after exposure
Study Design	• Prospective observational cohort, either cross-sectional or longitudinal • A priori defined diagnostic reference standard • Same specimen type(s)/methods collected from all enrolled subjects	• Prospective observational, longitudinal cohort • A priori defined diagnostic reference standard • Same specimen type(s)/methods collected from all enrolled subjects over time
Subjects	Symptomatic patients suspected to have COVID-19 stratified by URI, ILI and/or LRTI	Asymptomatic individuals known to have been exposed to a COVID-19 case
Required Clinical Information	Symptomatic patients suspected to have COVID-19 stratified by URI, ILI and/or LRTI	• Exposure assessment • Details of specimen collection • Timing of specimen collection relative to last exposure

URI: upper respiratory infection; **ILI**: influenza-like illness; **LRTI**: lower respiratory tract infection

Table 13. Proposed options for a diagnostic reference standard

CONFIRMED CASE OF COVID-19	
OPTION 1	Nucleic acid sequencing matches SARS-CoV-2 reference sequences
OPTION 2	Positive results from at least two different NAATs (one of the two may be the index test)
OPTION 3	Dual positive results from a single NAAT targeting two different genes (cannot be the index test)
OPTION 4	Compatible clinical signs and symptoms in a setting with known community transmission, negative reference NAAT and documented SARS-CoV-2 seroconversion.
OPTION 5	Compatible clinical signs and symptoms in a setting with known community transmission, negative reference NAAT and positive index test from two different anatomic sites.
PROBABLE CASE OF COVID-19	
OPTION 1	Compatible clinical signs and symptoms in a setting with known community transmission, negative reference NAAT and positive SARS-CoV-2-specific serology.

Conclusion

The guideline panel used a methodologically rigorous process to critically appraise the available diagnostic literature and formulate SARS-CoV-2 testing recommendations. The quality of existing evidence, however, was limited and not all of the data used to inform these recommendations had undergone peer-review. Based on low certainty evidence, the IDSA panel recommends nucleic acid testing for all symptomatic individuals suspected of having COVID-19. In addition, testing selected asymptomatic individuals is suggested when the results will have significant impact on isolation/quarantine/PPE usage, dictate eligibility for surgery, or inform use of immunosuppressive therapy. Ultimately, institutional resources will dictate test prioritization strategies. The critical components of future COVID-19 diagnostic studies include use of a well-defined reference standard with detailed descriptions of specimen types,

collection methods and their timeframe after symptom onset or exposure to a laboratory-confirmed case.

Notes

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COI Summary

The following list displays what has been reported to the IDSA. To provide thorough transparency, the IDSA requires full disclosure of all relationships, regardless of relevancy to the guideline topic. Evaluation of such relationships as potential conflicts of interest is determined by a review process which includes assessment by the Board of Directors liaison to the Standards and Practice Guideline Committee and, if necessary, the Conflicts of Interest (COI) and Ethics Committee. The assessment of disclosed relationships for possible COI is based on the relative weight of the financial relationship (i.e., monetary amount) and the

relevance of the relationship (i.e., the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. **K.H.** serves as an advisor for BioFire and Quideland and receives research funding from the National Institutes of Health (NIH). **A.C.** serves as an advisor for Roche Diagnostics, Danaher, Quidel, First Light, Day Zero, Visby, and Chroma Code; receives research funding from ArcBio and Hologic; and has served as an advisor for Luminex. **C.A.** receives royalties from UpToDate and receives research funding from Merck, MeMed Diagnostics, Entasis Pharmaceuticals and the National Institute of Allergy and Infectious Diseases (NIAID)/NIH. **M.H.** was a co-investigator on a research study for Sage, Medline, and Molnlycke; and received research funding from the Centers for Disease Control and Prevention. **J.E.** serves as a consultant for Sanofi Pasteur; an advisor/consultant for Meissa Vaccines; and receives research funding from the Centers for Disease Control and Prevention (CDC), Brotman Baty Research Institute, Merck, Novavax, GlaxoSmithKline, and AstraZeneca. **M.L.** serves as an advisor for Sanofi, Seqirus, and Medicago; has served as an advisor for Pfizer, Sunovion, and MD Brief; and receives research funding from the Canadian Institutes of Health Research and the Medical Research Council (United Kingdom). **R.P.** receives grants from Shionogi, CD Diagnostics, Merck, Hutchison Biofilm Medical Solutions, Accelerate Diagnostics, ContraFect, and TenNor; serves as a consultant for Curetis, Specific Technologies, Next Gen Diagnostics, Pathoquest, Selux Diagnostics, 1928 Diagnostics, PhAst, and Qvella; holds patent for *B. pertussis/parapertussis* PCR, device/method for sonification, and an anti-biofilm substance; receives research funding from the NIH, the National Science Foundation and the U.S. Department of Defense; and receives monies/reimbursement from the American Society for Microbiology (ASM), the Infectious Diseases Society of America (IDSA), the National Board of Medical Examiners, UpToDate, and the Infectious Disease Board Review Course. **Y.F.Y.** receives honoraria for evidence reviews and teaching from the Evidence Foundation, honoraria for evidence reviews for the American Gastroenterological Association, and serves as a Director for the Evidence Foundation and for the U.S. GRADE Network; and **M.H.M** receives research funding from the Agency for Healthcare Research and Quality (AHRQ), the Endocrine Society,

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nova scotia health authority

Primer on cycle threshold (Ct) values for the QEII laboratory, Central Zone Nova Scotia Health

The QEII Microbiology Laboratory has received multiple requests for how our polymerase chain reaction (PCR) tests are interpreted based on cycle threshold (Ct) values. The following is a brief FAQ on Ct values used in our laboratory for the detection of the virus that causes COVID-19, SARS-CoV-2. For a full discussion on interpretation of Ct values, please refer to the Public Health Ontario's excellent document Ct(Public Health Ontario)

What is a Ct value? Most nucleic acid amplification tests (NAAT) (like Reverse transcriptase PCR (RT-PCR) detect viral RNA through a process of amplifying targeted, specific strands of viral RNA The presence of the virus in a clinical specimen is determined by copying it in an exponential fashion through a temperature cycling reaction of up to 45 times. The presence of the viral copies are detected by a florescent signal produced during the reaction, which increases with the product. The number of amplification cycles required to create enough copies of the viral RNA to be detected is called the cycle threshold or Ct value.

How are Ct values used? The fewer amplification steps it takes to pass this threshold (a low Ct value) the more viral RNA is likely to have been present in the initial specimen; conversely more cycles required to amplify the viral RNA above the threshold (a high Ct value) suggests a lower amount of virus present in the initial sample. There can be up to 45 total number of cycles for many NAATs, and non-specific reactions can occur near the end of the cycling process that can mistakenly be flagged as positive by the instrument. The Ct value cutoff for positivity is defined by the vendor or the laboratory during the validation process to ensure that PCR is correctly detecting the presence of the virus.

Below is a table outlining how the different testing methods used at the QEII use Ct values to define positive results:

	Lab Developed Test[@]	GeneXpert SARS-CoV-2	Roche 6800 SARS-CoV-2	Panther
Total cycles	45	45	Not described	Not described
Genetic Targets	RdRp gene	E gene N2 gene	E gene ORF1 gene	ORF 1a/b gene
Definition of positive	RdRp Ct <35	Dual gene positive: E POS and Ct ≤ 37* N2 POS and Ct ≤ 37*	Dual gene positive: E POS and Ct ≤ 38* ORF1 POS and Ct ≤ 38*	As per instrument (does not produce a Ct value)
Definition of negative	RdRp Ct ≥38	E Neg N2 Neg	ORF1 Neg E Neg	As per instrument (does not

				produce a Ct value)
Definition of indeterminate**	RdRp Ct 35 - 38	Single gene positive: E POS and Ct ≤ 37* N2 Neg E Neg N2 POS and Ct ≤ 37*	Single gene positive: E POS and Ct ≤ 38* ORF1 Neg E Neg ORF1 POS and Ct ≤ 38*	As per instrument (does not produce a Ct value)

* Positive results with Ct above this value needs to be discussed with director who examines the amplification curve to help determine if this is a true or non-specific amplification

****Indeterminate report phrase:** SARS-CoV-2 (COVID 19) result indeterminate. This may represent early disease, late disease, or a false positive result. Please recollect once after 24 hrs if clinically warranted. If indeterminate result persist, please discuss with public health

¥ While RdRp is used for interpretation of the SARS-CoV-2 result in the LDT, the RT-PCR reaction also include a second target, the E gene (Corman et al) to increase specificity, and helps with the interpretation of specimens with high RdRp Ct values. A microbiologist would be notified of result where a single target detection with E gene only is observed, and the result would be interpreted using the same Ct value cutoffs as RdRp.

Important factors to consider in interpreting Ct values:

1) *Ct values will depend on the stage of infection* - During pre-symptomatic and early infection, the baseline viral load can be initially low which is associated with high Ct values i.e. >30 and above. This period may last hours to days. Ct value interpretation is further complicated by asymptomatic infections where the time of infection onset may be unknown. **Therefore, if clinically indicated, patients should undergo repeat testing within 24 to 48 hrs to determine if the Ct value is stable, rising or declining**.

2) *Individuals can shed detectable SARS-CoV-2 RNA for a prolonged period* – RT-PCR can be positive for over 100 days or more after infection, but in most cases are unlikely to transmit to others beyond 10 days post symptom onset.

3) *Ct values are affected by the type AND quality of the specimen* - Nasopharyngeal swabs (NPs) are the most sensitive specimen type in the outpatient setting; throat/nares swabs, and gargles may be less sensitive. Also in patient with lower tract infection (e.g. pneumonias), lower tract specimens are preferred as upper tract specimens may be negative. The quality of the sample collection directly impacts the amount of respiratory material collected and this directly affects the generated Ct value i.e., poorly collected samples can yield an artificially high Ct value (low RNA levels).

4) *Ct values are not comparable between different testing platforms* - The Ct ranges and distributions differ by the PCR technology used. There is no international standard to allow for comparison. Results of proficiency panels used in in other provinces where identical specimens were tested by different laboratories have seen variation of upto 8 Cts.

5) The impact of new variants on Ct values is not clear – While our current tests can detect the current SARS-CoV-2 variants identified in the UK and South Africa, ongoing surveillance is underway to identify novel variants and their potential impacts on diagnostic testing.

Does a certain Ct value predict who is infectious? This is a complex issue. There is good evidence that when more than 24 to 30 cycles are required to detect virus the virus concentration is so low that it becomes difficult to grow the virus in the laboratory (Bullard et al., 2020; Baslie et al., 2020; Singanayagam et al., 2020). However the cells used in the laboratory to grow the virus are different that cells in the back of the throat and nose (nasopharynx) or the lungs in people. So just because one can't grow the virus in a laboratory that does not mean that it won't transmit. Many

believe that with low copy numbers (high CT) values the virus is not likely to be transmitted. But we do not know how much virus is actually required to cause an infection in someone and there are other important factors that may influence infectiousness including the health of the person exposed and the type of exposure that has happened.

How does Public Health use Ct values? Considering the Ct values can be helpful when reviewing people with positive test results that are asymptomatic or in situations where there are concerns about potential false positive results.

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Look before diving into pooling of SARS-CoV-2 samples on high throughput analyzers

Jason J. LeBlanc[a,b,c,d,e#], Glenn Patriquin[a,b,c], Janice Pettipas[f], Michelle Warhuus[e], Darren Sarty[a], Colleen Jackson[a], Charles Heinstein[a], James MacDonald[a], David Haldane[a,b,c,d,f], Todd F Hatchette[a,b,c,d,e]

[a]Division of Microbiology, Department of Pathology and Laboratory Medicine, Nova Scotia Health, Halifax, Nova Scotia, Canada.

[b]Department of Pathology, Dalhousie University, Halifax, Nova Scotia, Canada.

[c]Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada.

[d]Department of Microbiology and Immunology, Dalhousie University, Halifax, Nova Scotia, Canada.

[e]Canadian Center for Vaccinology (CCfV), Dalhousie University, IWK Health Centre, and Nova Scotia Health, Halifax, Nova Scotia, Canada.

[f]Nova Scotia Provincial Public Health Laboratory Network (PPHLN), Halifax, Nova Scotia, Canada.

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[#]Corresponding Author:

Jason LeBlanc, PhD, FCCM, D(ABMM), Division of Microbiology, Department of Pathology and Laboratory Medicine, Nova Scotia Health, Room 404B, Mackenzie Bldg, Queen Elizabeth II Health Sciences Centre, 5788 University Ave, Halifax, NS B3H 1V8. Office: 902-473-7698; Fax: 902-473-7971; Email: jason.leblanc@nshealth.ca

Abstract

Given the unprecedented demand for SARS-CoV-2 testing during the COVID-19 pandemic, the benefits of specimen pooling have recently been explored. As previous studies were limited to mathematical modeling or testing on low throughput PCR instruments, this study aimed to assess pooling on high throughput analyzers. To assess the impact of pooling, SARS-CoV-2 dilutions were performed at varying pool depths (i.e. 1:2, 1:4, and 1:8) into test-negative nasopharyngeal or oropharynx/anterior nares swabs matrix. Testing was evaluated on the automated Roche Cobas 6800 system, or the Roche MagNApure LC 2.0 or MagNAPure 96 instruments paired with a laboratory-developed test using a 96-well PCR format. The frequency of detection in specimens with low viral loads was evaluated using archived specimens collected throughout the first pandemic wave. The proportion of detectable results per pool depths was used to estimate the potential impact. In addition, workflow at the analytical stage, and pre-and post-stages of testing were also considered. The current study estimated that pool depths of 1:2, 1:4, and 1:8 would have allowed the detection of 98.3%, 96.0%, and 92.6% of positive SARS-CoV-2 results identified in the first wave of the pandemic in Nova Scotia. Overall, this study demonstrated that pooling on high throughput instrumentation can dramatically increase the overall testing capacity to meet increased demands, with little compromising to sensitivity at low pool depths. However, the human resources required at the pre-analytical stage of testing is a particular challenging to achieve.

Introduction

In response to the 2019 novel coronavirus (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there has been an unprecedented demand for laboratory testing. Molecular methods such as real-time reverse transcription polymerase chain reaction (RT-qPCR) have been the primary testing method and a fundamental tool in patient management and public health containment and mitigation strategies.[1-5]

In the initial stages of the pandemic, testing was restricted to symptomatic individuals with a compatible travel history to an area of COVID-19 concern; however, our understanding of SARS-CoV-2 epidemiology improved and the recommendations for testing evolved over time. With global spread and data suggesting the possibility of SARS-CoV-2 transmission through asymptomatic or pre-symptomatic individuals, travel requirements or presence of compatible symptoms were no longer a prerequisite for testing.[6-9] Subsequently, the demand for testing became overwhelming, and laboratories were challenged by insufficient testing supplies.[1,10-13] As COVID-19 cases began to decline, the pressure on laboratories to meet testing demands continued, as testing remained a cornerstone to support the reopening of the economy and easing of public health restrictions.[14,15]

A possible strategy to increase testing capacity and gain laboratory efficiencies, is group testing (i.e. specimen pooling). While many pooling permutations are possible, its simplest application involves combining patient samples prior to testing, and retesting of individual specimens following identification of a positive pool.[16-23] The optimal number of specimens within pools (i.e. pool depth) can be estimated through mathematic modeling, and varies with disease prevalence and assay performance.[16-38] While larger pool depths may achieve higher efficiency, the trade-off is reduced sensitivity and the potential generation of false negative results.[18-23, 31-38] When prevalence is low, typically only a subset of specimens with low viral loads pass undetected.[18-23, 31-38]

Pooling using RT-qPCR has been applied for surveillance of various infectious diseases in both animals and humans.[39-42] For SARS-CoV-2, pooling has been applied in modelling or for relatively small throughput instruments with varying pool depths [16-38], but no studies have described the impact of pooling on automated high throughput analyzers. This study validated pooling of specimens for SARS-CoV-2 testing at different pooling depths on high throughput analyzers, and discusses some practical considerations prior to implementation.

Methods

Pooling efficiency modeling

The impact of prevalence and pooling depth on testing capacity was modeled as previously described [17] with online software (https://www.chrisbilder.com/shiny), using an assumption of RT-qPCR sensitivity of 95% and specificity of 99.9%. Testing capacity was calculated for prevalence values spanning 0.1 to 10%, and for pooling depths ranging for 3 to 10. A value above 100% indicates testing capacity is increased.

Specimen collection and pooling

The collection of specimens for SARS-CoV-2 RT-qPCR testing were performed using a flocked nasopharyngeal (NP) swabs collected in 3.0 ml of universal transport medium (UTM) (Copan Diagnostics Inc., Murrieta, CA), or a Aptima Multitest swab (Hologic Inc., San Diego, CA) for oropharynx/anterior nares (OP/Na) collection in 2.9 ml of specimen transport medium (STM).[10] Each specimen was stored at 4°C until testing, and aliquots were stored at -80°C. For pooling, specimens were diluted in triplicate using a Voyager 8-channel adjustable tip spacing pipette (Integra Biosciences Corp., Hudson, NH) at ratios of 1:2, 1:4, and 1:8, to achieve volumes of 1.5 ml. Dilutions were performed using negative matrix (UTM or STM), consisting of combined SARS-CoV-2 test-negative specimens (n≥48).

Nucleic acid extraction and RT-qPCR

Swabs material and dilutions were processed with one of three RT-qPCR methods. First, the SARS-CoV-2 assay was used on the automated Cobas 6800 system (Roche Diagnostics, Laval, QC). For NP specimens in UTM, 600 µl was processed directly, but for the OP/Na swabs in STM, 200 µl was diluted into 1 ml of Cobas omni Specimen Diluent prior to use.[10] Threshold cycles (Ct) values were categorized as positive with dual target positive results (E gene and Orf1a), indeterminate for single target results, or negative

in absence of Ct values. The two remaining methods used different extraction methods where a Total Nucleic Acid (TNA) extraction was performed on either a Roche MagNApure LC 2.0 or MagNAPure 96 instrument, and paired with a laboratory-developed test (LDT) [1,10,11]. Briefly, TNA was extracted from 200 µl of specimen, eluted into 50 µl of elution buffer, and 5 µl was used as template in a duplex RT-qPCR targeting the SARS-CoV-2 envelope (E) [43] and RNA-dependent RNA polymerase (RdRp). Amplification was performed on an Applied BioSystems 7500 Fast system (Thermo Fisher Scientific, Mississauga, ON). Results were categorized as positive with dual target positive results with Ct values ≥38, indeterminate for single target results between 35 and 38 (unless confirmed by another method with a different genetic target), or negative for Ct values ≥38.

Estimated impact of pooling on SARS-CoV-2 detection

For each instrument and swab type, a limit of detection (LoD) analysis was performed using 10-fold serial dilutions of previously positive SARS-CoV-2 specimens in UTM or STM, in comparison to viral dilution at varying pool depths (i.e. 1:2, 1:4, and 1:8). Virus concentration was estimated in relation to a standard curve with quantified virus provided by the National Microbiology Laboratory (NML) (Winnipeg, MB).[31] Ct values for specimens dilutions at different pooling depths were compared to undiluted specimens, and used to defined the subsequent analyses.

The frequency of detection in specimens with low viral loads (i.e. Ct values near the defined in the LoD for each pool), was assess retrospectively using archived specimens at -80°C. The proportion (%) of detectable results per Ct value category was used to estimate the potential impact of pooling in previous results obtained in Nova Scotia from January 24th, 2020 to June 26th, 2020. Results were categorized by Ct values, instruments, and RT-qPCR targets.

Considerations for specimen workflow, turnaround times, and human resources

Using direct observation, the average (n=10) hands-on times tasks required for each instrument was estimated, the theoretical daily maximum specimen throughput was estimated assuming ideal conditions, with no restrictions for human resources, reagents/consumables, or cost. Maximal testing capacity assumed retesting of individuals specimen from positive pools would occur on a separate instrument with equivalent sensitivity [1,17,44-47]. Human resources required for analytical, and pre and post-analytical processing were estimated. Pre-analytical steps accounted for the specimen registration into the hospital laboratory information system (LIS) (i.e. 3-5 min/specimen), labelling, and aliquoting. Analytical steps included specimen organization, pooling, and any instrument pre-processing steps. Post- analytical steps included result interpretation, reporting, and notifications to ordering physicians, infection prevention and control, and public health.

Results

Epidemiology and impact of prevalence on testing capacity at various pool depths

In Nova Scotia, the overall daily positivity rates varied from 0.0% to 8.0%, and daily fluctuations were evident (Figure 1A). Using mathematical modelling, it was demonstrated that pooling depths between 3 and 8 were inefficient at a prevalence of ≥8%, and pools of 9 or 10 were inefficient at a prevalence of ≥6% (Figure 2). However, at low prevalence, testing capacity increased with pool depth.

Estimated impact of pooling on SARS-CoV-2 detection

Using LoD analyses, the potential impact of pooling at depths of 1:2, 1:4, and 1:8 was assessed for each instrument (Figure 2). Compared to undiluted controls, increasing pool depths progressively reduced the analytical sensitivity, as seen by the decrease in SARS-CoV-2 RNA detection near the LoD, and the incremental increase of approximately 1 to 2 Ct values for each pooling dilution (Figure 2). Similar trends were noted for both NP and OP/Na swabs collections on each instrument (Figure 2). It should be noted

that OP/Na specimens required an initial pre-processing step (i.e. 1:6 dilution in manufacturer diluent) on the cobas 6800 instruments and, NP swabs in UTM therefore achieved lower LoDs.[10] Moreover, the cobas 6800 was more sensitive than the LDT paired with the MagNAPure 96and processing on the MagNAPure LC was the least sensitive method. Regardless of the comparative differences in analytical sensitivity, similar trends were noted for the relative reduction in sensitivity with increasing pool depths compared to the undiluted controls.

To further quantify the potential impact of pool depth, the frequency of detection was compared against previously tested specimens with low viral loads (i.e. Ct values ≥33 on the cobas 6800 or Ct values ≥32 on the LDT). Of 134 archived specimens retested on the cobas 6800, 113 yielded a detectable signal and Ct values were categorized (Figure 3A). Similar approaches were used for the LDT (Figure 3C). Overall, the frequency of SARS-CoV-2 detection with high Ct values decreased as the pooling depth increased (Figure 3). Using these proportions, the number of specimens that would have been missed during the first pandemic wave was estimated (Figure 3B and D). Excluding the 21 indeterminate results that were not reproducible, the proportion of specimens missed for pooling depths of 1:2, 1:4, and 1:8 would be 1.6% (9/570), 5.3% (30/570), and 11.1% (63/570), respectively (Figure 3B). Similarly, if the 17 indeterminate results were excluded for the LDT data, the proportion of specimens missed for pooling depths of 1:2, 1:4, and 1:8 would be 1.8% (12/677), 3.0% (20/677), and 4.4% (30/677), respectively (Figure 3D).

Considerations for workflow and maximal specimen throughput

The theoretical maximal daily specimen throughput for each instrument was estimated, and increased with pool depth (Figure 4). In terms of specimen processing, the FTEs required in the pre-analytical steps were prominent, and increased with pool depth. These were primarily attributed to specimen registration (Figure 5). The FTE requirements in analytical phase were unchanged by pool depths, and

158 only a small increase would be required in the post-analytical stage given the manual steps required
159 result interpretation, reporting, and communication.

160 **Discussion**

161 Given the unprecedented demand for COVID-19 testing, the benefits of pooling have recently been
162 explored for the diagnosis of SARS-CoV-2. To date, pooling for SARS-CoV-2 has been limited to
163 mathematical modeling or testing on low to moderate throughput RT-qPCR instruments.[16-38] In this
164 study, pooling assessed on high throughput analyzers was shown to increase testing capacity with
165 minimal reduction in analytical sensitivity at low pool depths. This study also considered the potential
166 impacts of pooling at the pre- and post-analytical stages. Overall, the theoretical capacity of high
167 throughput instruments could attain over 5,000 tests a day with a conservative pool depths of 1:4, but
168 the human resource required in the pre-analytical stage would be the most significant barrier to
169 implementation.

170 Since first proposed by Dorfman in 1943 [16], pooling has been well recognized as a strategy to gain
171 efficiency and increase testing capacity.[*] Mathematical models have been developed to help choose
172 the optimal pool depth that would achieve maximum testing capacity, for a defined disease prevalence
173 and instrument performance characteristics.[16-23] Using modeling data for the Cepheid Xpert COVID-
174 19 assay, Becker *et al.* [17] suggested that a pool size of 6 was ideal at a positivity rate of 3%, but at
175 7.6%, a pool size of 3 would be more efficient. However, in this study, when using modelling to assess
176 the value of pooling at a given prevalence, and establishing a cutoff to decide when to switch between
177 different pooling depths, it was shown that fluctuations in the daily positivity rates needed to be
178 considered. For example, during times of the peak detection of SARS-CoV-2 cases in Nova Scotia, the
179 daily positivity rates fluctuated between 2 and 8%. At these rates, and using a conservative pooling
180 depth of 1:4, testing capacity would range between being efficient (at 208%) and being inefficient (at

92.3%). However, rates as high as 8% were infrequent, so a pool depth of 1:4 would have been efficient throughout the entire pandemic wave with the exception of a single day that reach a positivity of 8%. Even a pool depth of 1:8 would have been efficient for all but 3 days, when prevalence exceeded 6%. Therefore, a significant amount of resources could have been saved by pooling in Nova Scotia.

Whether used to meet increased testing demands or as resource sparing strategies, the benefits of each pool depths must be balanced against the potential concomitant loss in sensitivity. Typically, in times of high disease prevalence, pool depth is kept as low as possible to achieve desired testing capacity. In times where prevalence is low (i.e. ≤2%), higher pool depths could be tolerated to conserve reagents in preparation for subsequent waves of COVID-19, or as a mechanism to increase testing capacity to support broader surveillance strategies.[8,15,28-34] This study, like others, showed that higher pool depths increase the risk of false negative results, as the inherent loss in sensitivity fails to identify a proportion of specimens with low viral loads.[17,18,21,23,31,33,36] Typical pool depths used for SARS-CoV-2 RT-qPCR testing range from 3 to 12 [17,31,37,38], yet higher pool depths have been attempted [18,21,23,26,34]. In an extreme example of high pooling depth, Hossain *et al.* [48] released an unpublished document that describes pooling of up to 19,200 RNA samples for simultaneous detection of SARS-CoV-2 using next-generation sequencing (NGS). While NGS technology could be a powerful tool for disease surveillance, this protocol was not validated for clinical testing, and the authors did not consider the significant loss of sensitivity that would likely occur from such a substantial level of pooling.

The extent to which specimens are pooled is predicated on the level of risk that is deemed acceptable. For example, the Canadian Blood Services (www.blood.ca) commonly used a pool depths of 1:6 for bloodborne pathogen screening using RT-qPCR, to ensure adequate sensitivity even if the overall disease prevalence is low. Overall, the current study estimated that pool depths of 1:2, 1:4, and 1:8 would have allowed the detection of 98.3%, 96.0%, and 92.6% of positive SARS-CoV-2 results identified

in the first wave of the pandemic in Nova Scotia. Without a prospective comparison, it is difficult to ascertain the true impact of the SARS-CoV-2 cases with low viral loads that would potentially have been missed with pooling. Specimen pooling should have a minimal impact on clinical sensitivity for detection of new symptomatic cases, as high viral loads are generally present during this stage of illness.[7,49-56] Similarly, missing SARS-CoV-2 in individuals with low viral loads in the recovery stage might impact the epidemiologic case counts, which is important for public health contact tracing, but would have little value for patient management as these individuals are likely no longer infectious.[18,36,49-52]. Conversely, undetected low viral loads may represent asymptomatic individuals or those in early or late stages of infection.[49-56] To mitigate the risk of missing early or pre-symptomatic infections with pooling, individuals should be encouraged to self-monitor for symptoms, self-isolate, and undergo repeat testing at defined time points.[5,8,14,15,17,28,29] On a population level, a combination of pooling, mass testing, and repeat testing could help cases that would otherwise not have been captured with routine individual testing.[8,14,15,28,32-34] In other words, the decreased sensitivity that is inherent to pooling could theoretically be offset by the reciprocal increased testing capacity, if mass testing and repeated testing over time would improve case finding.

From an analytical standpoint, testing capacity increases with pooling depth if prevalence is low, and the risk of generating false negative results with pooling is minimized by using the most sensitive method available. In this study, both the analytical sensitivity and daily specimen throughput was shown to be highest on the Cobas 6800, and specimen throughput increased with pool depth. The impact of high prevalence on testing capacity could be reduced by retesting positives pools on a secondary instrument, rather than resolution of pools on the subsequent run on the same instrument; however, the secondary assay should have equal or greater sensitivity. The Cepheid Xpert Xpress SARS-CoV-2 is a rapid molecular assay has been shown to have comparable performance to the Cobas 6800 [10,31,44-47], but was not assessed in parallel in this study due to the limited availability of tests. In times of low prevalence and

reduced test numbers, positive pool resolution could easily be accommodated on the same instrument used for initial pool testing; however, lower throughput analysers could be considered for smaller test volumes, recognizing the relative decrease in sensitivity of these methods would have less of an impact during times of low disease prevalence. Whether in time of high or low prevalence, testing should not be based on maximal instrument capacity, but on established turnaround time goals, to avoid delays in specimen result reporting. Overall, pooling on high throughput analyzers could be undertaken with only minor changes to the analytical workflow.

No previous study has described the potential impacts of pooling at the pre- and post-analytical stages of testing. First, there are a number of factors that influence pre-analytical steps that are outside the scope of this study (e.g. specimen type, quality and timing of collection, and transport conditions). Once specimens arrive to the laboratory, routine activities in the pre-analytical stage include registration, labelling, aliquoting, and any pre-processing steps required prior to testing. While automation (i.e. robotics) could be used to enhance specimen traceability, reduce the potential for contamination, and help with specimen organization [20,23], the biggest contributor to workload in the pre-analytical stage in our laboratory is specimen registration into the laboratory information systems (LIS). The LIS eventually communicates the test results to the ordering physician, and other healthcare providers (e.g. infection prevention and control, and public health). Specimen registration is crucial to all laboratory testing. Meeting the FTE requirements that accommodate higher testing capacity is one of the biggest barriers to pooling on high throughput analyzers in our laboratory. In contrast, at the post-analytical stage, FTE requirements required to increase testing capacity would be subtle, and largely dependent on the time required for result interpretation, reporting, and communications. These processes could potentially be streamlined with automation if the instruments are interfaced to the LIS. Future studies will explore the incremental benefits of automation at the pre- and post- analytical steps, paired with specimen pooling on high throughput analyzers.

252 This is the first study reporting the performance of pooling on a high throughput analyzers, with
253 considerations for workflow at the analytical stage, and pre-and post-stages of testing. Assuming
254 reagent availability, the most significant barrier to implementation of pooling in our laboratory is not the
255 instrumentation, but the number of FTEs required to support specimen collection and registration.
256 Careful consideration should be given to all aspects of testing prior to implementation of pooling.

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440

441 **Figure legends**

442 **Figure 1.** Epidemiology of SARS-CoV-2 in Nova Scotia, and impact of prevalence and pool size on testing
443 capacity. A) The total number of SARS-CoV-2 tests performed (histograms) and positivity rates (in red)
444 are plotted against a time. NP swabs in UTM are depicted in yellow, and OP/Na swab in STM are in blue.
445 B) Testing capacity is plotted against the positivity rate for each pool depth. A value of above 100% was
446 considered an increase in testing capacity, whereas values below 100% were deemed inefficient.

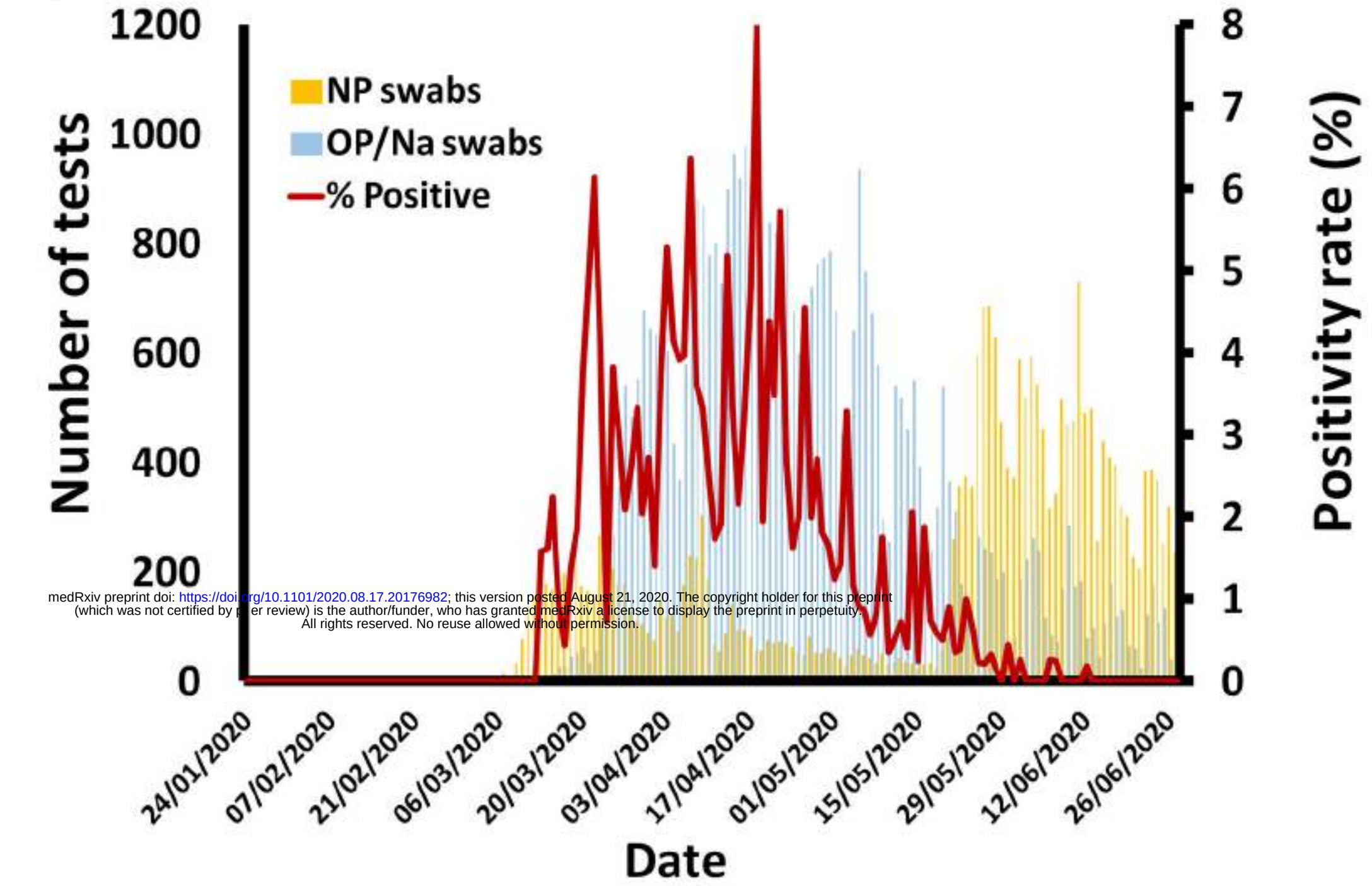
447 **Figure 2.** Impact of pool depth on the analytical sensitivity. Ten-fold serial dilutions of SARS-CoV-2 were
448 tested on each instrument and for each swab type, and compared to the same dilutions processed using
449 pooling depths of 1:2, 1:4, and 1:8. Note: The results for the E gene target for each instrument are
450 shown, but similar results were observed for the other RT-qPCR targets: RdRp in the LDT assay, or Orf1a
451 for the cobas 6800 (data not shown).

452 **Figure 3**. Impact of pooling on the detection of low SARS-Cov-2 viral loads. A) The frequency of
453 detection in specimens with low viral loads was assess using previously tested specimens. B) The
454 proportion (%) of detectable results per Ct value category obtained in A) applied to estimate the
455 potential impact of pooling a depths of 1:2, 1:4, and 1:8. Results were categorized by instruments and
456 RT-qPCR targets, and the E gene target results are depicted. Results for the alternative targets (i.e. Orf1a
457 on the cobas 6800, or the RdRp target on the LDT) showed similar trends as E gene for each instrument
458 (data not shown).

459 **Figure 4.** Estimated workflow for maximal specimen throughput on each study instrument based on
460 pool depth. Hands-on time (red), automation (blue), and times required specimens to be loaded onto
461 the instrument (triangles) are illustrated. Ideal workflow assumed resolution of positive pools using a
462 secondary method with equal or greater sensitivity (e.g. Cepheid Xpert Xpress SARS-CoV-2 assay,
463 annotated "Xpert" on the figure.

464 **Figure 5.** Estimated FTE requirements to achieve maximum instrument capacity. By monitoring the time
465 required for routine testing activities (n=10), the average time required for each tasks involved at the
466 pre-analytical, analytical, and post-analytical stages of testing were estimated for each instrument, and
467 expressed as the number of full-time employees (FTE) required to support testing at different pool
468 depths.

A)



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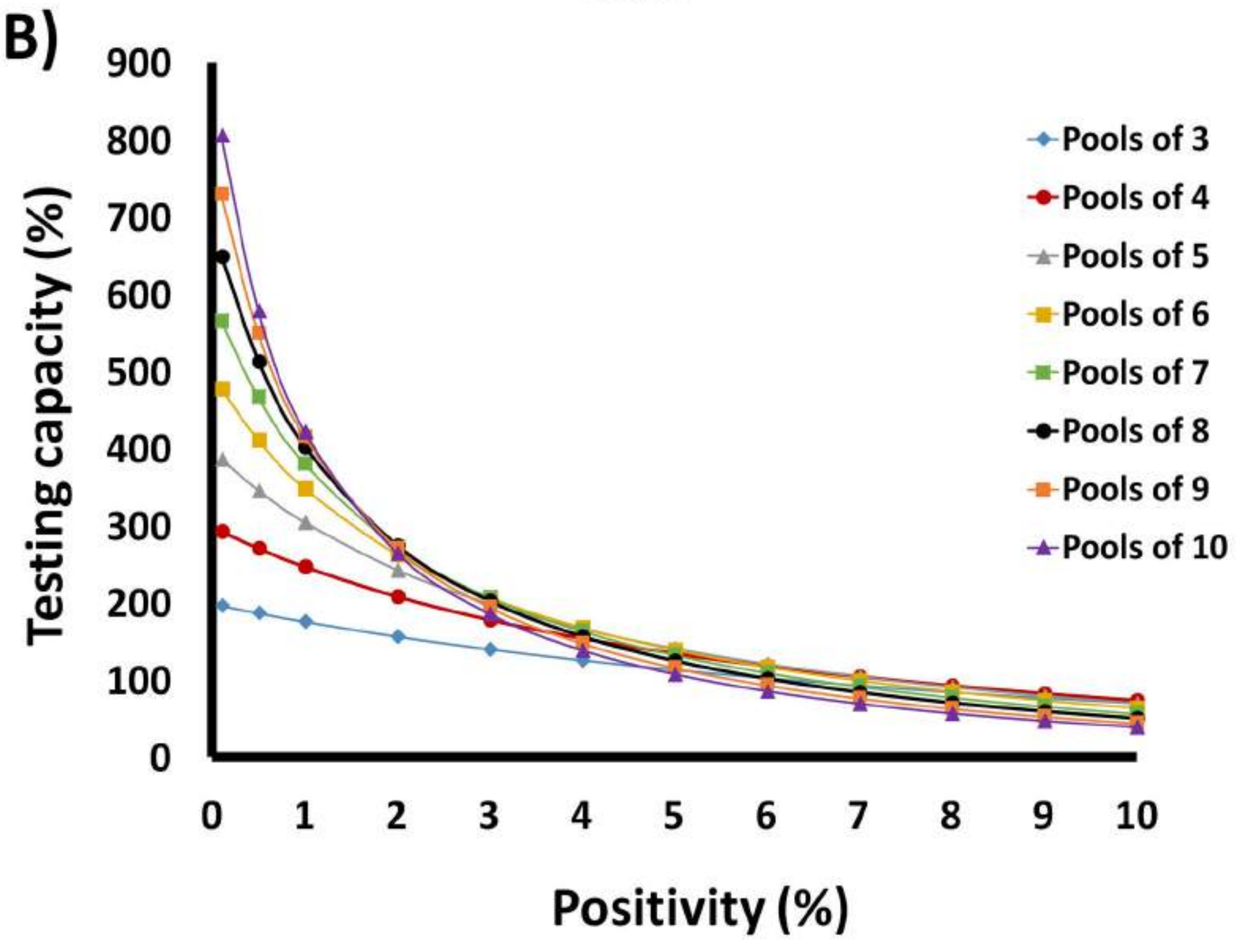

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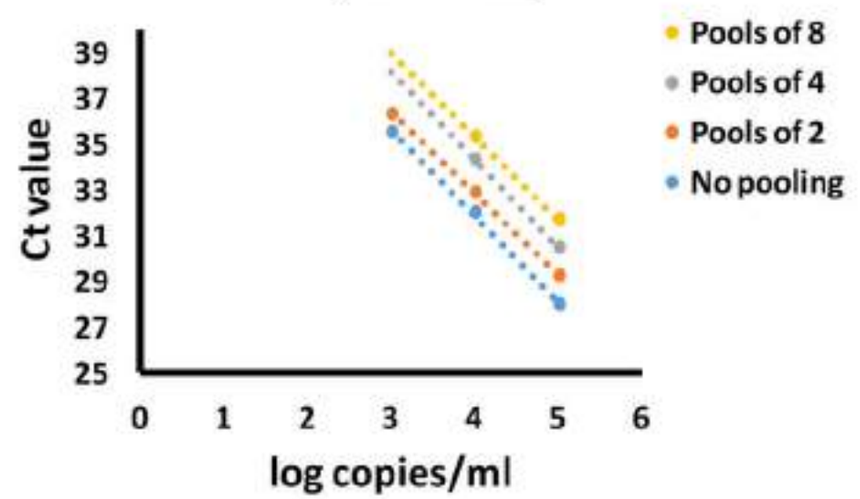

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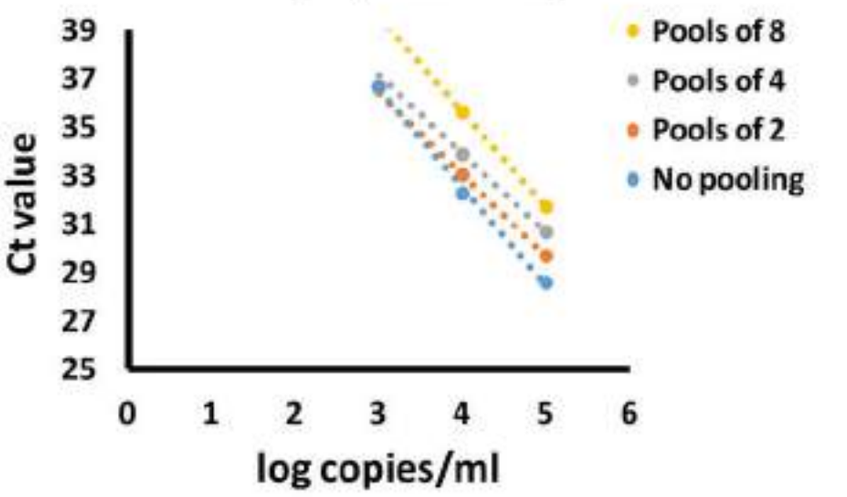

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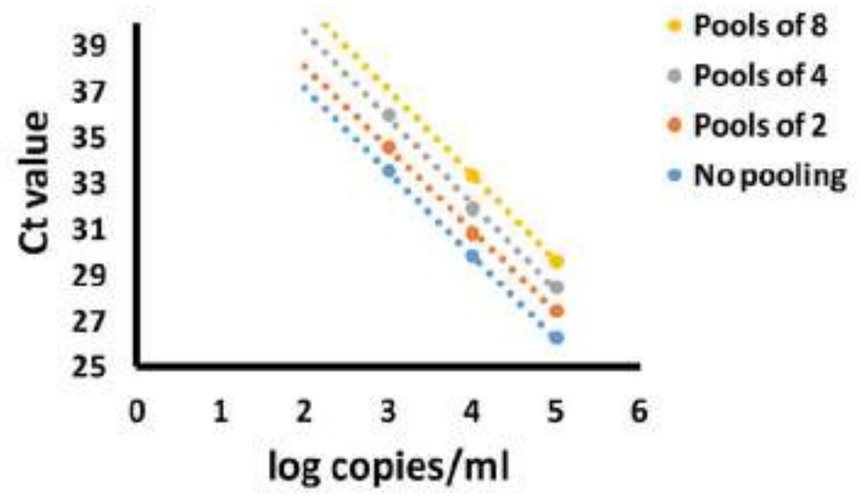

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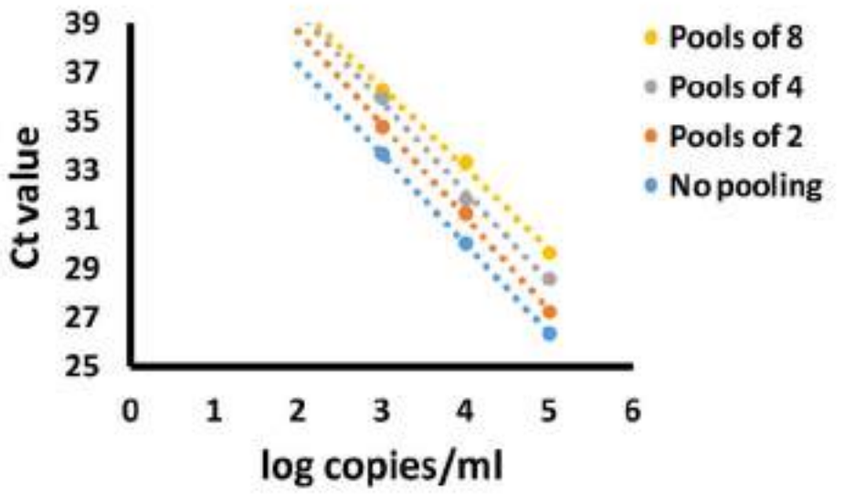

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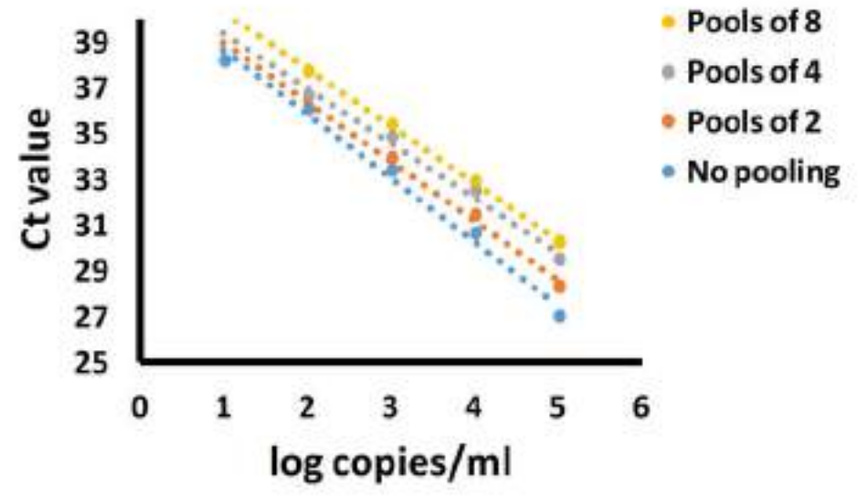

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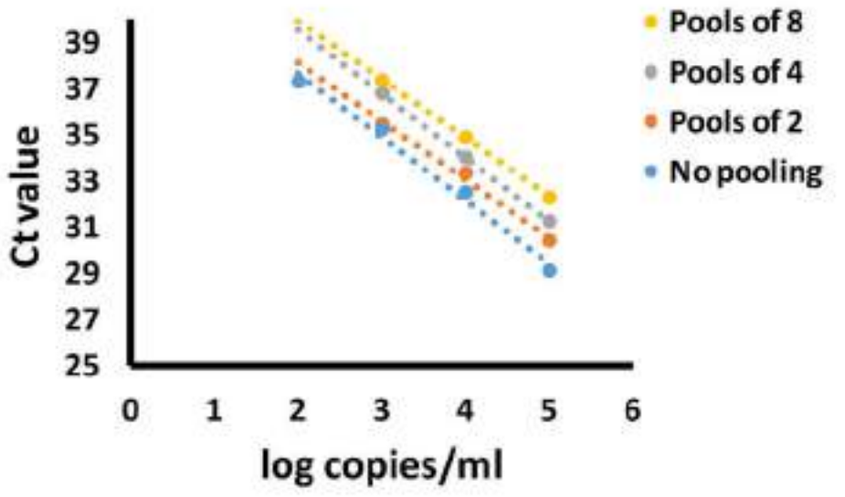
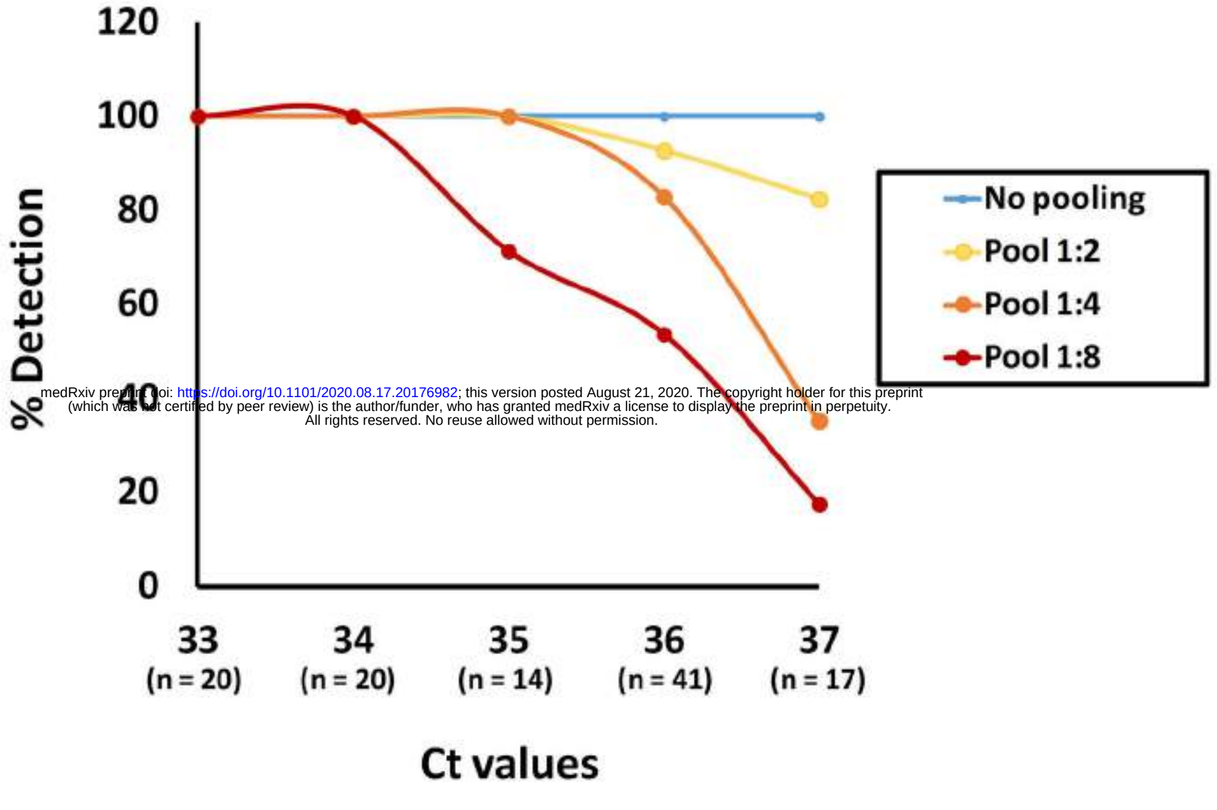


A)



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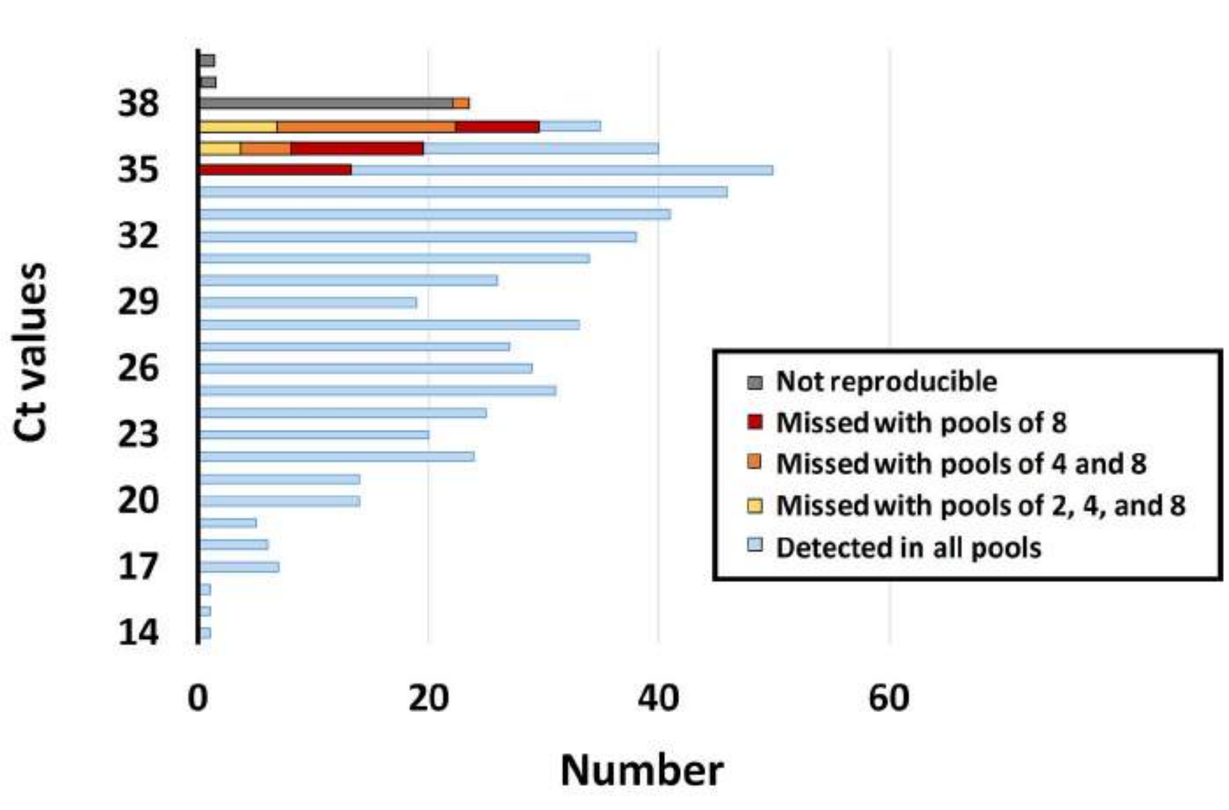

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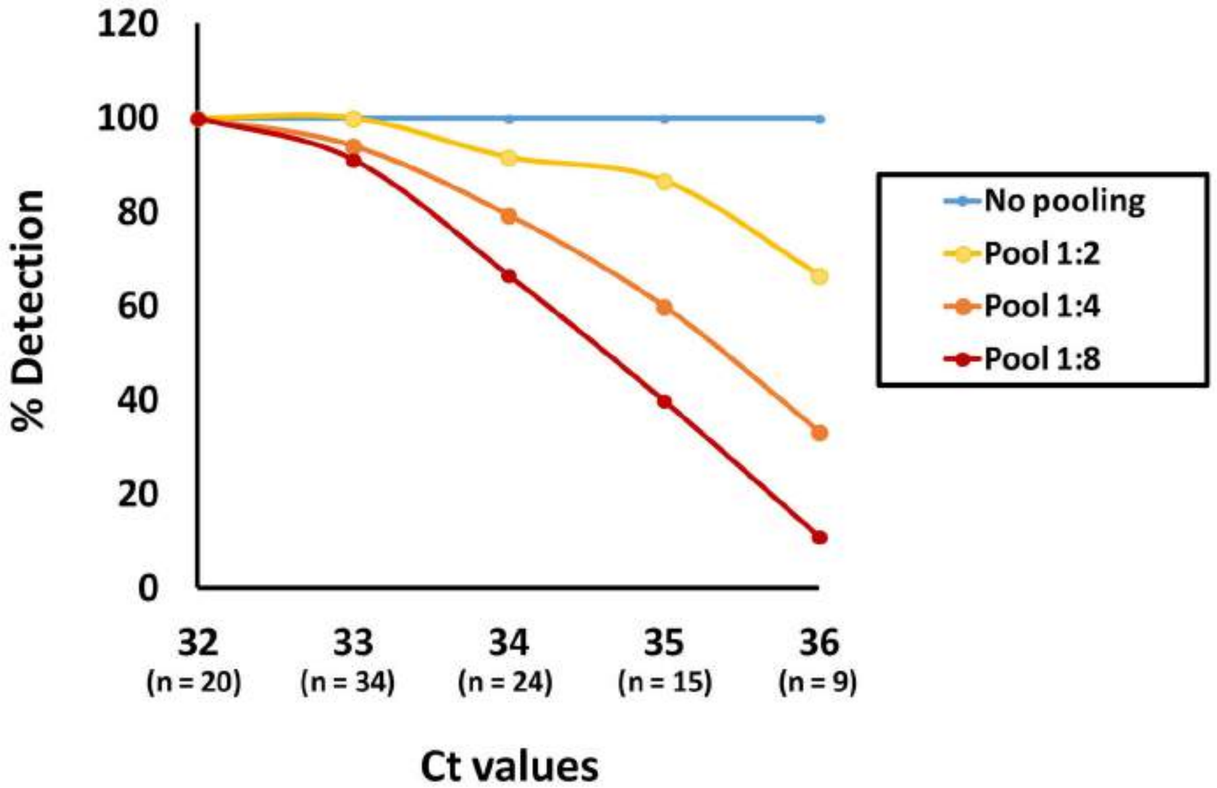

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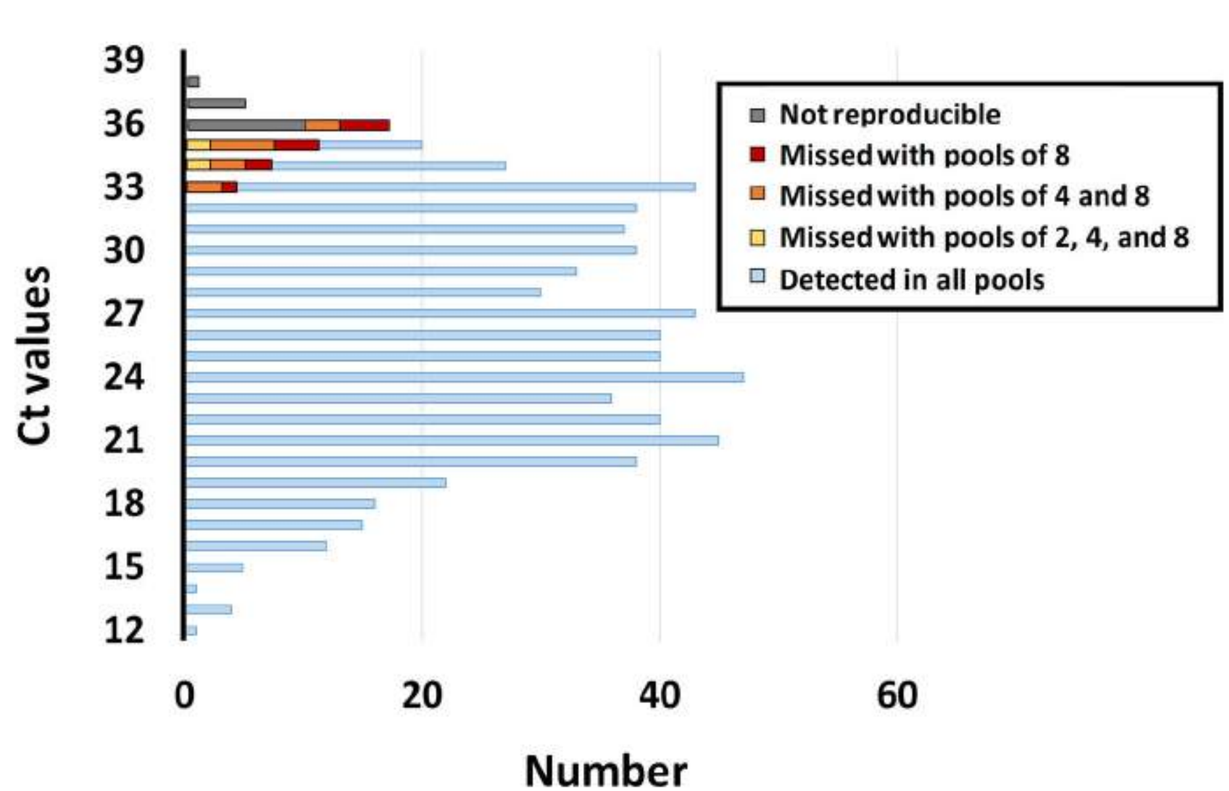

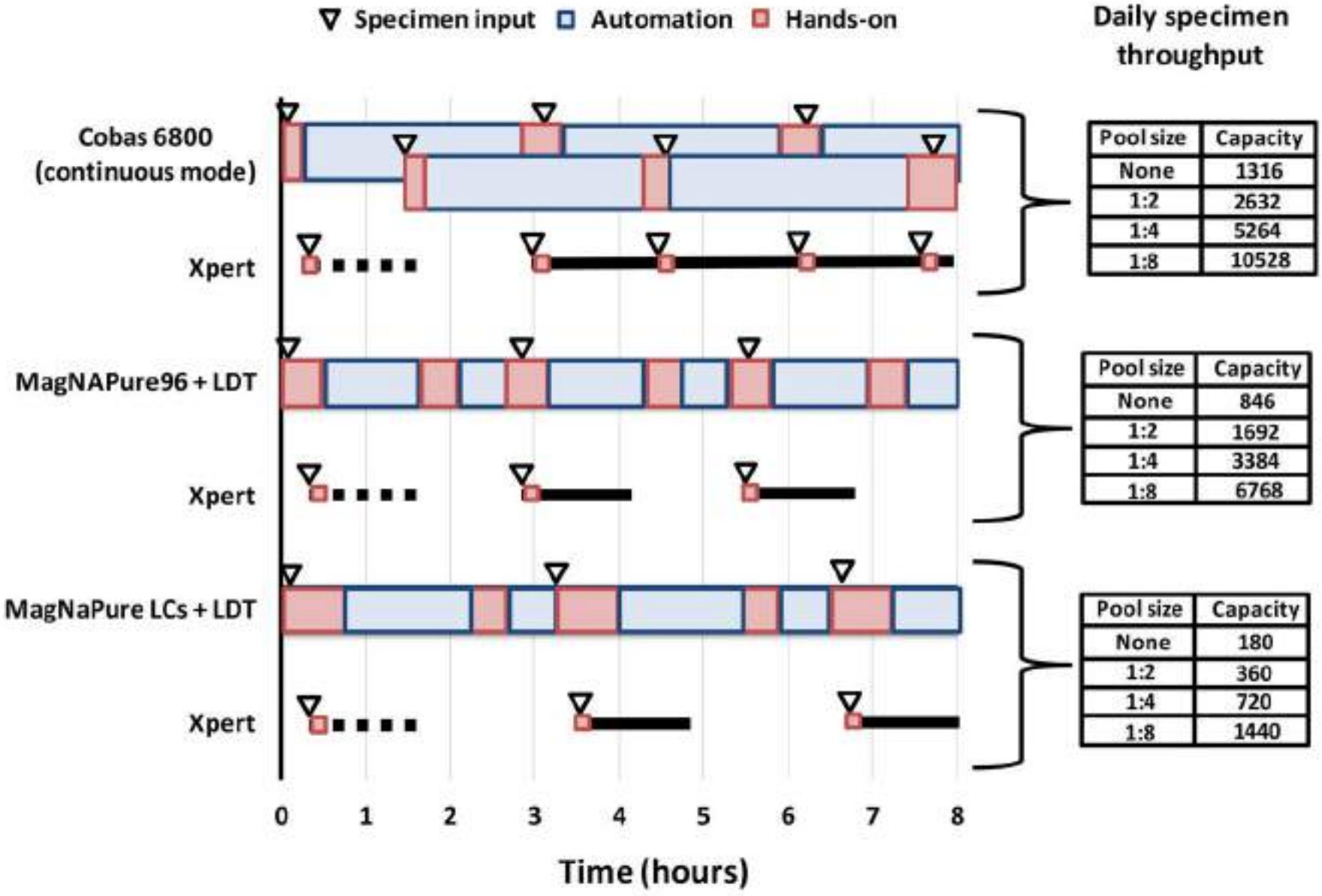

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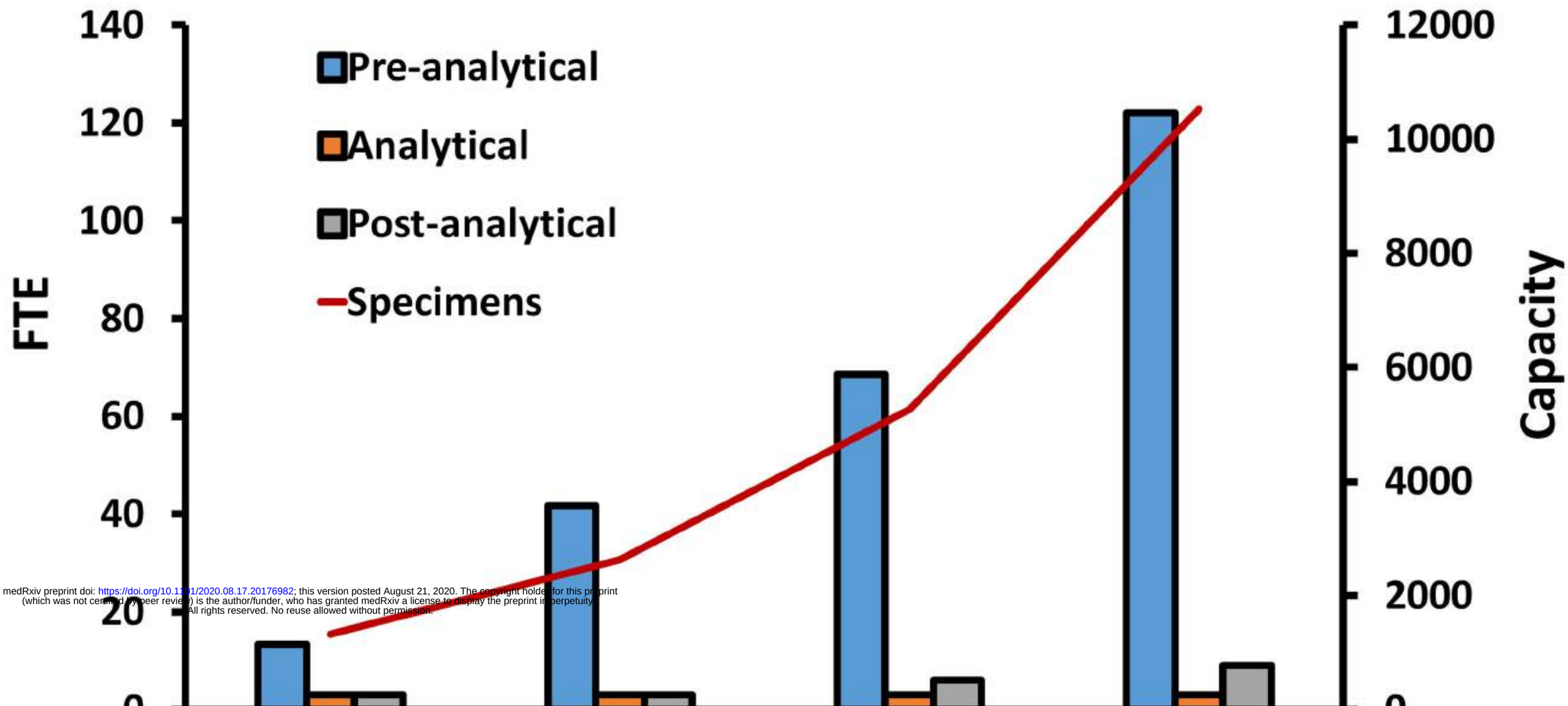

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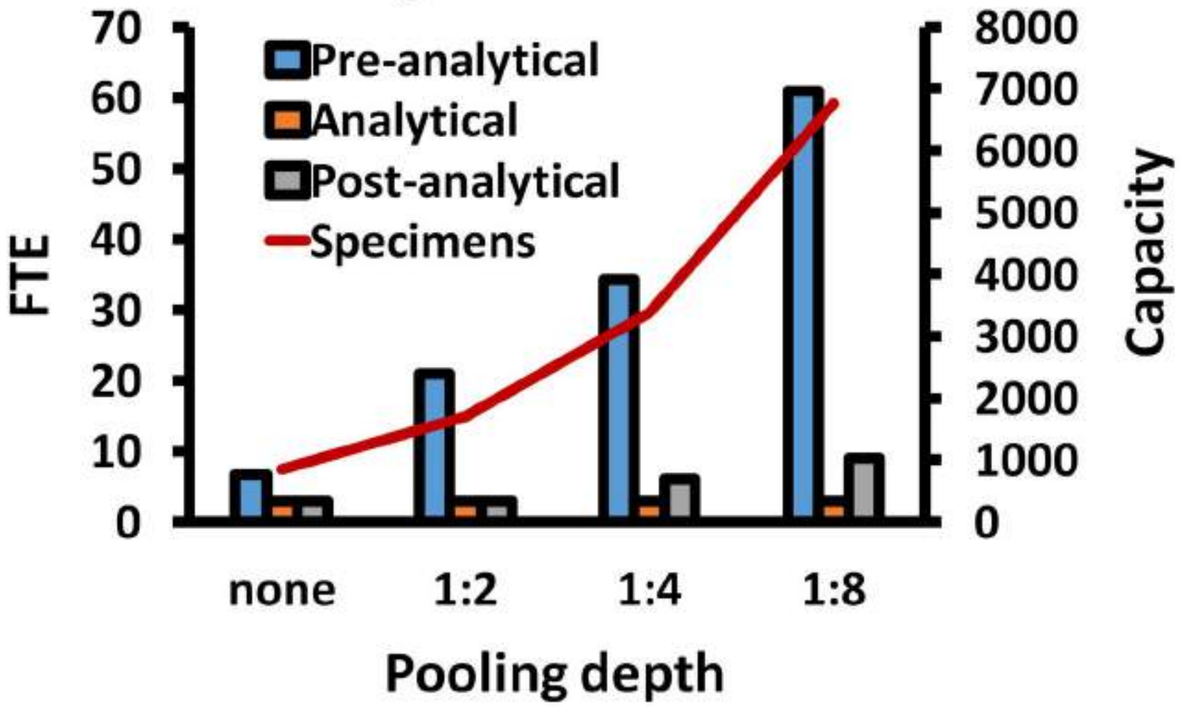

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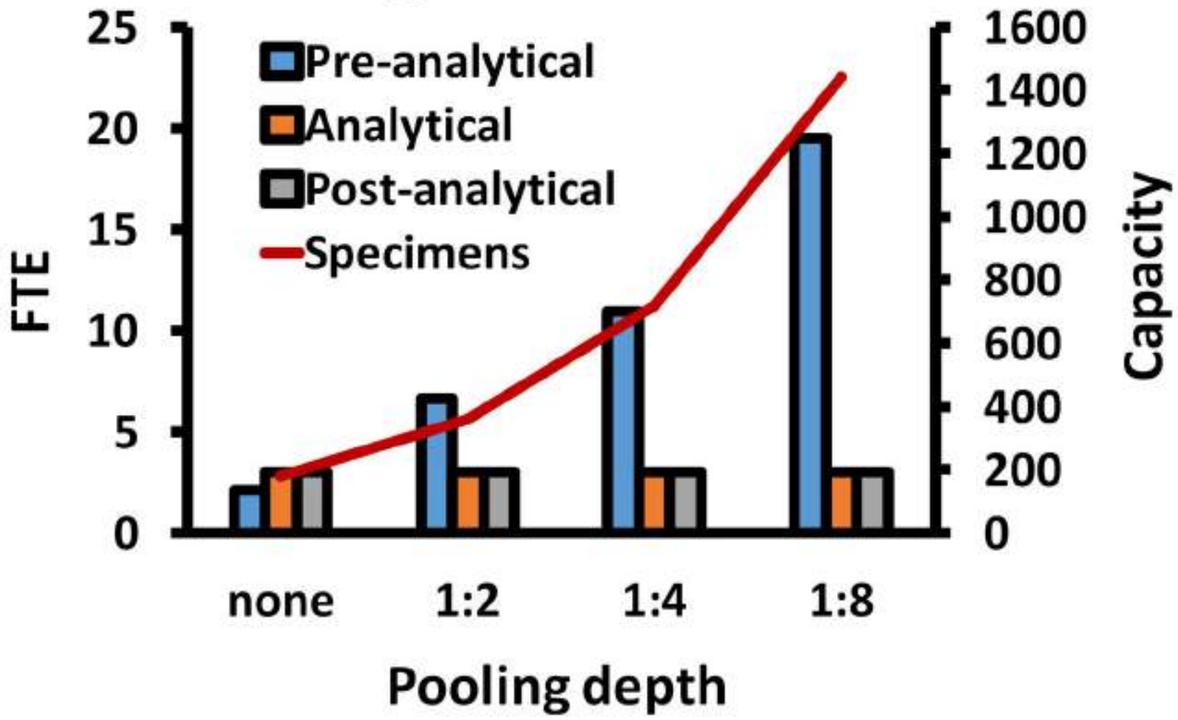

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Short communication

Real-time PCR-based SARS-CoV-2 detection in Canadian laboratories

Jason J. LeBlanc[a,b,*], Jonathan B. Gubbay[c,d,e], Yan Li[f], Robert Needle[g], Sandra Radons Arneson[f], Dionne Marcino[f], Hugues Charest[h], Guillaume Desnoyers[i], Kerry Dust[j], Ramzi Fattouh[k], Richard Garceau[l], Gregory German[l], Todd F Hatchette[a,b], Robert A. Kozak[c,m], Mel Krajden[n], Theodore Kuschak[f], Amanda L.S. Lang[o], Paul Levett[n], Tony Mazzulli[c,p], Ryan McDonald[o], Samira Mubareka[c,m], Natalie Prystajecky[n], Candy Rutherford[q], Marek Smieja[q], Yang Yu[g], George Zahariadis[g], Nathan Zelyas[a,r], Nathalie Bastien[f], on behalf of the COVID-19 Pandemic Diagnostics Investigation Team of the Canadian Public Health Laboratory Network (CPHLN) Respiratory Virus Working Group

[a] Division of Microbiology, Department of Pathology and Laboratory Medicine, Nova Scotia Health Authority (NSHA), Room 404B, MacKenzie Building, 5788 University Avenue, Halifax, Nova Scotia B3H 1V8, Canada
[b] Departments of Pathology, Medicine, and Microbiology and Immunology, Dalhousie University, Halifax, Nova Scotia, Canada
[c] Department of Laboratory Medicine and Pathobiology, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
[d] Public Health Ontario Laboratories, Toronto, Ontario, Canada
[e] Hospital for Sick Children, Toronto, Ontario, Canada
[f] National Microbiology Laboratory (NML), Public Health Agency of Canada (PHAC), Winnipeg, Manitoba, Canada
[g] Public Health and Microbiology Laboratory, St. John's, Newfoundland, Canada
[h] Laboratoire De Santé Publique Du Québec/INSPQ, Sainte-Anne-de-Bellevue, Quebec, Canada
[i] Centre Hospitalier Universitaire Dr. Georges L. Dumont, Moncton, New-Brunswick, Canada
[j] Cadham Provincial Laboratory, Winnipeg, Manitoba, Canada
[k] Department of Laboratory Medicine, St. Michael's Hospital, Toronto, Ontario, Canada
[l] Queen Elizabeth Hospital, Charlottetown, Prince Edward Island, Canada
[m] Sunnybrook Research Institute, Toronto, Ontario, Canada
[n] Public Health Laboratory, British Columbia Centre for Disease Control (BCCDC), Vancouver, British Columbia, Canada
[o] Roy Romanow Provincial Laboratory (RRPL), Saskatchewan Health Authority (SHA), Regina, Saskatchewan, Canada
[p] Department of Microbiology, Mount Sinai Hospital, Toronto, Ontario, Canada
[q] St Joseph's Healthcare, Hamilton, Ontario, Canada
[r] Provincial Laboratory for Public Health (ProvLab), Calgary, Alberta, Canada

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ABSTRACT

With emergence of pandemic COVID-19, rapid and accurate diagnostic testing is essential. This study compared laboratory-developed tests (LDTs) used for the detection of SARS-CoV-2 in Canadian hospital and public health laboratories, and some commercially available real-time RT-PCR assays. Overall, analytical sensitivities were equivalent between LDTs and most commercially available methods.

1. Introduction

Coronaviruses are part of a large family of viruses that infect humans and animals, and are classified into 4 genera (α, β, γ, and δ). Human coronaviruses belong to α and β genera. [1] Most human coronaviruses (229E, NL63, OC43, and HKU1) are causes of the common cold, and serious outcomes are rare. Some human β-coronaviruses have been associated with high morbidity and mortality, such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)] [1]. In

* Corresponding author at: Division of Microbiology, Department of Pathology and Laboratory Medicine, Nova Scotia Health Authority (NSHA), Room 404B, MacKenzie Building, 5788 University Avenue, Halifax, Nova Scotia B3H 1V8, Canada.
E-mail address: jason.leblanc@nshealth.ca (J.J. LeBlanc).

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December 2019, novel β-coronavirus now termed SARS-CoV-2 [2–5] emerged from China, and was associated with high morbidity and mortality in older adults or individuals with underlying medical conditions. [6–10]. Due to the severity and spread, the disease caused by SARS-CoV-2 (i.e. 2019 coronavirus disease, or COVID-19) was declared a pandemic on March 11, 2020 [6–12].

Laboratory testing for COVID-19 is an essential component of containment and mitigation strategies, as it allows the appropriate clinical management and public health interventions. [13–15] Nucleic acid amplification tests (NAAT) such as real-time reverse transcription polymerase chain reaction (rRT-PCR) are the methods of choice for SARS CoV-2 diagnostic testing. With the rapid availability of genome sequences [4,16], laboratory-developed tests (LDTs) for the detection of the SARS-CoV-2 were quickly developed. The first LDTs relied primarily on the detection of SARS-CoV-2 envelope (E), RNA-dependent RNA polymerase (RdRp), and nucleocapsid (N) genes [17,18], but more recent rRT-PCR method targets include open reading frame 1 a/b (Orf1a/b) and the gene encoding spike (S) protein. Recognizing the performance characteristics of PCR methods can vary with reagents, PCR, and instrumentation [19,20], this study compared the analytical sensitivity of LDTs used in hospital and provincial public health laboratories across Canada, as well as some commercially available NAATs that are available in Canada.

2. Methods

The lower limit of detection (LoD) of each method was determined by testing serial dilutions of RNA extracted from a cultured stock of SARS-CoV-2/Canada/VIDO-01/2020 [originally cultured by VIDO-Intervac at the University of Saskatchewan from a clinical specimen originating from Sunnybrook Health Sciences Centre, and propagated at the National Microbiology Laboratory (NML)]. To reduce inter-laboratory variability, specimen preparation, nucleic acid extraction and dilutions were carried out at the NML in Winnipeg (Manitoba, Canada). The viral stock was extracted using the QIAamp Viral RNA Mini kit (Qiagen Inc.), as recommended by the manufacturer. Ten-fold dilution of RNA was prepared in 10 mM Tris (Invitrogen, ThermoFisher) as a single batch. Five replicates of each dilution were shipped on dry ice to participating sites in sufficient volumes to ensure there would be only a single freeze thaw for each of the five independent experiments. Viral RNA was maintained at −70 °C until tested. The viral RNA used for the relative method comparison was quantified using a standard curve generated with in vitro transcribed RNA (Doc S1). All commercial assays were performed as recommended by the respective manufacturers and the various LDT were performed using reagents, instrumentation, and conditions summarized in Table 1. Results of each laboratory's tests were collated, and the LoD estimated using a Probit analysis (https://biostats.shinyapps.io/LOD_probit/) at a probability of 95%. The LoD of each method was expressed as $\log_{10}$ copies/mL in the PCR reaction, with 95% confidence intervals (CI) (Table 1).

3. Results

Our data shows that there is a wide spectrum of instruments, reagents, PCR targets, and reaction conditions between the different diagnostic and commercial rRT-PCR methods for the identification of SARS-CoV-2 (Table 1). Despite this variability, the LoD of the various LDTs were between 3.4 and 4.5 $\log_{10}$ copies/mL. Most commercial methods were equivalent to LDTs, with only a few assays that showed reduced sensitivity (Table 1).

4. Discussion

When COVID-19 first emerged in Canada, method validation in provincial public health and hospital laboratories was challenged by the lack or limited availability of control material for SARS-CoV-2, and limited data to help guide the choice of SARS-CoV-2 real-time PCR methods. Given the novelty of the virus, initial Public Health Agency of Canada (PHAC) case definitions for COVID-19 required laboratory detection of SARS-CoV-2 by real-time RT-PCR with confirmation from either sequencing, or rRT-PCR using a second genetic target. As such, many LDTs were performed in sequential algorithm, or using multiplex rRT-PCRs that enabled simultaneous detection of at least two SARS-CoV-2 targets (Table 1). Most methods were LDTs derived from those developed by the Centers for disease Control and Prevention (CDC), or from published literature. [17,18] While LDTs for COVID-19 testing were quickly implemented in Canadian laboratories, different instruments, reagents, and genetic targets were used.

Despite these differences, this study showed that the analytical sensitivity of LDTs were consistent between laboratories, and few exceptions noted in commercial assays. Most LDTs had LoDs between 3.4 and 4.5 $\log_{10}$ copies/mL, which is fairly consistent with those reported by others. [17,20] Corman et al. [17] reported analytical sensitivities for E gene at RdRp targets at 3.9 [95% CI: 2.8–9.8] and 3.6 copies/reaction [95% CI: 2.7–11.2] copies/reaction, which correlates to 2.9 [95% CI: 2.7–3.3] and 2.9 [95% CI: 2.7–3.4] $\log_{10}$ copies/mL, respectively. In another recent publication, Chan et al. [21] reported analytical sensitivity of 11.2 [95% CI: 7.2–52.6] copies/reaction for RdRp and 21.3 [95% CI: 11.6–177.0] copies/reaction for N gene. These values represent 3.4 [95% CI: 3.2–4.0] $\log_{10}$ copies/mL and 3.6 [95% CI: 3.4–4.5] $\log_{10}$ copies/mL, respectively, which is consistent with values from this study. Only a limited number of methods showed reduced sensitivity. For example, unlike the E gene target in the LightMix 2019-nCoV Real-time RT-PCR kit, the RdRp and N gene targets showed reduced sensitivity. This observation had previously been noted for N gene detection. [17]

It should be noted that the most recent case definition for COVID-19 requires detection of a single genetic target for laboratory detection of SARS-CoV-2. [22] While dual- or multi-target real-time RT-PCRs were initially developed to ensure specificity, sensitivity can in some cases be enhanced when the sum of all results from individuals targets in a multiplex PCR are considered. For example, the Allplex 2019-nCoV assay considers detection in any of its three SARS-CoV-2 targets as a positive result. Individually, each target showed LoD between 3.6 and 3.8 $\log_{10}$ copies/mL, whereas a LoD of 2.6 $\log_{10}$ copies/mL was observed with the sum of all results. As detection of SARS-CoV-2 can be variable at the LoD, relying on more than one target could increase the chances of identifying the virus in specimens with low viral loads. Low viral loads can occur in asymptomatic individuals, during the early or late stages of COVID-19 disease, or they could be attributed to improper specimen collection. [13,14] Such variables could greatly affect the performance of any laboratory method, and falls outside the scope of this study.

A noted limitation for this study includes the use of an RNA-based panel to assess the LoD of the various PCR methods. As such, evaluation of automated instrumentation with a paired nucleic acid extraction and nucleic acid amplification were excluded from the study. Using serial dilutions of cultured virus, future studies are underway to compare automated methods capable of SARS-CoV-2 detection.

As pandemic COVID-19 continues to spread, laboratory testing is essential, and understanding the limits of SARS-CoV-2 detection using rRT-PCR is fundamental. This study provided the first head-to head comparison of LDTs and commercial real-time methods used for the detection of SARS-CoV-2 in Canada. These findings could help guide the choice of molecular methods in diagnostic laboratories looking at introducing COVID-19 testing, or, given the challenges in procuring reagents during the pandemic, these data may provide a list of suitable alternatives for laboratories already offering COVID-19 testing.

Table 1
Limit of detection (LoD) at a 95% probability for various real-time RT-PCR methods for the detection of SARS-CoV-2.

Laboratory	Thermocycler	RT-PCR reagents	Reaction vol. (μL)	Template vol. (μL)	Positivity cutoff (Ct value)	SARS-CoV-2 Target	LoD (log copies/mL; 95% CI)
AB (ProvLab)	ABI 7500 Fast (Applied Biosystems)	TaqMan Fast Virus-1-Step Master Mix (Life Technologies)	20	10	35	RdRp	4.243 (3.472 – 5.013)
						E	3.776 (3.122 – 4.430)
						Any[3]	3.776 (3.122 – 4.430)
BC (BCCDC)	ABI 7500 Fast (Applied Biosystems)	TaqMan Fast Virus-1-Step Master Mix (Life Technologies)	20	5	35	RdRp	3.591 (3.245 – 3.937)
						E	3.579 (3.180 – 3.979)
						Any[3]	3.579 (3.180 – 3.979)
BC(BCCW)	ABI 7500 Fast (Applied Biosystems)	TaqMan Fast Virus-1-Step Master Mix (Life Technologies)	20	5	35	RdRp	4.243 (3.472 – 5.013)
						E	4.729 (3.683 – 5.774)
						Any[3]	3.901 (3.048 – 4.755)
BC (SPH)	LightCycler 480 (Roche Diagnostics)	LightMix 2019-nCoV Real-time RT-PCR kit (Tib Molbiol) with Lightcycler Multiplex RNA Master (Roche Diagnostics)	20	5	40	E	3.901 (3.048 – 4.755)
BC (VGH)	ABI 7500 Fast (Applied Biosystems)	TaqMan Fast Virus-1-Step Master Mix (Life Technologies)	20	5	35	RdRp	4.516 (3.677 – 5.354)
						E	4.516 (3.677 – 5.354)
						Any[3]	4.243 (3.472 – 5.013)
BC (VIHA)	ABI 7500 Fast (Applied Biosystems)	TaqMan Fast Virus-1-Step Master Mix (Life Technologies)	20	5	35	RdRp	4.375 (3.413 – 5.337)
						E	3.901 (3.048 – 4.755)
						Any[3]	3.809 (2.886 – 4.732)
MB (Cadham)	CFX96TM (Bio-Rad Laboratories, Ltd.)	TaqMan Fast Virus-1-Step Master Mix (Life Technologies)	20	5	36.5	E	3.901 (3.048 – 4.755)
						N1	3.776 (3.122 – 4.430)
						N2	3.632 (2.670 – 4.594)
						N3	3.901 (3.048 – 4.755)
NB (CHU-Dumont)	LightCycler 480 II (Roche Diagnostics)	Lightcycler Multiplex RNA Master (Roche Diagnostics)	20	5	40	E + N	3.776 (3.122 – 4.430)
NL	LightCycler 480 II (Roche Diagnostics)	Luna Universal Probe One-Step RT-qPCR Kit (New England Biolabs)	20	5	33	E + N2	3.575 (3.141 – 4.009)
NS (NSHA)	ABI 7500 Fast (Applied Biosystems)	TaqMan Fast Virus-1-Step Master Mix (Life Technologies)	20	5	35	E	3.901 (3.048 – 4.755)
						RdRp	3.776 (3.122 – 4.430)
						Any[3]	3.901 (3.048 – 4.755)
ON (PHOL)	Quantstudio 5 (ThermoFisher Scientific)	TaqPath 1-Step Multiplex Master Mix (Applied Biosystems)	10	5	38	E	3.715 (3.114 – 4.316)
						RdRp	4.292 (3.658 – 4.925)
						Any[3]	3.437 (2.829 – 4.045)
PE (QEH)	BD Max (Becton Dickinson and Company)	RealStar SARS-CoV-2 RT-PCR kit (Altona Diagnostics)	20	12.5	ND[1]	E	3.901 (3.048 – 4.755)
						S	4.558 (3.498 – 5.618)
						Any[3]	3.809 (2.886 – 4.732)
QC	QuantStudio3 (ThermoFisher Scientific)	TaqPath 1-Step Multiplex Master Mix (Applied Biosystems)	20	5	37	E	3.776 (3.122 – 4.430)
						N	4.234 (3.101 – 5.367)
SK (RRPL)	ABI 7500 Fast (Applied Biosystems)	TaqMan Fast Virus-1-Step Master Mix (Life Technologies)	20	5	36	E	3.752 (3.237 – 4.266)
						RdRp	3.566 (3.090 – 4.420)
						Any[3]	3.078 (2.539 – 3.617)
ON (St-Joseph's Healthcare)	CFX96TM (Bio-Rad Laboratories, Ltd.)	Luna Universal Probe One-Step RT-qPCR Kit (New England Biolabs)	20	5	45	UTR	3.809 (2.886 – 4.732)
						UTR + E	2.638 (2.068 – 3.209)
ON (St-Joseph's Healthcare)	Rotor-Gene Q (QIAGEN Inc.)	Luna Universal Probe One-Step RT-qPCR Kit (New England Biolabs)	20	5	45	UTR	3.878 (2.685 – 5.071)
						UTR + E	3.632 (2.670 – 4.594)
						Any[3]	3.878 (2.685 – 5.071)
ON (St. Michael's Hospital)	Quantstudio 5 (ThermoFisher Scientific)	RealStar SARS-CoV-2 RT-PCR kit (Altona Diagnostics)	30	10	ND[1]	E	3.375 (2.796 – 3.954)
						S	3.493 (2.951 – 4.034)
						Any[3]	3.078 (2.539 – 3.617)
ON (Mt-Sinai)	CFX96TM (Bio-Rad Laboratories, Ltd.)	Allplex 2019-nCoV Assay (Seegene Inc.)	25	8	40	E	3.632 (2.670 – 4.594)
						RdRp	3.809 (2.886 – 4.732)
						N	3.632 (2.670 – 4.594)
						Any[3]	2.638 (2.068 – 3.209)

(*continued on next page*)

Table 1 (*continued*)

Laboratory	Thermocycler	RT-PCR reagents	Reaction vol. (µL)	Template vol. (µL)	Positivity cutoff (Ct value)	SARS-CoV-2 Target	LoD (log copies/mL; 95% CI)
–	ABI 7500 Fast (Applied Biosystems)	Taqpath RT-PCR COVID-19 Kit with TaqPath 1-Step Multiplex Master Mix (Applied Biosystems)	20	5	ND[1]	Orf1a/b	4.243 (3.472 – 5.013)
						N	4.434 (4.002 – 4.866)
						S	4.434 (4.002 – 4.866)
						Any[3]	3.776 (3.122 – 4.430)
–	ABI 7500 Fast (Applied Biosystems)	RIDA GENE SARS-CoV-2 (r-Biopharm AG)	20	5	ND[1]	E	3.901 (3.048 – 4.755)
–	ABI 7500 Fast (Applied Biosystems)	Lyra SARS-CoV-2 assay (Quidel Corp.)	15	5	30[2]	Orf1a/b	4.712 (3.837 – 5.587)
–	ABI 7500 Fast (Applied Biosystems)	DiaPlexQ Novel Coronavirus (2019-nCoV) Detection Kit (SolGent Co., Ltd)	20	5	40	N	3.901 3.048 – 4.755)
						Orf1a	3.809 (2.886 – 4.732)
						Any[3]	3.809 (2.886 – 4.732)
–	ABI 7500 Fast (Applied Biosystems) in Standard mode	New Coronavirus Nucleic Acid Detection Kit (Perkin–Elmer)	20	40	42	N	4.516 (3.677 – 5.354)
						Orf1ab	3.776 (3.122 – 4.430)
					N/A	Any[3]	3.776 (3.122 – 4.430)
–	LighCycler 2.0 (Roche Diagnostics)	LightMix 2019-nCoV Real-time RT-PCR kit (Tib Molbiol) with Lightcycler Multiplex RNA Master (Roche Diagnostics)	20	10	36	E	3.632 (2.670 – 4.594)
					39	RdRp	5.591 (4.769 – 6.412)
					37	N	5.523 (4.636 – 6.410)
					N/A	Any[3]	3.632 (2.670 – 4.594)

[1] Not defined (ND).

[2] Amplification using Lyra SARS-CoV-2 assay (Quidel Corp.) on the ABI 7500 Fast includes 10 "blind" cycles where fluorescence is not capture, and therefore, the cutoff for positivity is set after the 30 cycles where florescence was captured.

[3] For multiplexed assays, LoD were assessed for individual targets; however, the LoD was also considered for the sum of results where any target detected would be considered a positive results. Note: Indeterminate results were characterizes as positive for the Probit analysis. An indeterminate result on an rRT-PCR assay is defined as a late amplification signal, below the predetermined Ct value for positivity.

Declaration of Competing Interest

The authors have no conflicts to declare

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Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Short communication

A combined oropharyngeal/nares swab is a suitable alternative to nasopharyngeal swabs for the detection of SARS-CoV-2

Jason J. LeBlanc[a,b], Charles Heinstein[a], Jimmy MacDonald[a], Janice Pettipas[c], Todd F Hatchette[a,b], Glenn Patriquin[a,b,*]

[a] Division of Microbiology, Department of Pathology and Laboratory Medicine, Nova Scotia Health Authority (NSHA), Halifax, Nova Scotia, Canada
[b] Departments of Pathology, Medicine, and Microbiology and Immunology, Dalhousie University, Halifax, Nova Scotia, Canada
[c] Nova Scotia Provincial Public Health Laboratory Network (PPHLN), Halifax, Nova Scotia, Canada

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ABSTRACT

Given the global shortage of nasopharyngeal (NP) swabs typically used for respiratory virus detection, alternative collection methods were evaluated during the COVID-19 pandemic. This study showed that a combined oropharyngeal/nares swab is a suitable alternative to NP swabs for the detection of SARS-CoV-2, with sensitivities of 91.7% and 94.4%, respectively.

1. Introduction

The first reports of 2019 novel coronavirus disease (COVID 19) caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV 2) emerged from China in December 2019, but quickly spread as a pandemic. [1 3] Laboratory testing for SARS CoV 2 plays an essential role in infection control and public health mitigation strategies; however, testing has been hampered by global supply chain shortage nasopharyngeal (NP) swabs and universal transport medium (UTM). As such, alternative collection methods were rapidly evaluated, including nasal swabs, oropharyngeal (OP) swabs, throat washings, and saliva [4 8]. While NP swabs in UTM are the specimen of choice for respiratory virus testing, a recent study demonstrated the feasibility of COVID 19 testing from nasal sample collected with a swab typically used for chlamydia and gonorrhea testing: the Aptima Multitest swab (Hologic, Inc.) and its accompanying specimen transport medium (STM). [9] This study sought to further validate the Aptima swab/STM collection kit for the detection of SARS CoV 2 using a single swab approach to sample the oropharynx and anterior nares (OP/Na).

2. Methods

In assessment centers prioritizing areas with suspected community spread of SARS CoV 2, specimens were collected for COVID 19 testing from 190 individuals using two different collection devices: a flocked NP swab in 3 mL UTM (Copan Diagnostics Inc., Murrieta, CA) and combined OP/Na sampling using the Aptima Multitest swab in 2.9 mL of STM (Hologic, Inc., San Diego CA), according to an accompanying instructional video (https://vimeo.com/397169241). Each specimen was stored at 4 °C until testing, and an aliquot was stored at −80 °C. Both swabs were run in parallel within 12 h of collection using two molecular methods. First, the SARS CoV 2 assay, was performed on a Cobas 6800 system (Roche Diagnostics). For UTM (NP swab material), 600 µL was processed directly, as recommended by the manufacturer, whereas for the OP/Na, 200 µL of STM was diluted into 1 mL of Cobas omni Specimen Diluent prior to use due to the presence of high concentrations of detergents. [9] Second, a Total Nucleic Acid (TNA) extraction on a MagNApure LC 2.0 instrument (Roche Diagnostics) was performed, followed by real time RT PCR [i.e. laboratory developed test (LDT) designed at the British Columbia Centre for Disease Control (BCCDC) (Vancouver, BC)]. Briefly, TNA was extracted from 200 µL of specimen (NP or OP/Na), eluted into 50 µL of elution buffer, and 5 µL was used as template in a triplex real time RT PCR, with primers and probes targeting the SARS CoV 2 envelope (E) [10] and RNA dependent RNA polymerase (RdRp), as well as those targeting an endogenous internal control, ribonuclease P (RNaseP). Amplification was performed on an Applied BioSystems 7500 Fast system (Thermo Fisher Scientific), and threshold cycles (Ct) values were determined by the manufacturer

* Corresponding author at: Division of Microbiology, Department of Pathology and Laboratory Medicine, Nova Scotia Health Authority (NSHA),Room 315, MacKenzie Building, 5788 University Avenue, Halifax, Nova Scotia, B3H 1V8, Canada.
E-mail address: glenn.patriquin@nshealth.ca (G. Patriquin).

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software. Results for each instrument were classified as positive or negative, and specimens yielding discrepant results were subjected to testing using the Xpert Xpress SARS CoV 2 assay (Cepheid). Each test was compared to a modified reference standard defined as concordant results from at least two methods with different genetic targets. Sensitivity and specificity were calculated from 2 × 2 contingency tables with 95% confidence intervals (CI) for each collection (NP or OP/Na swabs) and instrument (LDT and commercial assay) using online software (https://www.medcalc.org/calc/diagnostic test.php). A Fisher exact test was used to assess differences and $P \leq 0.05$ was considered statistically significant.

3. Results and discussion

The limited and unpredictable supply of NP swabs during the COVID 19 pandemic prompted the evaluation of swabs that were readily available and commonly used for sexually transmitted infections. Of 190 paired NP and OP/Na specimens collected, 154 negative results were obtained and 36 patients tested positive by at least one molecular method (18.9% positivity rate). Regardless of the swab (NP or OP/Na) or methods used (LDT or commercial), the specificity was 100.0% (155/155) [95% CI: 97.7 100.0%]. Using the LDT, the sensitivity of NP swabs for the detection of SARS CoV 2 was 94.4% (34/36) [95% CI: 81.3% 99.3%] compared to 91.7% (33/36) [95% CI: 77.5 98.3%] for the OP/Na swabs. Using the commercial assay, the sensitivity for NP swabs was 100.0% (36/36) [95% CI: 90.3% 100.0%] compared to 88.9% (32/36) [95% CI: 73.9 96.9%] for the OP/Na specimens. While the sensitivity of OP/Na was lower than NP swabs using the LDT or commercial assays, no significant differences were observed ($P = 0.679$ and 0.115, respectively).

Patients with discrepant NP and OP/Na results are summarized in (Table 1). With the exception of patient 4, the other five patients with discrepant NP and OP/Na results had specimens with low viral loads (Table 1). Low viral loads are known to occur in the early and late stages of COVID 19 illness [4 6,11 19], and false negative results can arise from differences in analytical sensitivity between methods (Table S1) [20,21], the variability in specimen collection, or factors influencing specimen stability or recovery of SARS CoV 2 RNA during specimen transport, storage or processing [4,13]. For example, three different SARS CoV 2 targets were detected between the various PCR methods used for testing of specimens from patient 1, yet high Ct values were observed for these targets (Table 1). High Ct values are suggestive of low viral loads, and it is known that detection of PCR targets near the limit of detection lacks reproducibility. [20,21] Therefore, low viral loads and differences in analytical sensitivity of the various molecular methods could explain differences in SARS CoV 2 detection between the NP and OP/Na collections (Table S1). Similar arguments could be made for patients 2 4, who were either asymptomatic or in the pre symptomatic stage of infection where low viral loads can occur [4 6,11 19]. Discrepant results for patients 5 and 6 were in the setting of known positive cases, with symptoms predating their sample collection by 14 and 18 days, respectively. Waning viral loads over time in the upper respiratory tract are well documented for SARS CoV 2; however, discrepant NP and OP/Na results from sampling in the later stages of illness may be of little clinical significance, as detection of SARS CoV 2 RNA does not imply infectivity [4,6,11,19]. Further analyses are underway to correlate SARS CoV 2 detection, and better understand viral shedding from various anatomical sites in patients stratified by disease onset, clinical presentation, and outcomes.

Interestingly, patient 4 had a positive NP swab with low Ct values (i.e. high viral load) by three different methods, but the OP/Na on the same patient was negative. The exogenous internal control in the commercial assay was amplified from the OP/Na specimen (arguing against the presence of PCR inhibitors); however, the LDT endogenous control in the OP/Na reaction was near the cutoff (Ct value of 34.9). While an unlikely alternative explanation could be a false positive

Table 1
Relevant characteristics among ambulatory patients in whom results of paired nasopharyngeal and oropharyngeal/nares swabs were discrepant for the detection of SARS-CoV-2.

Patient	LDT				6800						Xpert			Symptoms	Comments
	NP		OP/Na		NP			OP/Na			NP				
	Ct (RdRp)	Ct (E)	Result	Ct (RdRp)	Ct (E)	Result	Ct (Orf1ab)	Ct (E)	Result	Ct (Orf1ab)	Ct (E)	Result	Ct (E)	Ct (N2)	Result		
1	ND	ND	NEG	ND	35.3	POS	ND	38.6	POS	35.8	37.6	POS	ND	40.0	POS	Yes, but onset not recorded	High Ct values (low viral load)
2	ND	ND	NEG	36.2	34.7	POS	ND	38.3	POS	33.9	36.2	POS	41.6	41.2	POS	No	High Ct values (low viral load)
3	37.8	35.7	POS	ND	37.6	POS	33.6	35.9	POS	ND	ND	NEG	35.2	37.5	POS	No	High Ct values (low viral load)
4	27.3	26.8	POS	ND	ND	NEG	27.5	28.2	POS	ND	ND	NEG	25.4	28.2	POS	No	High Ct value (35.9) observed for RNaseP with the OP/Na during testing with the LDT suggests issue in collection or transport
5	33.7	33.1	POS	ND	ND	NEG	30.7	33.1	POS	ND	ND	NEG	30.5	33.5	POS	Yes, with onset 18 days prior	High Ct values (low viral load)
6	33.6	33.4	POS	ND	ND	NEG	32.1	34.1	POS	ND	ND	NEG	34.2	37.4	POS	Yes, with onset 14 day prior	High Ct values (low viral load)

*Discrepant analysis using Xpert testing was only performed on nasopharyngeal swabs in UTM, as the OP/Na showed reduced sensitivity for this assay (Table S1). Abbreviations: Threshold cycle (Ct), envelope (E); laboratory-developed test (LDT); nucleoprotein (N2); not available (N/A); not detected (ND); negative (NEG); nasopharyngeal (NP); oropharyngeal/nares (OP/Na); positive (POS); RNA-dependent RNA polymerase (RdRp); ribonuclease P (RNaseP).

result for the NP swab, it is more likely that there were collection or transport deficiencies for the OP/Na specimen.

The data obtained from this study represents a relatively short time period in a community setting with a mixed population of asympto matic and mildly symptomatic patients. While OP/Na swabs collection showed excellent performance for the detection of SARS CoV 2, as previously shown for nasal sampling [9], one should exercise caution in applying these findings to other patient populations, collection devices, or laboratory methods [4,22]. For example, upper respiratory speci mens like NP or OP/Na might have poor performance in hospitalized adults with progression of COVID 19 to lower tract disease [4].

Overall, this study demonstrated that OP/Na sampling is a suitable alternative to NP swabs for the detection of SARS CoV 2 in ambulatory patients, especially when symptomatic. To our knowledge, this is the largest head to head comparison of NP and OP/Na swabs for the de tection of SARS CoV 2, and the first study to evaluate the performance of the OP/Na collection with an Aptima Multitest swab for SARS CoV 2 detection.

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Ethics

This project was a quality assurance initiative and did not require research ethics board review.

Declaration of Competing Interest

The authors have no conflicts to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jcv.2020.104442.

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Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Exploring alternative swabs for use in SARS-CoV-2 detection from the oropharynx and anterior nares

Glenn Patriquin [a,b,*], Ian Davis [a,b], Charles Heinstein [a], Jimmy MacDonald [a], Todd F. Hatchette [a,b], Jason J. LeBlanc [a,b]

[a] Division of Microbiology, Department of Pathology and Laboratory Medicine, Nova Scotia Health Authority (NSHA), Halifax, Nova Scotia, Canada
[b] Departments of Pathology, Medicine, and Microbiology and Immunology, Dalhousie University, Halifax, Nova Scotia, Canada

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ABSTRACT

The COVID-19 pandemic has led to a worldwide shortage of nasopharyngeal swabs and universal transport media. This study evaluated a combined oropharynx/nares (OP/Na) sample collection using two readily-available non-flocked swabs, transported in phosphate-buffered saline, and demonstrates equivalent performance in SARS-CoV-2 detection compared to a previously-validated OP/Na collection kit.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the etiological agent of 2019 novel coronavirus disease (COVID-19) that quickly spread as a pandemic (Zhu et al., 2020; Zhou et al., 2020; Gorbalenya et al., 2020). Like other respiratory viruses, molecular testing is the mainstay of COVID-19 diagnosis (Tang et al., 2020; LeBlanc et al., 2020a; Corman et al., 2020), the preferred specimens being from the upper respiratory tract, collected with a flocked nasopharyngeal (NP) swab placed into universal transport medium (UTM) (Marty et al., 2020). During the pandemic, global supply chain disruptions of NPs and UTM limited testing capacity worldwide, and alternatives were sought. A commercial collection kit commonly used for sexually transmitted infection (STI) testing, the Aptima Multitest Kit in specimen transport media (STM) (Hologic Inc), has been validated for SARS-CoV-2 detection (LeBlanc et al., 2020b; Avanias-Aghajani et al., 2020). In a recent study, a combined sampling of the posterior oropharynx and bilateral anterior nares (OP/Na) using the Aptima swabs in STM was shown to be equivalent to NP swabs transported in UTM (LeBlanc et al., 2020b). However, with increased demand for SARS-CoV-2 testing in clinical laboratories, availability of the Aptima swab collection kits has also become limited. Other recent studies demonstrated that phosphate buffered saline (PBS) was a suitable media for specimen transport as it supported the recovery of SARS-CoV-2 RNA for molecular detection (Perchetti et al., 2020; Radbel et al., 2020; Rodino et al., 2020). This study evaluated the feasibility of using PBS as transport medium following an OP/Na collection with one of two non-flocked swabs: 1) the M40 Transystem (Copan Italia, Brescia, Italy), a swab commonly used for bacterial culture (Morosini et al., 2006; Tano and Melhus, 2011); and 2) the BD ProbeTec Qx Collection Kit for Endocervical and Lesion Specimens (Becton, Dickinson and Company, Sparks MD, USA), a swab used for molecular detection of STIs on the BD Viper instrument (Tumje et al., 2014; Lang et al., 2014).

2. Methods

Real-time reverse transcription polymerase chain reaction (rRT-PCR) was performed using the SARS-CoV-2 assay on the Cobas 6800 system (Roche Diagnostics), and a positive result was defined as amplification of at least one of two genetic targets (Orf1a or E gene). To ensure compatibility of PBS on the instrument, analytical sensitivity was estimated using 10-fold serial dilutions of a SARS-CoV-2 derived from a positive clinical specimen, which were spiked 1:10 (v/v) into each transport medium (i.e. UTM, STM, and PBS). Experiments are the results of triplicate values obtained in three independent experiments using the same clinical specimen. For clinical specimens or viral dilutions prepared in UTM, 600 µL was processed directly on the Cobas 6800 instrument, as recommended by the manufacturer. Specimens or viral

* Corresponding author at: Division of Microbiology, Department of Pathology and Laboratory Medicine, Nova Scotia Health Authority (NSHA), Room 315, MacKenzie Building 5788 University Avenue, Halifax, Nova Scotia, B3H 1V8, Canada.
E-mail address: glenn.patriquin@nshealth.ca (G. Patriquin).

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dilutions in PBS mirrored the processing of those in UTM. For specimens or viral dilutions in STM, a pre-processing dilution step (1:6) was required to overcome the deleterious effects its high concentrations of detergent (LeBlanc et al., 2020b). Briefly, 200 µL of STM was diluted into 1 mL of Cobas Omni Specimen Diluent (Roche Diagnostics), mixed with gentle pipetting to avoid the formation of bubbles, and specimens were processed within 2 h of preparation. Viral dilutions were quantified relative to a standard curve generated from quantified in vitro transcribed RNA which was provided in-kind by the National Microbiology Laboratory (Winnipeg, MB) (Table S1).

To assess the clinical performance of the two alternative non-flocked swabs (i.e. M40 Transystem and the BD ProbeTec Qx Collection Kit), 15 patients previously identified as COVID-positive with mild to moderate disease (living in long-term care or admitted to acute care) were enrolled into the study, after obtaining informed consent. OP/Na collections were performed sequentially on the same patient, using the M40 Transystem featuring a plastic shaft (Copan Italia, Brescia, Italy), the BD ProbeTec Qx Collection Kit for Endocervical and Lesion Specimens with a polyurethane tip (Becton, Dickinson and Company, Sparks MD, USA), and the Aptima Multitest Kit (Hologic Inc) was used as the reference method (LeBlanc et al., 2020b). Following collection, both the M40 Transystem and the BD ProbeTec Qx endocervical swabs were placed in a 15 mL conical tube (Falcon, Corning Incorporated, Corning, NY, USA) containing 3 mL of sterile 1 × PBS, pH 7.4 (Gibco, ThermoFisher Scientific), whereas the Aptima Multitest swab was placed into 2.9 mL of STM provided in the collection kit. Samples were transported to the laboratory and were processed in parallel within 4 h, or alternatively, held at 4 °C until processed within 12 h of collection.

3. Results

The analytical sensitivity for SARS-CoV-2 was not impacted by the different transport media, and the limit of detection at 95% for each was below 1 copy/mL (Table S1). While not significant, STM showed a lower

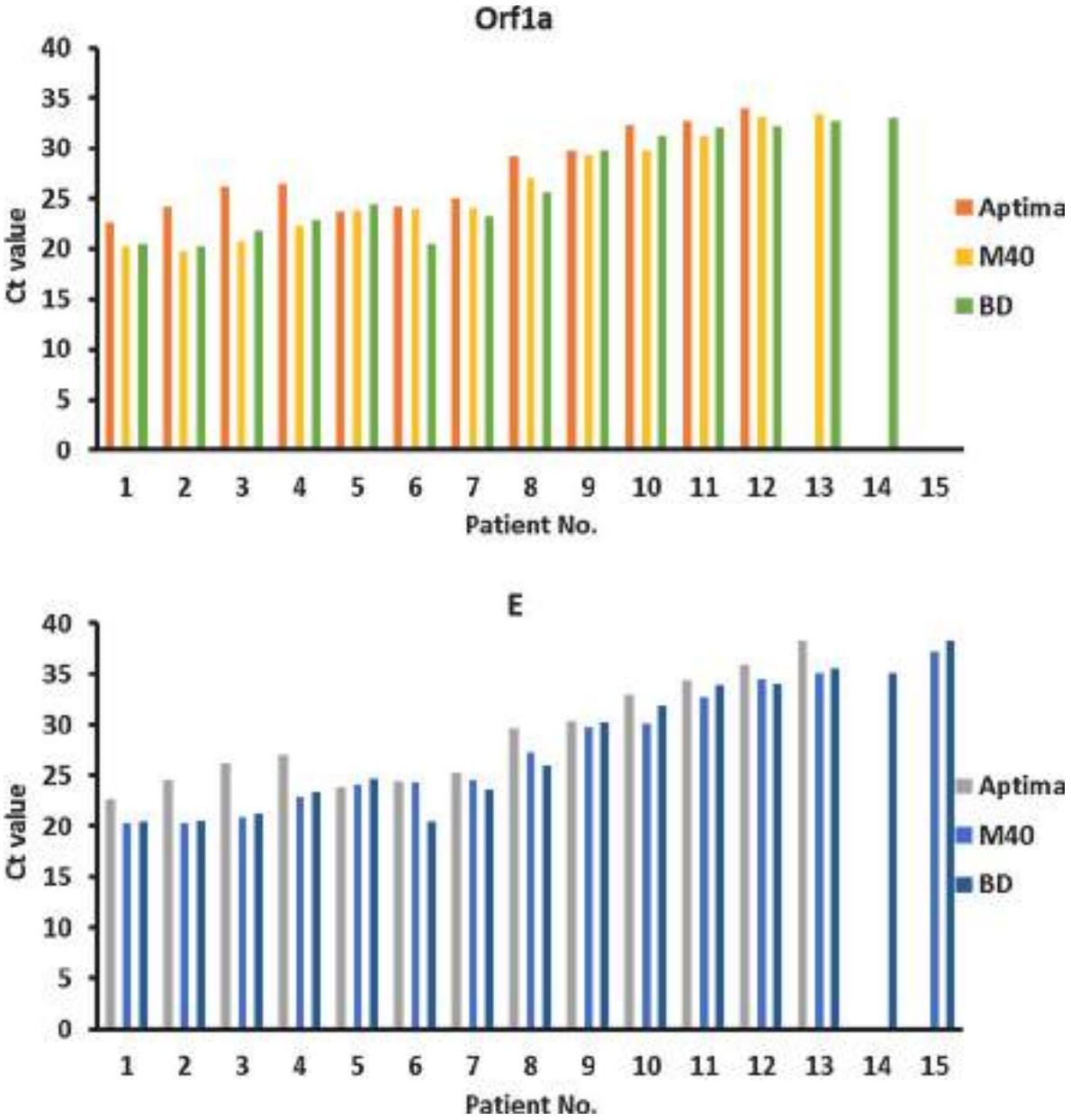

Fig. 1. Ct values for SARS-CoV-2 RT-PCR from 15 known positive patients. Two gene targets' (Orf1a and E gene) Ct values obtained on the Cobas 6800 RT-PCR assay. Triplicate combined oropharyngeal/nares swabs obtained using Aptima Multitest kits, M40 bacterial swabs in phosphate-buffered saline (PBS), and BD ProbeTec Qx swabs in PBS.

proportion of viral detection in dilution near the limit of detection, which might be attributed to the 1:6 dilution required for preprocessing of specimens in STM (LeBlanc et al., 2020b).

For clinical validation of OP/Na collection using the M40 and BD swabs compared to the Aptima swab, fifteen COVID-19 positive patients participated, with an average age of 74.2 years (range 48–92 years). The mean number of days since their initial positive result was 3.9 (median 2 days; range 2–13 days), 93.3% (14/15) of whom were originally diagnosed using the Aptima Multitest swab and one having been diagnosed with a NP swab in UTM. Of the participants, 86.7% (13/15) had consistent results across all three swabs. Fourteen patients (93.3%) were positive by two swab types. Interestingly, the reference method (i.e. Aptima swab) failed to detect SARS-CoV-2 in two patients (Fig. 1 and Table S2). In the first patient, both the M40 and BD swabs detected the E gene target in a specimen that was negative with the Aptima swab collection. In the second patient, SARS-CoV-2 was solely detected using a M40 swab collection, but both genetic targets were positive (Fig. 1 and Table S2).

4. Discussion

This study assessed the feasibility of an OP/Na collection with either M40 or BD swabs placed in PBS. While this study could not perform a head-to-head comparison of M40 and BD swabs in PBS against the preferred collection device (i.e. NP in UTM) due to global supply chain shortages, the swabs collected in PBS were compared to the Aptima Multitest swab in STM - a reference collection shown not to be significantly different than NP swabs in UTM when using the SARS-CoV-2 assay on the Roche 6800 instrument (LeBlanc et al., 2020b).

The study initially assessed the ability to recover SARS-CoV-2 RNA from PBS, compared to both the study reference (i.e. STM) and traditional reference media (i.e. UTM). Overall, PBS had comparable analytical sensitivity to UTM. During testing using a 10-fold serial dilution of SARS-CoV-2 virus, the proportion of viral dilutions in STM detected were lower than PBS or UTM, but differences did not achieve significance. A possible explanation for this observation might be the 1:6 dilution required for pre-processing of specimens in STM, given the high concentration of detergents (LeBlanc et al., 2020b). More importantly, the analytical sensitivity for SARS-CoV-2 detection in PBS was equivalent to UTM. The ability to use PBS as a transport medium for the detection of SARS-CoV-2 is congruent with previous reports (Perchetti et al., 2020; Radbel et al., 2020; Rodino et al., 2020). Rodino et al. (2020) showed that PBS was a reasonable substitute to viral transport media, as SARS-CoV-2 RNA could be recovered for up to 7 days. Similarly, a study of swabs from endotracheal secretions of COVID-19 patients demonstrated stability and recovery of SARS-CoV-2 RNA from PBS when compared to UTM, even after 18 h at room temperature (Radbel et al., 2020). A more recent study compared the performance of PBS transport for SARS-CoV-2 at various temperatures and extended periods of time (Perchetti et al., 2020). While temperature and stability analyses were not performed in this study, under conditions for PBS transport (4 °C), minimal degradation of SARS-CoV-2 RNA occurred up to 28 days (Perchetti et al., 2020). This far exceeds the maximum transport time required for transport to hospital or public health laboratories performing SARS-CoV-2 rRT-PCR in Canada (LeBlanc et al., 2020a).

For the clinical validation, OP/Na collection using M40 and BD swabs with PBS transport media were compared to a similar collection with Aptima swabs in STM (LeBlanc et al., 2020b). This study targeted OP/Na collections in known positive patients with mild to moderate disease, as patients progressing to more severe COVID-19 disease might only be detected in lower respiratory tract specimens (Hanson et al., 2020). In the 15 patients enrolled in the study, Ct values for all swabs spanned a large range, with values spanning the mid-twenties to values near the assay limit of detection in the high thirties. Ct values of the two alternative swabs were strikingly similar, and were consistently lower than those of the accompanying reference swab. This is likely owing to the requirement of a 1:6 dilution during pre-processing of specimens collected in STM, which could lower the analytical sensitivity and possibly impact detection of patients with low viral loads (i.e. early or late disease). In fact, the Aptima swab collection missed the identification of 2 cases. The Ct values in discrepant results were near the limit of detection, ranging from 33.1–38.3, suggesting low viral loads in the upper respiratory tract. Interestingly, the collection using ProbeTec Qx swabs in PBS identified all previously known cases of COVID-19. The M40 swabs in PBS identified 93.3% (14/15), missing only a single case with a low viral load. At low viral loads, the molecular detection of SARS-CoV-2 molecular lacks reproducibility (LeBlanc et al., 2020a). Low viral loads have been demonstrated early in infection, and late in disease, possibly leading to false-negative results (Kucirka et al., 2020), highlighting the importance of repeat testing in those with initial negative results but high clinical suspicion (Watson et al., 2020).

Though limited to known-positive patients with mild-moderate symptoms, and by a low number of study participants, this study provided clinical evidence that an OP/Na collection using non-flocked swabs designed for bacterial culture or cervical investigations can perform as well for the diagnosis of COVID-19 as the previously validated Aptima Multitest Kit. This report supports the use of PBS as a transport medium. Our results are supportive of those recently published, demonstrating the diagnostic reliability of cotton-tipped plastic swabs for NP sampling as compared to rayon-tipped swabs, transported in TRIS-EDTA (Freire-Paspuel et al., 2020) Repurposed commonly used non-flocked swabs, paired with a readily available buffer provides a solution for COVID-19 testing during times of UTM and flocked NP swab shortages.

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Ethics

This project was a quality assurance initiative and did not require research ethics board review.

CRediT authorship contribution statement

Glenn Patriquin: Conceptualization, Methodology, Writing - review & editing. **Ian Davis:** Conceptualization, Methodology, Writing - review & editing. **Charles Heinstein:** Investigation, Resources, Writing - review & editing. **Jimmy MacDonald:** Investigation, Resources, Writing - review & editing. **Todd F. Hatchette:** Conceptualization, Methodology, Investigation, Resources, Writing - review & editing. **Jason J. LeBlanc:** Conceptualization, Methodology, Investigation, Resources, Writing - review & editing.

Declaration of Competing Interest

The authors have no conflicts to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jviromet.2020.113948.

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The Canadian Public Health Laboratory Network protocol for microbiological investigations of emerging respiratory pathogens, including severe acute respiratory infections

Respiratory Virus Infections Working Group[1]

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Affiliation

[1] Canad an Pub c Hea th Laboratory Networ , W nn peg, MB

***Correspondence:**
d onne.marc no@canada.ca

Introduction

A protoco for severe acute resp ratory nfect ons (SARI) was n t a y deve oped as a response to the 2003 severe acute resp ratory syndrome (SARS) outbreak (1). The protoco 's ntended use was to fac tate the d agnos s of nove and emerg ng resp ratory nfect ons, nc ud ng SARI, due to both unknown and known resp ratory pathogens that have the potent a for arge sca e ep dem cs. W th both the M dd e East resp ratory syndrome coronav rus (MERS CoV) and the nfluenza A(H7N9) v rus, a key factor n d agnos s s the determ nat on of r sk based on ep dem o og c factors, wh ch, n turn, s re ated to exposure n an "area of concern". W th the more h gh y transm ss b e severe acute resp ratory syndrome coronav rus 2 (SARS CoV 2), the cause of the coronav rus d sease 2019 (COVID 19) pandem c, test ng gu de nes have changed as the pandem c has deve oped. In t a y, test ng focused on those w th trave assoc ated r sk factors; w th a sh ft to broader test ng once more cases were oca y acqu red (w th n Canada). Th s n t a r sk assessment must be done n concert w th the oca M n stry of Hea th. S gna s of nove and emerg ng resp ratory nfect ons, nc ud ng SARI a erts, shou d tr gger c n c ans to "th nk, te and test":

- Think about the poss b ty of an emerg ng resp ratory nfect on (e.g. nove nfluenza A v rus)
- Tell the oca med ca officer of hea th or oca pub c hea th offic a ; not fy your oca aboratory and prov nc a pub c hea th aboratory (PPHL) that you suspect a nove pathogen
- Test for pathogen based on c n ca symptoms and on y after appropr ate consu tat on

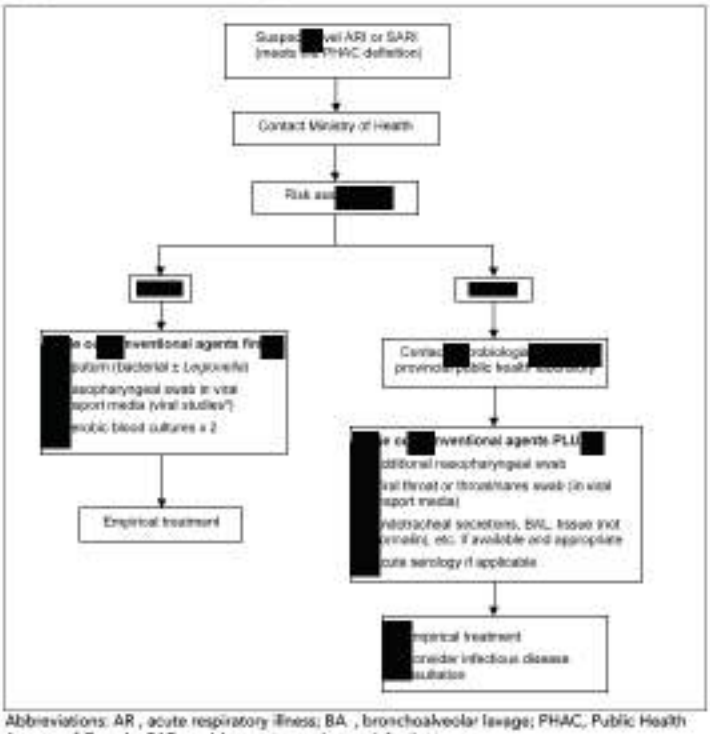
Laboratory protocol

When to test

Gu dance on when to test for nove or emerg ng pathogens s nfluenced by many ep dem o og ca factors. At the t me of the emergence of a nove pathogen, before w despread human nfect on, the probab ty that a SARI s due to a nove pathogen s extreme y ow. Therefore, n pat ents w th no ep dem o og ca r sk factors, the most common pathogens shou d be ru ed out before cons der ng a nove , unusua or more h gh y v ru ent pathogen. When appropr ate r sk factors ex st, nove pathogens shou d st be ru ed out regard ess of whether another pathogen s detected, as v ra co nfect ons have been we documented w th nove v ra resp ratory pathogens (e.g. MERS CoV, nfluenza A(H7N9) and SARS CoV 2) **Figure 1.**

A though test ng s n t a y focused on nd v dua s w th ep dem o og c nks, such as those who have trave ed to a reg on where the pathogen s c rcu at ng, once there s w despread act v ty, such as n the COVID 19 pandem c, hea thcare prov ders shou d have a ow thresho d to cons der test ng for the nove pathogen when rev ew ng pat ents w th acute resp ratory ness (ARI). Th s thresho d for test ng w cont nue to be nfluenced by the ep dem o ogy of the nfect on such as 1) the stage of the pandem c wave that the jur sd ct on s n, 2) whether there s oca or w despread act v ty and 3) whether the response s n a conta nment or m t gat on phase. Spec fic test ng gu de nes are deve oped at the prov nc a eve , and w vary across Canada. Other factors that may nfluence approaches to test ng nc ude the ava ab ty of test ng supp es and reagents,

Figure 1: Laboratory protocol



Abbreviations: AR, acute respiratory illness; BA, bronchoalveolar lavage; PHAC, Public Health Agency of Canada; SAR, sudden acute respiratory infection
Contact microbiologist on call for guidance regarding appropriate test

wh ch may be n short supp y at var ous t mes dur ng a pandem c. Th s test ng may be done at the oca aboratory or the PPHL depend ng on oca capac ty and expert se.

Specimens to collect

Unt the dea spec men to detect an emerg ng pathogen has been dent fied, a broad range of spec mens shou d be co ected nc ud ng nasopharyngea swab (NPS), throat or comb ned throat/nares swab, bronchoa veo ar avage (BAL), endotrachea secret ons, and sputum. For ped atr c pat ents, a nasopharyngea asp rate s a su tab e rep acement to a NPS, a though t s an aeroso generat ng med ca procedure wh ch requ res a rborne precaut ons whereas NPS does not. A though sa va has been suggested for detect on of some emerg ng pathogens ke SARS CoV 2, t requ res more va dat on pr or to be ng recommended as the so e, spec men for co ect on.

For pat ents not adm tted to hosp ta , nc ud ng those n emergency room sett ngs, a s ng e upper resp ratory tract spec men s usua y suffic ent for test ng emerg ng resp ratory v r a pathogens (such as SARS CoV 2 or H7N9). Upper resp ratory tract spec mens nc ude a NPS, throat OR comb ned throat/nares swab co ected n un versa transport med um. An NPS s the preferred spec men due to poss b e ncreased sens t v ty n compar son w th a throat swab. A comb ned throat/nares spec men may a so be co ected, prov ded the test ng aboratory has approved the subm ss on of th s comb ned spec men source type.

For hosp ta zed pat ents, n part cu ar those w th SARI, subm ss on of both upper and ower resp ratory tract spec mens s recommended when poss b e. As above, NPS s the preferred upper resp ratory tract spec men. A throat or comb ned throat/nares swab co ected n un versa transport med um may be subm tted as an add t ona upper tract spec men. Lower resp ratory tract spec mens shou d a so be subm tted when poss b e. These ower tract spec mens nc ude sputum, endotrachea asp rates and BAL. For a number of emerg ng pathogens, nc ud ng av an nfluenza and nove coronav ruses, there have been reports of pat ents who were found to be negat ve on upper resp ratory tract test ng but pos t ve on ower resp ratory tract test ng.

Recommended pathogens and specimens to test

At the t me of the emergence of a nove pathogen, before w despread human nfect on, the probab ty that a severe acute resp ratory ness s due to the nove pathogen s extreme y ow. Therefore, n pat ents w th no ep dem o og ca r sk factors the most common pathogens shou d be ru ed out before cons der ng an unusua or more h gh y v ru ent pathogen. Th s nc udes the fo ow ng:

Conventional bacteria

- Sputum for rout ne bacter a Gram sta n and cu ture

Atypical bacteria

- *Legionella* sputum, BAL, endotrachea asp rate, ung t ssue for po ymerase cha n react on (PCR) and/or cu ture
- Ur ne for *Legionella* ur nary ant gen test ng
- *Mycoplasma/Chlamydia* NPS, throat swab, and/or ower tract spec men for PCR and/or cu ture

Conventional respiratory viruses

- Inc ud ng human nfluenza, para nfluenza, resp ratory syncyt a v rus, adenov rus, human metapneumov rus, rh nov rus/enterov rus, coronav rus
- Spec mens NPS, endotrachea secret ons, BAL, w th or w thout throat swab (or comb ned throat/nares swab) and sputum
- NPS s the pr mary spec men type for resp ratory v ruses nc ud ng seasona nfluenza. However, based on our exper ence w th pandem c H1N1, deeper spec mens, such as endotrachea secret ons or BAL, must be co ected n cases of severe resp ratory nfect on w th negat ve NPS
- A number of av an nfluenza A v ruses, nc ud ng H7N9, has been detected n throat swabs. Influenza A (H7N9) was on y detectab e n sputum spec men n one of four pat ents. Wh e sputum and throat swabs are not dea for most nfluenza v ruses, mu t p e spec mens types shou d be cons dered n pat ents suspected of hav ng av an nfluenza A v ruses

Testing methods

Test ng shou d be conducted us ng assays va dated for the spec fic pathogen:

- SARS CoV 2 shou d be tested by rea t me reverse transcr pt on PCR (rRT PCR) (see above)
- The pr mary method for detect on of nfluenza A and B (24 hour turnaround t me) shou d be rRT PCR w th subtyp ng (H3N2 or H1N1). Preferred protoco s for detect on of nove nfluenza v ruses are those deve oped by the Un ted States Centers for D sease Contro
- For para nfluenza, human metapneumov rus, coronav rus, rh nov rus/enterov rus and adenov rus, resp ratory mu t p ex RT PCR shou d be done on a spec mens f poss b e; or on nfluenza negat ve spec mens when there s a c n ca nd cat on to detect non nfluenza v ruses
- Rap d nfluenza d agnost c tests shou d not be used to ru e out nfluenza A. The sens t v ty of current y ava ab e rap d nfluenza d agnost c tests for human nfluenza stra ns s subopt ma . The sens t v ty of current y ava ab e commerc a tests for detect on of H7N9 s poor and shou d not be used for c n ca test ng
- SARS CoV 2, nove nfluenza A v ruses and MERS CoV are c ass fied as RG3 pathogens. Rout ne cu tur ng of spec mens from suspect pat ents shou d on y be cons dered n PPHLs w th conta nment eve (CL) 3 fac t es. V rus cu ture n a CL2 aboratory may be cons dered f the spec men has been tested for the re evant emerg ng pathogens and s negat ve by rRT PCR

If more nvas ve samp es are co ected they shou d be processed for a w de range of pathogens:

- BAL for test ng for a broad range of pathogens (bacter a, v ruses, mycobacter a, fung)
- Open ung b opsy bacter a , mycobacter a and funga , cu tures, RT PCR and h sto ogy (ensure spec men s NOT PUT IN FORMALIN

When to suspect SARS-CoV-2 virus

Dur ng the ear y phases of the pandem c, wh ch began n Wuhan, Ch na n December 2019, on y persons who returned from Wuhan, then the prov nce of Hube , Ch na, w th ARI were cons dered for test ng. W th the progress on of the ep dem c, test ng of those w th ARI after return from trave to countr es w th COVID 19 act v ty was nd cated.

Fo ow ng the evo ut on of COVID 19 to a pandem c and oca transm ss on n most jur sd ct ons n Canada, test ng approaches were broadened, w th an n t a focus on case dent ficat on for contact trac ng and test ng to support the conta nment strategy. Test ng focuses on the fo ow ng groups:

- Persons w th ARI who are trave ers return ng from areas w th oca COVID 19 act v ty
- Hosp ta zed persons; contacts of outbreak cases
- Inst tut ona zed persons
- Hea thcare workers
- Remote, so ated and/or Ind genous commun t es
- Vu nerab e popu at ons

Once the case numbers ncrease, w th more extens ve commun ty transm ss on and pressures on test ng resources, the goa of test ng may need to be pr or t zed to support the m t gat on strategy nc ud ng the fo ow ng:

- Test ng persons at r sk for ser ous d sease
- Those ke y to transm t v rus w th n a hea thcare fac ty or vu nerab e commun ty sett ng
- Those from whom COVID 19 d sease wou d have an mpact on de ver ng hea thcare or cr t ca nfrastructure
- Those for whom exposure wou d put them at r sk of test ng pos t ve

Add t ona groups may be cons dered for test ng, depend ng on the stage of the pandem c, oca po cy and ava ab ty of reagents.

The COVID 19 test ng shou d be comp eted for pat ents who meet test ng cr ter a regard ess of whether another pathogen s dent fied. Ear y data suggests that up to 30% of pat ents w th COVID 19 can have co nfect on w th other resp ratory v ruses.

Further nformat on on aboratory test ng for COVID 19 s ava ab e from the Canad an Pub c Hea th Laboratory Network (CPHLN) COVID 19 Best Pract ces document (2).

When to suspect the Middle East respiratory syndrome coronavirus

L m ted data suggest that MERS CoV can present as a co nfect on w th other v ra pathogens. As such, n add t on to spec mens that are negat ve for convent ona pathogens, those that do have other dent fied pathogens **but are consistent with suspect cases of MERS-CoV based on the Public Health Agency of Canada (PHAC) case definition, or alternatively provincial testing guidelines** shou d be tested. The deta s regard ng test ng and some contro mater a s for method deve opment are ava ab e from the Nat ona M crob o ogy Laboratory (NML). To date on y a few PPHLs have deve oped the capac ty to test for th s pathogen n house; a other PPHLs shou d forward the suspect spec mens to the NML for further test ng.

When to suspect a novel influenza virus (including H7N9)

Influenza v ruses that are pos t ve on the n t a nfluenza dent ficat on test but cannot be subtyped us ng RT PCR shou d be further character zed. Laborator es that have the capac ty to further character ze the spec mens by nove subtyp ng PCRs or sequenc ng methods (e.g. sequence the HA, N, M or other

genes) to determ ne the subtype of the v rus shou d do so. Those that ack th s capac ty shou d re y on the NML for further character zat on. However, g ven that subtyp ng assays are usua y ess sens t ve than the dent ficat on assays, weak pos t ve resu ts may not be typab e. Based on oca exper ence, each aboratory shou d eva uate these on a case by case bas s, n concert w th the r oca c n c ans and pub c hea th co eagues.

Influenza pos t ve spec mens outs de the nfluenza season or obta ned from pat ents w th a h story of exposure to an ma s (e.g. p gs or ch ckens) shou d be rout ne y subm tted to the PPHL and/or NML for character zat on.

Note: Wh e n t a ana ys s of the n house assays used by many aborator es suggests they shou d be effect ve n dent fy ng H7N9, t s d fficu t to determ ne the r effect on the sens t v ty of test ng. Th s s part cu ar y true of the performance of commerc a assays whose pr mer sequences are not known. It s mportant for aborator es to have vendors supp y nformat on about the ab ty of the r assays to detect nove nfluenza v ruses. Laborator es us ng Leve of Detect on Tests shou d mon tor v ra sequences and the r matches to the pr mers and probes n the assays.

If a front line laboratory suspects a novel/emerging respiratory pathogen

The n t a tests (as out ned above) wou d be s m ar but supp ementa test ng w be requ red at the PPHL. The aboratory shou d commun cate w th the c n c an to ensure that the fo ow ng spec mens are co ected:

- A second NPS/endotrachea asp rate or BAL to be used for confirmat on by the NML
- A v ra throat swab (n v ra transport med a) a number of av an nfluenza A v ruses, nc ud ng H7N9, have been detected n throat swabs. Mu t p e spec men types shou d be co ected when nove nfluenza v ruses are cons dered and, when poss b e, nc ude both upper and ower resp ratory tract spec mens
- Acute and conva escent sera co ect on may be appropr ate, depend ng on the spec fic v rus suspected, and adv ce from NML and PPHLs. Sero ogy s not recommended for pat ents suspected of nfluenza A(H7N9) or MERS CoV nfect on. Some SARS CoV 2 sero ogy assays have been deve oped by severa commerc a prov ders and are be ng eva uated by NML and some PPHLs. These nc ude ELISA based and mmunochromatograph c po nt of care tests. The r ro e n c n ca test ng and pub c hea th has yet to be c ar fied, as nsuffic ent data are ava ab e on sens t v ty, spec fic ty and pos t ve and negat ve pred ct ve va ues. Test ng gu de nes w be deve oped once assay performance character st cs have been e uc dated and assays are va dated for c n ca test ng

If a provincial public health laboratory suspects a novel respiratory pathogen

- The PPHL shou d not fy the pat ent's hea thcare prov der, oca pub c hea th un t and M n stry of Hea th mmed ate y when a suspect spec men s dent fied
- A spec mens w th suspected nove resp ratory pathogens (as out ned be ow) must be forwarded to the NML for confirmatory test ng. If a nove resp ratory pathogen causes an ep dem c or pandem c, w th oca transm ss on, on y ear y spec mens w be sent to NML for confirmatory test ng. In add t on, test ng may be mp emented at hosp ta or commun ty aborator es, as has occurred dur ng the SARS CoV 2 pandem c
- Spec mens suspected to conta n a nove resp ratory v rus shou d be hand ed us ng CL2 w th enhanced persona protect ve equ pment **if manipulated outside a biosafety cabinet**

Note: V rus cu ture shou d not be conducted on resp ratory spec mens n a CL2 aboratory when a nove or emerg ng pathogen s suspected, as they are RG3 pathogens. V rus cu ture, f requ red, may be cons dered n a CL2 sett ng f the spec men has been tested for these pathogens and s negat ve by RT PCR.

Specimen transport

Spec mens shou d be transported to the aboratory as soon as poss b e, preferab y w th n 72 hours on ce packs. If a onger de ay s ant c pated, spec mens shou d be frozen at 70°C, and transported on dry ce. However, spec mens shou d not be frozen at 20°C, as th s may affect the recovery of the v rus f cu ture s requ red. If 70°C/dry ce s not ava ab e spec mens shou d rema n at 4°C and sh pped as soon as poss b e. Spec mens shou d be transported as d agnost c spec mens per the usua pract ce for seasona nfluenza spec mens, and no enhanced precaut ons are necessary. See the PHAC SARS CoV 2 B osafety Adv sory for more nformat on (3).

Spec men tubes must be abe ed and requ s t on comp eted correct y and fu y, w th match ng pat ent names, un que dent fiers and re evant c n ca nformat on.

Authors' statement

The Resp ratory V rus Infect on Work ng Group of the Canad an Pub c Hea th Laboratory Network (CPHLN) s ded cated to prov d ng eadersh p and gu dance on top cs re ated to resp ratory v ra pathogens, nc ud ng aboratory response to emerg ng resp ratory v ruses. The Resp ratory V rus Infect on Work ng Group s compr sed of eaders from pub c hea th aborator es across Canada.

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Canadian Public Health Laboratory Network Best Practices for COVID-19

Respiratory Virus Infections Working Group[1]

Affiliation

[1] Canadian Public Health Laboratory Network, Winnipeg, MB

***Correspondence:**
dominique.marchand@canada.ca

Abstract

The ability to detect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, is a foundational component of Canada's containment and mitigation strategies. Laboratory confirmation of COVID-19 cases allows the appropriate clinical management and public health interventions. Whether the focal goal is containment or mitigation will depend on local epidemiology of the pandemic. The Respiratory Virus Infections Working Group of the Canadian Public Health Laboratory Network has developed comprehensive Best Practice Guidelines for detection of SARS-CoV-2. Best practices for specimen collection, transportation, testing and biosafety are addressed from the perspective of Canadian public health laboratories to ensure a consistent approach across the country:

1. Population based testing for COVID-19 should not at any time be carried out for surveillance
2. Nasopharyngeal swabs is the specimen of choice for routine testing
3. Nucleic acid amplification tests (such as real-time reverse transcription polymerase chain reaction) are the method of choice for routine testing of SARS-CoV-2
4. The decentralization of nucleic acid amplification testing for COVID-19 to hospital or other high complexity medical laboratories should be promoted to increase test capacity and meet increased demands
5. In the early stages of the pandemic, positive (approximately 10–20) and negative (approximately 50) tests by a provincial laboratory require confirmation at the National Microbiology Laboratory
6. Co-circulation of other viral agents associated with influenza-like illnesses (e.g. influenza A and B and respiratory syncytial virus) should be monitored as capacity permits, as part of ongoing surveillance
7. Once validated, serological testing may be utilized for assessing the presence/absence of immune response to the SARS-CoV-2 at either the population or individual level for selected indications, but is likely to be of limited utility in diagnosis of acute COVID-19 illness

These recommendations will be updated as new information becomes available.

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Keywords: COVID-19, best practices, Canada, testing, surveillance

Introduction

Since the report of the novel coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2 in late December 2019 in Wuhan, Hubei Province of China, the vast majority of countries have now reported laboratory confirmed cases of COVID-19. Due to the continued spread of COVID-19, the situation was declared a pandemic by the World Health Organization on March 11, 2020 (1).

The clinical presentation of COVID-19, which is caused by SARS-CoV-2, is non-specific and overlaps with other seasonal respiratory viruses, including influenza. The ability to detect SARS-CoV-2 in patients is critical for surveillance, diagnosis and clinical management of persons presenting with acute respiratory illness (ARI), influenza-like illness (ILI) and severe respiratory illness to support Canada's containment and mitigation strategies.

The purpose of SARS-CoV-2 testing can fall into two broad categories, and will depend on the local epidemiology and goals of public health strategies (containment vs. mitigation):

1) Test ng for the purpose of h gh probab ty case find ng among persons present ng w th ARI and ILI and appropr ate exposure cr ter a s cr t ca to ensure COVID 19 cases are dent fied n a t me y fash on to ensure appropr ate c n ca and pub c hea th management can occur dur ng the conta nment phase of the pandem c. In add t on, when oca numbers are ow, test ng w ke y support aggress ve case find ng strateg es for ear y contact trac ng and mp ementat on of se f so at on. Once the v rus becomes w despread, test ng of commun ty samp es shou d be reserved for commun ty based surve ance programs, w th the rema nder of test ng focused on hosp ta zed pat ents w th ARI and those w th r sk factors for severe d sease where the resu ts of the test may nfluence dec s ons regard ng care and treatment, nfect on contro (nc ud ng outbreaks), management of c ose contacts, and to support remote commun t es. It s mportant that the above management and prevent on dec s ons shou d not be de ayed pend ng test ng resu ts. Cases of COVID 19 have had co nfect ons w th other v ruses nc ud ng nfluenza. Test ng for nfluenza shou d cont nue for hosp ta zed pat ents to he p support pat ent management w th ant v ra s.

2) Popu at on based surve ance shou d occur for ongo ng dent ficat on of COVID 19 cases and fac tate track ng of other common v ra agents, such as resp ratory syncyt a v rus, para nfluenza, adenov rus and rh nov ruses, that co c rcu ate dur ng the nfluenza season and dur ng other t mes of the year.

Th s *Best Practices* gu dance shou d be used n conjunct on w th re evant prov nc a and terr tor a gu de nes. The Pub c Hea th Agency of Canada w be post ng regu ar updates and re ated documents (2).

Surveillance

Popu at on based surve ance s mportant dur ng d fferent stages of the COVID 19 pandem c. The areas of focus of surve ance w sh ft as test ng pr or t es are rea gned when the hea th system moves from a conta nment to m t gat on phase. It s mportant to note that the ex st ng techno og es for COVID 19 detect on are not suffic ent n the r performance to be app ed as a genera popu at on screen ng too , and targeted use of test ng n popu at ons where pretest probab ty s h ghest, or where potent a benefit rema ns h ghest, rema ns an mportant pr nc p e of samp e se ect on.

Dur ng conta nment, popu at on based surve ance s very mportant, as m d y symptomat c SARS CoV 2 nfect on may p ay some ro e n commun ty transm ss on. At th s stage, the major ty of pat ents tested for SARS CoV 2 are ambu atory, w th few hosp ta zed pat ents meet ng exposure cr ter a to be a suspect case (3). Dur ng th s t me, t s mportant to conduct surve ance test ng on a subset of hosp ta zed persons, and persons seen n ambu atory sett ngs w th ARI/ILI but no spec fic r sk factors for COVID 19. Add t ona commun ty surve ance shou d occur at ong term care homes, where the e der y pat ent popu at on, often w th comorb d t es, are at greatest r sk for comp cat ons and fata nfect on. Th s surve ance cou d occur by test ng an appropr ate se ect on (as gu ded by outbreak contro author t es) or a resp ratory outbreak samp es for SARS CoV 2.

Dur ng m t gat on, t s presumed that there w be w despread c rcu at on of the v rus throughout d fferent sectors of the commun ty. Dur ng th s t me, COVID 19 test ng w sh ft to dent fy ng cases among hosp ta zed pat ents, who represent the more severe y . Commun ty test ng for SARS CoV 2 w be ess rout ne y ava ab e for ambu atory pat ents, though shou d be cont nued for ambu atory hea thcare workers w th ILI (and poss b y ARI), nst tut ona outbreaks, remote and confined/ congregate commun t es, and may be prov ded to popu at ons w th r sk factors for severe d sease (e.g. age 60 years or o der, presence of comorb d t es). Spec fic screen ng, samp ng, spec men co ect on and test ng gu de nes w be deve oped by the oca prov nc a hea thcare system. Ambu atory surve ance programs shou d cont nue dur ng a m t gat on phase n order to prov de some data on commun ty preva ence of SARS CoV 2, as th s w support track ng the progress of the pandem c.

To ass st w th max m z ng use of aboratory test ng data to enab e COVID 19 surve ance, hosp ta s or other h gh comp ex ty aborator es do ng test ng shou d contr bute summary test ng data to comp ement the data from test ng at the r prov nc a pub c hea th aboratory. These data can then he p nform a oca , prov nc a and federa snapshot of pandem c act v ty. Prov nces shou d seek to perform adequate surve ance and case find ng test vo umes, wh ch w prov de approx mate y a da y snapshot of d sease preva ence n the r test jur sd ct ons. The determ nat on of that m n mum vo ume s based on a number of factors and shou d be determ ned n cooperat on w th b ostat st ca or ep dem og ca support.

Surve ance shou d a so be n p ace to he p w th the g oba mon tor ng of the mo ecu ar ep dem o ogy of SARS CoV 2. Th s w he p estab sh any geograph c d fferences n stra ns c rcu at ng, and poss b e c n ca y re evant genom c var ants. Mo ecu ar surve ance w a so prov de data to ass st w th mon tor ng for any d agnost c assay pr mer or probe m smatches to SARS CoV 2 that m ght affect the performance character st cs of d agnost c assays. Such efforts shou d be coord nated across a jur sd ct ons, and ed by Wor d Hea th Organ zat on connected fac t es such as the Nat ona M crob o ogy Laboratory (NML) n W nn peg. Wh e further research s necessary, t may nform quest ons of post nfect on mmun ty and potent a for re nfect on, as we as ass st w th vacc ne p ann ng and des gn. Wh e there current y s no spec fic ant v ra therapy for SARS CoV 2, genom c sequence data may be he pfu n pred ct ng res stant phenotypes f effect ve ant v ra s are deve oped.

Seropreva ence stud es may a so be conducted to ass st w th document ng the popu at on attack rates from COVID 19 dur ng the pandem c. These wou d be conducted by perform ng SARS CoV 2 sero ogy on a representat ve set of res dua sera

from across a age groups, and repeat ng th s at set nterva s over the com ng months. The ma n cha enge to conduct ng th s act v ty s that no commerc a assay has been va dated for c n ca test ng at th s t me, a though efforts for va dat on are underway n Canada, and the ut ty of such assays on a broad popu at on sca e s not yet affirmed.

Diagnostic testing

Dur ng the conta nment per od, efforts w be d rected at ntense case find ng to ensure ear y dent ficat on, ear y so at on, ear y d agnos s and ear y treatment as we as appropr ate contact management and fo ow up. Th s w nc ude both outpat ent (ambu atory) and npat ent sett ngs. Once the ep dem o ogy of the outbreak suggests that conta nment s not feas b e and resources w become stra ned, the aboratory w support the goa of m t gat on and pr or t ze test ng to the fo ow ng groups of pat ents: 1) hosp ta zed pat ents w th a degrees of ARI, nc ud ng severe resp ratory ness and ILI and m der resp ratory ness; 2) pat ents for whom d agnost c test ng w ass st dec s ons regard ng care, nfect on contro (nc ud ng outbreaks), or management of c ose contacts; 3) persons who d ed of an acute ness n wh ch nfluenza or another resp ratory v rus such as SARS CoV 2 s suspected; 4) hea thcare workers w th ARI/ILI; and 5) persons v ng n remote and so ated commun t es.

In the m t gat on phase, when v ra c rcu at on n the commun ty s estab shed, test ng may on y occas ona y be performed on outpat ents; spec fic test ng a gor thms w be dec ded on by each prov nc a hea th system, w th a ke y focus s m ar to what s out ned above. Test ng s not nd cated for c n ca management of persons w th uncomp cated resp ratory nfect on res d ng n commun t es where SARS CoV 2 s c rcu at ng.

Specimen type and collection

The Wor d Hea th Organ zat on recent y reported that SARS CoV 2 has been detected n resp ratory, feca and b ood spec mens (4). Pre m nary data report v rus detect on n upper resp ratory samp es 1 2 days before symptom onset, wh ch pers sts for 7 12 days n moderate cases and up to two weeks n severe cases. V rus has been cu tured from resp ratory tract samp es up to e ght days fo ow ng symptom onset. A though SARS COV 2 v rus has a so been detected n sa va, ts use for d agnost c test ng requ res further nvest gat ons.

V ra r bonuc e c ac d (RNA) has been detected n feces n up to 30% of pat ents commenc ng day 5 after symptom onset, and th s cont nues for up to five weeks n moderate cases. However, t s not c ear whether th s reflects shedd ng of nfect ous v rus. Wh e ve v rus has been cu tured from stoo n some cases, the ro e of feca ora transm ss on s not yet we understood.

At th s t me the focus of test ng s on resp ratory samp es. Ear y data suggest that ower v ra oads can be detected n nasopharyngea swabs than n throat swabs (5), and as such they are the preferred upper resp ratory tract spec men. In add t on, they are a so the preferred spec men for nfluenza detect on, wh ch can have a s m ar c n ca presentat on. Sputum s a usefu ower resp ratory tract spec men, and can be co ected from pat ents w th a product ve cough. However, sputum nduct on s not recommended due to the r sk of generat ng aeroso s. F ocked swabs are recommended to co ect on of nasopharyngea or nasa /throat spec mens.

Alternative collection devices

In the event of a supp y cha n nterrupt on and an nab ty to obta n flocked swabs or v ra transport med a, a ternat ve opt ons such as rayon on p ast c or w res can be cons dered. Cons derat on to a ternat ves to v ra transport med a nc ude phosphate buffered sa ne or a coho for stab zat on. Wooden swabs are cons dered nh b tory to nuc e c ac d based test ng, and therefore un ess va dated to the contrary, are not recommended. Any a ternat ve spec men co ect on dev ces or transport med a w requ re va dat on for use n c n ca test ng. Further nformat on on a ternat ve co ect on k ts s ava ab e from U.S. Food and Drug Adm n strat on (6).

Specimen pooling

Poo ng mu t p e spec mens may be cons dered as a means of ncreas ng throughput dur ng per ods of h gh subm ss ons, and to preserve reagents dur ng t mes of shortages. If the poo s pos t ve, then each nd v dua spec men w th n the poo must be retested to determ ne wh ch spec men s pos t ve. There s a trade off of decreased sens t v ty when spec mens are poo ed. Any aboratory cons der ng poo ng shou d do the r own eva uat on of the mpact on sens t v ty as th s w be assay and aboratory spec fic, and use th s to dec de on the opt ma number to poo n the r sett ng. Work w th nfluenza outbreaks has shown that sens t v ty s gn ficant y drops f poo ng more than four spec mens. Laborator es may choose to run on y non cr t ca spec mens through a poo ng protoco and preserve s ng e spec men test ng for pat ents w th more severe ness (e.g. hosp ta zed pat ents). As percent pos t v ty ncreases, the number of spec mens w th n the poo for th s to be effic ent w need to be reduced; n genera , once the test pos t ve rate reaches the 8% 10% range, there s no benefit to poo ng any number of spec mens (**Table 1**).

Specimen transport

Spec mens shou d be transported to the aboratory as soon as poss b e, preferab y w th n 72 hours, on ce packs. If a onger de ay s ant c pated, spec mens shou d be frozen at 70°C or co der, and transported on dry ce. However, spec mens shou d not be frozen at 20°C, as th s may affect the recovery of the v rus f cu ture s requ red. If 70°C or be ow/dry ce s not ava ab e, spec mens shou d rema n at 4°C and be sh pped as

Table 1: Preferred and alternative specimen types

Nature of illness	Specimen of choice	Alternative specimens
M d/ moderate nfluenza ke ness	Nasopharyngea swab V deo demonstrat on of nasopharyngea swab co ect on can be accessed at http://www.youtube.com/watch?v TFwSefez HU	Deep nasa swab, throat swab or both https://v meo.com/397169241
Severe resp ratory ness	Nasopharyngea swab AND endotrachea or bronchoa veo ar avage. Sputum (f product ve cough)	Sputum, throat swab
Autopsy	Nasopharyngea swab AND throat swab Lung t ssue or other t ssues from suspected organ nvo vement. Spec mens shou d be fresh or frozen at 70°C or be ow. Do not put nto forma n fixat ve	Not app cab e

soon as poss b e. Spec mens shou d be transported as Transport of Dangerous Goods defined d agnost c spec mens per the usua pract ce for seasona nfluenza spec mens, and no enhanced precaut ons are necessary. See the PHAC SARS CoV 2 B osafety Adv sory for more nformat on (7).

Spec men tubes shou d be appropr ate y abe ed and requ s t on correct y and fu y comp eted, w th match ng pat ent names and un que dent fiers, and re evant c n ca and/or pub c hea th requ red nformat on.

Testing methods

Wh e other methods ex sts for the detect on of SARS CoV 2, detect on methods n c n ca aborator es are m ted to mo ecu ar detect on us ng nuc e c ac d amp ficat on tests (NAAT) and v ra cu ture.

Nucleic acid amplification tests

At the t me of th s pub cat on, there are an ncreas ng number of commerc a assays ava ab e for detect on of SARS CoV 2. Many aborator es are mp ement ng n house, aboratory deve oped tests based on the detect on of the RNA dependent RNA po ymerase, enve ope and nuc eocaps d genes, wh e others are mp ement ng commerc a assays that detect a var ety of v ra targets. Some aborator es have a pan beta coronav rus RNA po ymerase NAAT, wh ch s then confirmed by nuc e c ac d sequenc ng, a though most aborator es have moved to rea t me methods that d rect y dent fy two d fferent genet c targets gene sequenc ng s reserved for cases where a s ng e target s ndeterm nate on the rea t me reverse transcr pt on po ymerase cha n react on (rRT PCR) assay and further c ar ficat on of the aboratory resu t s c n ca y nd cated.

As a resu t of the evo ut on of the outbreak nto a pandem c, and SARS CoV 2 no onger be ng a rare aboratory test find ng, detect on of a s ng e target under we va dated cond t ons s suffic ent for aboratory confirmat on of SARS CoV 2.

A though tt e data ex st on the d agnost c performance of current NAAT tests, based on pre m nary data from Canad an aborator es the eve of detect on tests have exce ent ana yt ca sens t v ty (95% m t of detect on be ow 10 cop es per react on) and spec fic ty. Dur ng eve of detect on tests va dat on, aborator es shou d determ ne the max mum cyc e thresho d va ue for target detect on, us ng the 95% m t of detect on generated n the r aboratory as a gu de. They shou d a so dec de whether an ndeterm nate cyc e thresho d range for that part cu ar assay s requ red, and what cyc e thresho d va ues to nc ude n the ndeterm nate range. Pat ents who n t a y test negat ve shou d be retested f the c n ca susp c on of COVID 19 rema ns h gh, n part cu ar among hosp ta zed pat ents who are not c n ca y mprov ng. Lower resp ratory tract samp es shou d be obta ned from pat ents w th ev dence of pneumon a to ncrease c n ca sens t v ty. Test performance among pat ents w th d fferent sever t es of ness (e.g. asymptomat c, m d ness, hosp ta zed) s ke y to d ffer, and these d fferences have not been we character zed. Rout ne test ng of asymptomat c pat ents s not recommended. Ongo ng eva uat on of commerc a y ava ab e tests, as they are deve oped, w be mportant to character ze the r performance n the c n ca sett ng and throughout the pandem c. Pub c hea th aborator es shou d take appropr ate n t at ves and he p estab sh add t ona test ng s tes n the r respect ve jur sd ct ons.

Point-of-care molecular testing

Commerc a mo ecu ar detect on assays are, and more w become, censed by Hea th Canada for po nt of care (POC) use outs de the aboratory. Before fac t es n Canada cons der us ng any POC or a non c ass III dev ce "off abe " for near POC test ng, an mp ementat on and qua ty p an shou d be made w th a c n ca or med ca m crob o og st and an appropr ate aboratory med ca d rector. Where poss b e, a prov nc a system shou d be set up for captur ng the data generated from POC test ng to ass st w th aboratory surve ance. As w th any med ca aboratory act v t es, adherence to any appropr ate persona hea th nformat on, med ca aboratory accred tat on and med ca aboratory censure regu at ons and standards must be cons dered n advance of offer ng such test ng.

Virus isolation

V rus so at on s m ted to aborator es that have censed conta nment eve (CL) 3 capab t es, and w not p ay a major ro e n the d agnos s of COVID 19 pat ents. It w ma n y be used to propagate v rus for the generat on of pos t ve RNA contro mater a requ red for NAATs. It may a so be requ red to support growth based sero og ca assays f deve oped (e.g. m croneutra zat on), vacc ne deve opment, and other areas of research.

Serology

Methods for sero og c d agnos s are be ng deve oped but have not yet been ntroduced nto rout ne c n ca use n Canada or other countr es. Severa p atforms target ng var ous mmunog obu ns (IgM, IgG, IgA) and tota ant bod es aga nst d fferent SARS CoV 2 ant gens, such as sp ke prote n and nuc eocaps d prote n, are ava ab e for eva uat on. Based on ava ab e terature, detect on of sero og ca response appears to be ess re ab e n the first week post symptom onset where sens t v ty s ow. The sens t v ty of detect on ncreases by 14 days post symptoms onset. Durat on of seropos t v ty post nfect on and whether the mmune response offers or corre ates w th protect on from re nfect on needs to be determ ned before nterpretat on re at ng to mmun ty can be made.

The ro e of sero ogy n d agnos s of acute ness and pat ent management s ke y to be of m ted ut ty. Once the dynam cs of sero og ca response are better understood, sero ogy may have a ro e n the fo ow ng: use n seroep dem o ogy stud es to better understand the proport on und agnosed n the popu at on over t me and prov de a more accurate est mate of attack rate; an adjunct to rRT PCR for d agnost c test ng n pat ents who are rRTP CR negat ve, ate n the course of the r ness, and have s gn ficant contact management cha enges that wou d be we nformed by support ve sero ogy; to mp ement contro measures and to effect ve y manage s gn ficant y at r sk popu at ons, nc ud ng assess ng them for serostatus; and once a vacc ne s ava ab e t may be used to determ ne, among h gh r sk popu at ons, who shou d be pr or t zed for ear er vacc nat on.

Two test ng moda t es are current y ava ab e commerc a y, enzyme nked mmunosorbent assay (ELISA) based assays and POC assays. The performance character st cs of both moda t es need to be determ ned; n part cu ar, sens t v ty, spec fic ty, pos t ve pred ct ve va ue and negat ve pred ct ve va ue, n add t on to the nterpretat on of pos t ve resu ts.

The ELISA based methods are amenab e to h gh throughput process ng, appropr ate qua ty contro and assurance, are ess suscept b e to operator subject v ty n nterpretat on and report ng of the r resu ts can be eas y ntegrated nto ex st ng aboratory nformat on systems. The ELISA methods are a so capab e of prov d ng some quant tat ve est mate of how much ant body s present. They are, however, more abor ntens ve, requ re spec a equ pment, reagents and aboratory expert se and do not prov de rap d resu ts. As an est mate of protect on of the mmune response, ELISA resu ts shou d be compared w th resu ts of v rus neutra zat on assays. However, at present, neutra zat on assays are not produced commerc a y and can on y be emp oyed n h gh comp ex ty aborator es capab e of t ssue and v ra cu ture, m t ng the r w despread use.

Most POC tests are mmunochromatograph c and atera flow based and as a resu t, prov de easy to read resu ts n as tt e as 30 m nutes w thout the requ rement of extens ve tra n ng or spec a zed equ pment. They are part cu ar y benefic a for use n remote areas w th m ted access to centra zed aboratory based test ng and/or m ted oca aboratory nfrastructure. The same gu de nes out ned above for POC mo ecu ar assays app y to POC sero ogy assays. Use under such cond t ons requ res part cu ar attent on and effort to ensure qua ty contro and assurance, such as part c pat on n externa qua ty assessment, to ma nta n h gh qua ty test ng. S m ar y, prov s ons for ma nta n ng appropr ate data and qua ty records of POC test resu ts are necessary before the r mp ementat on nto rout ne use.

External quality assurance

Any aboratory mp ement ng test ng for SARS CoV 2 shou d do so accord ng to the med ca aboratory regu at ons n p ace n the r jur sd ct on. As s requ red for other m crob o ogy c n ca tests, they must be enro ed n ava ab e externa qua ty assessment programs that can be accessed prov nc a y, nat ona y and/or nternat ona y. Th s s part cu ar y mportant when prov d ng test ng for an emerg ng pathogen such as SARS CoV 2. The deve opment and prov s on of standard zed sero ogy pane s to support mp ementat on and profic ency test ng w be key to the successfu mp ementat on of sero ogy assays n Canad an aborator es.

Detection of other respiratory viruses

The emergence of COVID 19 comes at a t me when many reg ons n the Northern Hem sphere are exper enc ng the r resp ratory v rus season and there are data to suggest that co nfect ons can occur; however, the c n ca mp cat ons of co nfect on on pat ent outcomes are not c ear. It s expected that w th w de spread c rcu at on of the v rus, the d agnost c capac t es of aborator es may be exceeded and w requ re the suspens on of some serv ces or the use of cont ngency p ans thus mak ng t unrea st c to expect broad rout ne test ng for the other v ruses. However, the detect on of nfluenza, part cu ar y n pat ents requ r ng hosp ta zat on or those w th comorb d t es putt ng them at r sk for comp cat ons, shou d cont nue to he p gu de pat ent management w th ant nfluenza agents.

Biosafety considerations

The SARS CoV 2 s a r sk group (RG) 3 pathogen. Propagat on or cu ture of the v rus s restr cted to aborator es that have federa y censed CL3 fac t es. The SARS CoV 2 s transm tted from resp ratory drop et spread and, as such, resp ratory spec mens wou d be cons dered potent a sources of v rus. A though there are m ted data that suggest SARS CoV 2 can be detected n b ood and stoo , there are no data at th s t me that suggest these are a source of nfect on. Non propagat ve d agnost c act v t es us ng spec mens that do not resu t n the

concentrat on or extract on of the pathogen, such as rout ne chem stry, hemato ogy or ur na ys s can cont nue us ng standard precaut ons. Resp ratory spec mens from pat ents w th suspect COVID 19 can be safe y hand ed n CL2 fac t es w th add t ona precaut ons nc ud ng the fo ow ng: a ab coat, g oves, and eye protect on are worn when hand ng pr mary spec mens; centr fugat on of pr mary spec mens s carr ed out n sea ed safety cups, or rotors, that are oaded/un oaded n a C ass II b o og ca safety cab net (BSC) or other pr mary conta nment dev ce; a cert fied C ass II BSC, or other pr mary conta nment dev ce, s used for procedures that may produce nfect ous aeroso s nc ud ng p pett ng; and resp ratory protect on that prov des a eve of fi trat on of 95% or greater (e.g. N95) s worn where aeroso generat ng act v t es cannot be conta ned w th n a BSC or other pr mary conta nment dev ce.

It s recommended that aborator es perform a oca r sk assessment on act v t es nvo v ng spec mens from COVID 19 pat ents to determ ne f add t ona precaut ons are requ red.

V rus cu ture shou d not be conducted on resp ratory spec mens n a CL2 aboratory when a nove or emerg ng pathogen s suspected as they are RG 3 pathogens. V rus cu ture, f requ red, may be cons dered f the spec men has been tested for these pathogens and s negat ve by rRT PCR.

Disinfection

Based on current y ava ab e ev dence, chem ca d s nfectants that are effect ve aga nst enve oped v ruses are su tab e for decontam nat on of SARS CoV 2, prov ded they are used accord ng to manufacturer's recommendat ons. Part cu ar attent on shou d a so be g ven to the correct contact t me (e.g. 10 m nutes), d ut on (.e. concentrat on of the act ve ngred ent) and exp ry date of the work ng so ut on preparat on. Such effect ve d s nfectants nc ude sod um hypoch or te (b each), 70% ethano , 0.5% hydrogen perox de, quaternary ammon um compounds and pheno c compounds. It s poss b e other b oc da agents may be ess effect ve (e.g. 0.05% 0.2% benza kon um ch or de, 0.02% ch orhex d ne d g uconate).

Sod um hypoch or te (b each) at a concentrat on of 1,000 ppm (0.1%) s recommended for genera surface d s nfect on and 10,000 ppm (1%) for d s nfect on of b ood sp s.

See the PHAC SARS CoV 2 B osafety Adv sory (7) and WHO Laboratory B osafety Gu dance Re ated to the Nove Coronav rus (2019 nCoV): Inter m Gu dance (4) for more nformat on.

Authors' statement

The Resp ratory V rus Infect on (ReVI) Work ng Group of the Canad an Pub c Hea th Laboratory Network (CPHLN) s ded cated to prov d ng eadersh p and gu dance on top cs re ated to resp ratory v ra pathogens, nc ud ng aboratory response to emerg ng resp ratory v ruses. The ReVI Work ng Group s compr sed of eaders from pub c hea th aborator es across Canada.

Conflict of interest

None.

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Diagnostic testing for SARS-CoV-2

Interim guidance

11 September 2020

World Health Organization

Introduction

This document provides interim guidance to laboratories and other stakeholders involved in diagnostics for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It covers the main considerations for specimen collection, nucleic acid amplification testing (NAAT), antigen (Ag), antibody (Ab) detection and quality assurance. This document will be updated as new information becomes available. Feedback can be sent to WHElab@who.int.

Changes from the previous version

The title of this interim guidance has changed from "Laboratory testing for COVID-19 in suspected human cases" to "Diagnostic testing for SARS-CoV-2". Additional relevant background information and a clinical diagnostic algorithm has been added to the document. Furthermore, the guidance has been updated with new findings from the literature and best practices.

Relevant WHO documents

WHO has developed interim guidance and technical briefs to assist policy-makers and laboratories on testing for SARS-CoV-2. These documents cover laboratory testing strategy [1], laboratory assessment tool [2], laboratory biosafety [3], advice on the use of point-of-care immunodiagnostic tests [4], antigen detection in diagnosis of SARS-CoV-2 infection using rapid immunoassays [5], guidance for the investigations of clusters [6], public health surveillance [7] and operational considerations for surveillance using GISRS [8]. In addition, early investigation protocols [9] can be used by countries to implement epidemiological studies and enhance understanding of transmission patterns, disease severity and prevalence, clinical features and risk factors of SARS-CoV-2 infection.

Background on SARS-CoV-2

WHO was first alerted to a cluster of pneumonia of unknown etiology in Wuhan, People's Republic of China on 31 December 2019. The virus was initially tentatively named 2019 novel coronavirus (2019-nCoV).

Subsequently the International Committee of Taxonomy of Viruses (ICTV) named the virus SARS-CoV-2 [10]. COVID-19 is the name of the illness caused by SARS-CoV-2.

SARS-CoV-2 is classified within the genus *Betacoronavirus* (subgenus *Sarbecovirus*) of the family *Coronaviridae* [11]. It is an enveloped, positive sense, single-stranded ribonucleic acid (RNA) virus with a 30-kb genome [10]. The virus has an RNA proofreading mechanism keeping the mutation rate relatively low. The genome encodes for non-structural proteins (some of these are essential in forming the replicase transcriptase complex), four structural proteins (spike (S), envelope (E), membrane (M), nucleocapsid (N)) and putative accessory proteins [12-14]. The virus binds to an angiotensin-converting enzyme 2 (ACE2) receptor for cell entry [15-17].

SARS-CoV-2 is the seventh coronavirus identified that is known to infect humans (HCoV). Four of these viruses, HCoV-229E, HCoV-NL63, HCoV-HKU1 and HCoV-OC43, are endemic, seasonal and tend to cause mild respiratory disease. The other two viruses are the more virulent zoonotic Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus type 1 (SARS-CoV-1). SARS-CoV-2 is most genetically similar to SARS-CoV-1, and both of these viruses belong to the subgenus *Sarbecovirus* within the genus *Betacoronavirus* [11]. However, SARS-CoV-1 is currently not known to circulate in the human population.

The clinical presentation of SARS-CoV-2 infection can range from asymptomatic infection to severe disease [18-27]. Mortality rates differ per country [28]. Early laboratory diagnosis of a SARS-CoV-2 infection can aid clinical management and outbreak control. Diagnostic testing can involve detecting the virus itself (viral RNA or antigen) or detecting the human immune response to infection (antibodies or other biomarkers).

While our understanding of SARS-CoV-2 has rapidly expanded, there are still many outstanding questions that need to be addressed. WHO encourages research and the sharing of results that may contribute toward an improved characterization of SARS-CoV-2 [29, 30].

Background information on SARS-CoV-2 RNA detection

Standard confirmation of acute SARS-CoV-2 infections is based on the detection of unique viral sequences by nucleic acid amplification tests (NAATs), such as real-time reverse-transcription polymerase chain reaction (rRT-PCR). The assays' targets include regions on the E, RdRP, N and S genes.

Once an individual has been infected by the virus, the mean time it takes to develop symptoms (incubation period) is 5-6 days, with a range of between 1 and 14 days following exposure [31-35]. The virus may be detectable in the upper respiratory tract (URT) 1-3 days before the onset of symptoms. The concentration of SARS-CoV-2 in the URT is highest around the time of symptom onset, after which it gradually declines [36-42]. Some studies report higher viral loads in the severely ill compared with patients with mild disease, while other studies do not report such differences [36, 43-49]. The presence of viral RNA in the lower respiratory tract (LRT), and for a subset of individuals in the faeces, increases during the second week of illness [38]. In some patients the viral RNA may only be detectable for several days, while in other patients it can be detected for several weeks, possibly months [44, 50-60]. Prolonged presence of viral RNA does not necessarily signify prolonged infectiousness. Several studies describe the correlation between reduced infectiousness and i) increased number of days that have elapsed since symptom onset and resolution, ii) decrease in viral load in respiratory secretions [37, 61-64] and iii) an increase in neutralizing antibodies [37, 61]. More information can be found on this in Criteria to release COVID-19 patients from isolation [65].

Respiratory secretions may be quite variable in composition, and the adequacy of sampling efforts may also vary, which can occasionally result in false-negative PCR results [40, 42, 58, 66-74]. In patients for whom SARS-CoV-2 infection is strongly suspected and URT swabs are negative, viral RNA may be detected in LRT secretions, such as sputum or bronchoalveolar lavage [70, 71, 75, 76]. Faeces or rectal swabs have been shown to be positive for SARS-CoV-2 RNA in a subset of patients, with some studies suggesting that this positivity is prolonged compared to that of respiratory tract specimens [46, 56, 59, 75, 77]. In some patients, SARS-CoV-2 RNA detection in blood samples has been reported and some studies suggest that detection in the blood is associated with disease severity, however, more studies on this potential association are required [75, 78-81]. In oral fluid specimens (e.g. induced saliva) [28, 49, 82-88], reported detection rates compared with URT specimens from the same patient vary widely, and limited data are available on adequacy of SARS-CoV-2 detection in gargling/mouth washes [85]. The striking differences in sensitivity of oral fluids evaluations are potentially due to large differences in collection, transport and storage techniques, as well as the evaluation of different testing populations. Occasionally, SARS-CoV-2 can be detected in ocular fluids in patients with and without signs of conjunctivitis [89-93]. Some studies have not detected SARS-CoV-2 in urine [58, 75, 94], while others were able to detect viral RNA in urine in a limited number of patients [57, 95]. One study reported several patients with positive semen samples [96]. In addition, positive RNA detection for brain tissue [97] and cerebrospinal fluid [98] have been described in case reports. Thus, SARS-CoV-2 can be detected in a wide range of other body fluids and compartments, but it is most frequently detected in respiratory material and, therefore, respiratory samples remain the sample type of choice for diagnostics.

Laboratory testing guiding principles

The decision to test should be based on both clinical and epidemiological factors. See the interim guidance clinical management of COVID-19 [99], investigations of clusters [6] and public health surveillance [7].

Rapid collection of appropriate specimens from and accurate laboratory diagnosis of patients in whom SARS-CoV-2 infection is strongly suspected are the two priorities to support clinical management of patients and infection control measures. Given the complexity of adequate sampling, laboratory analysis, and interpretation of results, collection and laboratory diagnosis should be performed by trained and competent operators.

Individuals infected with SARS-CoV-2 may never develop symptoms (asymptomatic cases), they may have very mild disease (pauci-symptomatic), or they may develop moderate to severe COVID-19 disease [18-26]. The most robust evidence for viral infection comes from the detection of fragments of the virus, such as proteins or nucleic acids, through virological testing. Infected individuals may test positive for viral nucleic acids or viral proteins without symptoms (asymptomatic), or before symptom onset (pre-symptomatic), and throughout a disease episode (symptomatic). For those who develop COVID-19 illness, symptoms can be wide-ranging at initial presentation of disease. Individuals may present with very mild symptoms, with apparent pneumonia, febrile illnesses/sepsis, and less commonly with gastro-enteritis or neurological symptoms [99]. If required for case management, patients should also be tested for other pathogens, as recommended in local clinical management guidelines, but this should never delay testing for SARS-CoV-2 [99, 100]. Co-infections of SARS-CoV-2 with other pathogens have been reported, thus a positive test for another pathogen does not rule out COVID-19 and vice versa [27, 101-109]. Cases of false positive dengue antibody test results using a dengue rapid diagnostic test (RDT) in COVID-19 patients have been reported [110, 111]. There is also a risk of false positive or false negative SARS-CoV-2 results, if testing is not performed with adequate assays or not done under adequate conditions.

Specimen collection, shipment and storage

Safety procedures during specimen collection

Ensure that health workers collecting clinical specimens from suspect cases adhere rigorously to infection prevention and control guidelines (IPC) and wear appropriate personal protective equipment (PPE), see also COVID-19 WHO interim guidance on infection prevention and control during health care [7].

Ensure that adequate standard operating procedures (SOP) are in place and that staff are appropriately trained in specimen collection, packaging, shipment and storage. It should be assumed that all specimens collected for investigations may be infected with SARS-CoV-2 and other pathogens. See also WHO interim guidance on laboratory biosafety for SARS-CoV-2 [3]. Local guidelines, including on informed consent, should be followed for specimen collection, testing, storage and research.

Specimens to be collected

The optimal specimen depends on clinical presentation and time since symptom onset. At minimum, respiratory specimens should be collected.

Respiratory specimens

- **Upper respiratory specimens** are adequate for testing early-stage infections, especially in asymptomatic or mild cases. Testing combined nasopharyngeal and oropharyngeal swabs from one individual has been shown to increase sensitivity for detection of respiratory viruses and improve the reliability of the result [60, 86, 112-114]. Two individual swabs can be combined in one collection tube or a combined nasopharyngeal and oropharyngeal swab can be taken [115]. A few studies have found that individual nasopharyngeal swabs yield a more reliable result than oropharyngeal swabs [40, 75, 76, 114].
- **Lower respiratory specimens** are advised if collected later in the course of the COVID-19 disease or in patients with a negative URT sampling and there is a strong clinical suspicion of COVID-19 [70, 71, 75, 76, 86]. LRT specimens can consist of sputum, if spontaneously produced (induced sputum is not recommended as this poses an increased risk of aerosol transmission [99]) and/or endotracheal aspirate or bronchoalveolar lavage in patients with more severe respiratory disease. Caution should be exercised due to the high risk of aerosolization; therefore strict adherence to IPC procedures during sample collection is required. The indication for an invasive procedure should be evaluated by a physician.

Before implementing other respiratory or oral fluid sampling methods, the sampling method should first pass validation in the laboratory for the intended patient groups.

Simplified and optimized specimen collection

There is a high demand for simplified and optimized specimen collection for SARS-CoV-2 detection. Studies on combined oropharyngeal and nares/nasal swab [116, 117], others on midturbinate [118-120] or lower nasal or nares swabs [120, 121] or tongue swab [120] either by a trained sampler or by self-sampling have been conducted. While some of these studies show that these approaches perform reasonably well, these studies focus mostly on specific patient groups and their sample sizes are limited. Before broad implementation of these alternatives can be recommended, further assessment and validation is needed to determine the indications for which these collection methods serve as appropriate alternatives.

There are specific cases where collecting nasopharyngeal and oropharyngeal swabs can be problematic, such as mass screening in schools or nursing homes, especially when elderly people with dementia or young children are involved. In these scenarios, oral fluids could potentially be a suitable specimen, as the collection methods are less invasive and there is a lower risk of exposure to others upon collection, as compared with the collection of URT specimens.

Oral fluid collection methods vary widely: from posterior oropharyngeal fluids/saliva collected by spitting or drooling, or collection of oral fluid with pipet or special sponges. Gargling with saline solutions is another alternative that has been studied. Sensitivity of these specimens has a wide performance range compared with naso- and/or oropharyngeal sampling [28, 49, 82, 83, 85-88, 122-125]. Due to the large variety of collection methods and processing steps, laboratories must collect their own performance data linked to the local method of collection and in the relevant population for testing. At this time, WHO does not recommend the use of saliva as the sole specimen type for routine clinical diagnostics. If nonstandard collection methods are intended to be used to diagnose other respiratory pathogens, the detection of these pathogens needs to be part of the validation procedure.

Faecal specimens

From the second week after symptom onset and onwards, NAAT can be considered for faecal specimens in cases where URT and LRT are negative and the clinical suspicion of a COVID-19 infection remains [126]. When testing faeces, ensure that the intended extraction method and NAAT has been validated for this type of sample.

Post-mortem specimens

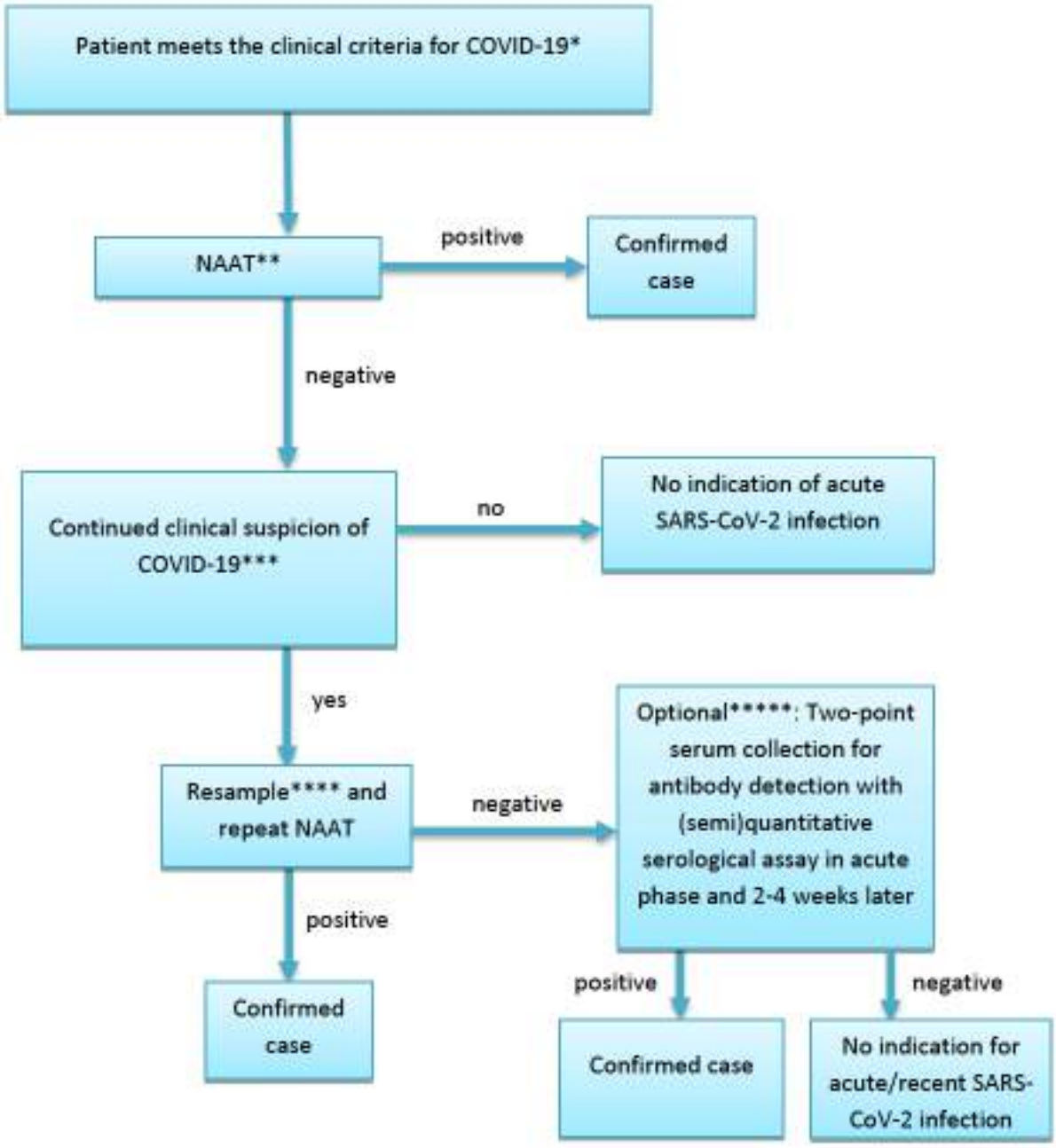
If the person is deceased, consider taking a post-mortem swab, needle biopsy or tissue specimens from the autopsy, including lung tissue for further pathological and microbiological testing [127-133].

Serum specimens

If negative NAAT results are obtained from a patient in whom SARS-CoV-2 infection is strongly suspected, a paired serum specimen could be collected. One specimen taken in the acute phase and one in the convalescent phase 2-4 weeks later can be used to look for seroconversion or a rise in antibody titres. These two samples can be used retrospectively to determine whether the individual has had COVID-19, especially when the infection could not be detected using NAAT.

See Figure 1 for the diagnostic algorithm for cases requiring clinical care and are suspected to have COVID-19.

Figure 1: Diagnostic flow diagram for the detection of acute SARS-CoV-2 infection in individuals with clinical suspicion for COVID-19



* Clinical management of COVID-19 (Interim Guidance), World Health Organization [99].

** If antigen detection would be incorporated into the testing algorithm, how this needs to be done depends on the sensitivity and specificity of the antigen test and on the prevalence of SARS-CoV-2 infection in the intended testing population. For more information see section below on "Rapid diagnostic tests based on antigen detection" and the specific guidance Interim guidance on antigen detection in diagnosis of SARS-CoV-2 infection using rapid immunoassays [3].

*** Continued clinical suspicion can, for example, be the absence of another obvious etiology, the presence of an epidemiological link, or suggestive clinical finding (e.g. typical radiological signs).

**** The selection of specimen type will depend on the clinical presentation, see section "Specimens to be collected". Increasing the number of samples tested will also increase the sensitivity of testing for COVID-19. More than two samples might be needed on some occasions to detect SARS-CoV-2 [73].

***** For interpretation of serology, see section "Implementation and interpretation of antibody testing in the clinical laboratory". Serology cannot be used as a standalone diagnostic for acute SARS-CoV-2 infections and clinical management.

Packaging and shipment of clinical specimens

Specimens for virus detection should reach the laboratory as soon as possible after collection. Correct handling of specimens during transportation and in the laboratory is essential. For guidance on this see Annex 1.

Transportation of specimens within national borders should comply with the applicable national regulations. International transport of specimens that may contain SARS-CoV-2 should follow the United Nations Model Regulations, Biological Substance, Category B (UN 3373), and any other applicable regulations depending on the mode of transport.

More information may be found in the WHO Guidance on regulations for the transport of infectious substances 2019-2020 [134] and specific SARS-CoV-2 laboratory biosafety guidance [3] and shipment instructions [135].

Maintain open and efficient lines of communication with the laboratory and provide all requested information. Specimens should be correctly labelled and accompanied by a diagnostic request form (see Annex 2 for a request form template, including minimal required clinical information). Alerting the laboratory before sending specimens and providing the essential background information with the diagnostic request allows for the proper and timely processing of specimens and reporting of results.

Biosafety practices in the laboratory

Laboratories undertaking testing for SARS-CoV-2 should adhere strictly to the appropriate biosafety practices. Testing clinical specimens that may contain SARS-CoV-2 should be performed in appropriately equipped laboratories by staff trained in the relevant technical and safety procedures. National guidelines on laboratory biosafety should be followed in all circumstances. Specimen handling for molecular testing using standard rRT-PCR requires biosafety level (BSL) 2 or equivalent facilities with the use of a biosafety cabinet (BSC) or a primary containment device that is recommended for sample manipulation before inactivation.

Attempts to isolate the virus in cell culture require BSL-3 facilities at a minimum. When performing viral culture on potentially SARS-CoV-2 positive clinical specimens for other purposes, a risk assessment needs to be conducted followed by required safety measures and procedures [136].

Specific considerations of biosafety requirements may allow certain point-of-care (POC) or near-patient assays to be performed outside a biosafety cabinet, once local regulations have been reviewed, after performing risk assessment and having put in place adequate risk-mitigation measures. For further details on laboratory biosafety, see specific laboratory biosafety interim guidance [3]. For general laboratory biosafety guidelines, see the WHO Laboratory biosafety manual, 3rd edition [136].

Testing for SARS-CoV-2

Nucleic acid amplification test (NAAT)

Wherever possible, suspected active SARS-CoV-2 infections should be tested with NAAT, such as rRT-PCR. NAAT assays should target the SARS-CoV-2 genome. Since there is currently no known circulation of SARS-CoV-1 globally, a sarbecovirus-specific sequence is also a reasonable target. For commercial assays, interpretation of results should be done according to the instructions for use. Optimal diagnostics consist of a NAAT assay with at least two independent targets on the SARS-CoV-2 genome, however, in areas with widespread transmission of SARS-CoV-2, a simple algorithm might be adopted with one single discriminatory target. When using a one-target assay, it is recommended to have a strategy in place to monitor for mutations that might affect performance. For more details, see section below on “Background information on monitoring for mutations in primer and probe regions”.

Background information on monitoring for mutations in primer and probe regions

As SARS-CoV-2 continues to acquire genetic changes over time, mismatches between primers and/or probes, and corresponding binding sites within SARS-CoV-2 genomes may reduce NAAT sensitivity. Where feasible, monitor for primer and probe mismatches due to SARS-CoV-2 mutations, and assess their impact. By routinely testing all specimens with two different primer/probe sets that target different genomic regions it is possible to reduce the risk of false-negative results. Several tools monitoring for relevant mutations are available, including searches done by GISAID (the Global Initiative on Sharing All Influenza Data) and other tools including PrimerCheck (Erasmus Medical Centre), PrimerScan (European Centre for Disease prevention and Control) and CoV-GLUE (COVID-19 UK Genomics Consortium and MRC-University of Glasgow Centre for Virus Research). Primercheck and COV-GLUE allows researchers to use their own sequence data confidentially as input. Not all mutations in primer/probe regions lead to significant changes in performance. *In silico* predictions of binding efficiency are insufficient to quantify the effect of a mismatch on the sensitivity of a NAAT, so it is essential to do an experimental comparison of the assay’s sensitivity for both variant and reference virus isolates. For commercial assays, it is vital to keep track of possible incidents of suboptimal performance. Inform the manufacturer of the assay and WHO of any concerns you may experience with a specific assay.

Many in-house and commercial rRT-PCR assays have become available and several have been independently validated [137-143]. Some considerations for selecting the right NAAT for the laboratory are listed in Annex 3. A few of the NAAT systems have the capacity for fully automated testing that integrates sample processing as well as the capacity for RNA extraction, amplification and

reporting. Such systems provide access to testing in locations with limited laboratory capacity and rapid turnaround time when used for near-patient testing. Validation data of some of these assays are now available [144]. When implementing these assays in specific settings, staff performing the test should be appropriately trained, performance should be assessed in those specific settings and a system to monitor quality should be put in place. Additional potentially valuable amplification/detection methods, such as CRISPR (targeting clustered regularly interspaced short palindromic repeats), isothermal nucleic acid amplification technologies (e.g. reverse transcription loop-mediated isothermal amplification (RT-LAMP), and molecular microarray assays are under development or in the process of being commercialized [145-147]. Validation of the analytic and clinical performance of these assays, demonstration of their potential operational utility, rapid sharing of data, as well as emergency regulatory review of manufacturable, well-performing tests are encouraged to increase access to SARS-CoV-2 testing.

Careful interpretation of weak positive NAAT results is needed, as some of the assays have shown to produce false signals at high Ct values. When test results turn out to be invalid or questionable, the patient should be resampled and retested. If additional samples from the patient are not available, RNA should be re-extracted from the original samples and retested by highly experienced staff. Results can be confirmed by an alternative NAAT test or via virus sequencing if the viral load is sufficiently high. Laboratories are urged to seek reference laboratory confirmation of any unexpected results.

One or more negative results do not necessarily rule out the SARS-CoV-2 infection [40, 42, 58, 66-74]. A number of factors could lead to a negative result in an infected individual, including:

- poor quality of the specimen, because it contains too little patient material;
- the specimen was collected late in the course of the disease, or the specimen was taken from a body compartment that did not contain the virus at that given time;
- the specimen was not handled and/or shipped appropriately;
- technical reasons inherent in the test, e.g. PCR inhibition or virus mutation.

For clinical case management a proposed testing algorithm is depicted in Figure 1.

Alternatives to RNA extraction

Most conventional molecular diagnostic workflows require RNA extraction before an rRT-PCR test is conducted. However, there are global shortages of commercial extraction kits due to the COVID-19 pandemic. Direct rRT-PCR from nasopharyngeal swabs may provide an emergency or temporary alternative to RNA extraction, but limitations to the input volume, as well as an increased risk of RNA degradation and PCR inhibition can lead to a loss of sensitivity of the assay [148, 149]. Heat treatment prior to sample processing can affect the RNA quality [149, 150]. Other factors that can affect RNA quality and which should be evaluated before implementation are the addition of detergents, transport media, the volume of the specimen used, and the polymerase enzyme used [148, 151-154]. The biosafety implications of alternative extraction workflows should also be considered. Laboratories considering alternative methods that bypass the need for RNA extraction should validate their protocols thoroughly and conduct a risk assessment that weighs the benefits and risks, before integrating such protocols into a diagnostic workflow.

Pooling of specimens for NAAT

Pooling of samples from multiple individuals can increase the diagnostic capacity for detecting SARS-CoV-2 when the rate of testing does not meet the demand in some settings [155-159]. There are several strategies for pooling specimens. If the pooled result is negative, all individual specimens in the pool are regarded as negative. If the pool tests positive the follow-up steps depend on the strategy, but in general each specimen needs to undergo individual testing (pool deconvolution) to identify the positive specimen(s). Another approach is matrix pooling. This means that pools are made per row and per column, and tested by PCR, the position in the matrix identifies the positive specimen without additional testing if prevalence is sufficiently low. Depending how robust the matrix testing method is in the specific context, it might still be advisable to retest the identified positive samples for confirmation. Pooling of specimens could be considered in population groups with a low/very low expected prevalence of SARS-CoV-2 infection, but not for cases or cohorts that more likely to be infected with SARS-CoV-2. Routine use of the pooling of specimens from multiple individuals in clinical care and for contact tracing purposes is not recommended. Studies have been conducted to determine the optimal sample pooling number and design pooling strategies in different outbreak settings [156, 160-162].

Before any sample pooling protocols can be implemented, they must be validated in the appropriate populations and settings. An inappropriate testing strategy may lead to missed cases or other laboratory errors that may, in turn, negatively affect patient management and public health control measures. In addition, the risk of cross-contamination and the potential increase in workload complexity and volume must be considered. To perform reliable pooling, adequate automation is key (e.g. robotic systems, software supporting the algorithms to identify positive samples, laboratory information systems and middle-ware that can work with sample pooling).

Based on currently available data, intra-individual pooling (multiple specimens from one individual that are pooled and tested as a single sample) from upper respiratory tract samples can be used. Intra-individual pooling of sputum and faeces with URT samples is not recommended because the former may contain compounds that inhibit rRT-PCR.

Rapid diagnostic tests based on antigen detection

Rapid diagnostic tests that detect the presence of SARS-CoV-2 viral proteins (antigens) in respiratory tract specimens are being developed and commercialized. Most of these are lateral flow immunoassays (LFI), which are typically completed within 30 minutes. In contrast to NAATs, there is no amplification of the target that is detected, making antigen tests less sensitive. Additionally, false-positive (indicating that a person is infected when they are not) results may occur if the antibodies on the test strip also recognize antigens of viruses other than SARS-CoV-2, such other human coronaviruses.

The sensitivity of different RDTs compared to rRT-PCR in specimens from URT (nasopharyngeal swabs) appears to be highly variable [144, 163-165], but specificity is consistently reported to be high. Currently, data on antigen performance in the clinical setting is still limited: paired NAAT and antigen validations in clinical studies are encouraged to identify which of the antigen detection tests that are either under development or have already been commercialized demonstrate acceptable performance in representative field studies. When performance is acceptable, antigen RDTs could be implemented in a diagnostic algorithm to reduce the number of molecular tests that need to be performed and to support rapid identification and management of COVID-19 cases. How antigen detection would be incorporated into the testing algorithm depends on the sensitivity and specificity of the antigen test and on the prevalence of SARS-CoV-2 infection in the intended testing population. Higher viral loads are associated with improved antigen test performance; therefore test performance is expected to be best around symptom onset and in the initial phase of a SARS-CoV-2 infection. For specific guidance on antigen detection tests see the WHO Interim guidance on antigen-detection in diagnosis of SARS-CoV-2 infection using rapid immunoassays [5].

Antibody testing

Serological assays that detect antibodies produced by the human body in response to infection with the SARS-CoV-2 can be useful in various settings.

For example, serosurveillance studies can be used to support the investigation of an ongoing outbreak and to support the retrospective assessment of the attack rate or the size of an outbreak [9]. As SARS-CoV-2 is a novel pathogen, our understanding of the antibody responses it engenders is still emerging and therefore antibody detection tests should be used with caution, and not used to determine acute infections.

Non-quantitative assays (e.g. lateral flow assays) cannot detect an increase in antibody titres, in contrast to (semi)quantitative or quantitative assays. Lateral flow antibody detection assays (or other non-quantitative assays) are currently not recommended for acute diagnosis and clinical management and their role in epidemiologic surveys is being studied. For more information on the utility of rapid immunodiagnostic tests, we refer to the WHO scientific brief with advice on the specific SARS-CoV-2 point-of-care immunodiagnostic tests [4].

Serology should not be used as a standalone diagnostic to identify acute cases in clinical care or for contact tracing purposes. Interpretations should be made by an expert and are dependent on several factors including the timing of the disease, clinical morbidity, the epidemiology and prevalence within the setting, the type of test used, the validation method, and the reliability of the results.

Seroconversion (development of measurable antibody response after infection) has been observed to be more robust and faster in patients with severe disease compared to those with milder disease or asymptomatic infections. Antibodies have been detected as early as in the end of the first week of illness in a fraction of patients, but can also take weeks to develop in patients with subclinical/mild infection [37, 166-173]. A reliable diagnosis of COVID-19 infection based on patients' antibody response will often only be possible in the recovery phase, when opportunities for clinical intervention or interruption of disease transmission have passed. Therefore, serology is not a suitable replacement for virological assays to inform contact tracing or clinical management. The duration of the persistence of antibodies generated in response to SARS-CoV-2 is still under study [49, 174]. Furthermore, the presence of antibodies that bind to SARS-CoV-2 does not guarantee that they are neutralizing antibodies, or that they offer protective immunity.

Available serological tests for detecting antibodies

Commercial and non-commercial tests measuring binding antibodies (Total immunoglobulins (Ig), IgG, IgM, and/or IgA in different combinations) utilizing various techniques including LFI, enzyme-linked immunosorbent assay (ELISA) and chemiluminescence immunoassay (CLIA) have become available. A number of validations and systematic reviews on these assays have been published [170, 171, 173, 175-177]. The performance of serologic assays varies widely in different testing groups (such as in patients with mild versus moderate-to-severe disease as well as in young versus old), timing of testing and the target viral protein. Understanding these performance variations will require further study. Antibody detection tests for coronavirus may also cross-react with other pathogens, including other human coronaviruses, [167, 178-180] or with pre-existing conditions (e.g. pregnancy, autoimmune diseases) and thus yield false-positive results.

Virus neutralization assays are considered to be the gold standard test for detecting the presence of functional antibodies. These tests require highly skilled staff and BSL-3 culture facilities and, therefore, are unsuitable for use in routine diagnostic testing.

Implementation and interpretation of antibody testing in the clinical laboratory

When implementing serological assays in the clinical laboratory, an in-house validation or verification of the specific assays is advisable. Even if commercial tests have been authorized for use in emergencies, an in-house verification (or if required by local authorities a validation) is still required. Protocols and examples with suggestions as to how to do this are now available [170, 171, 181].

Each serological test is different. With regard to commercial tests, follow the manufacturer's instructions for use. Studies show that several commercial assays measuring total Ig or IgG have performed well. Most of these studies show no advantage of IgM over IgG, as IgM does not appear much earlier than IgG [173]. The additional role of IgA testing in routine diagnostics has not been established. For confirmation of a recent infection, acute and convalescent sera must be tested using a validated (semi)quantitative or quantitative assay. The first sample should be collected during the acute phase of illness, and the second sample at least 14 days after the initial sera was collected. Maximum antibody levels are expected to occur in the third/fourth week after symptom onset. Seroconversion or a rise in antibody titres in paired sera will help to confirm whether the infection is recent and/or acute. If the initial sample tests positive, this result could be due to a past infection that is not related to the current illness.

The first known case of reinfection with SARS-CoV-2 has been documented [182]. Only limited information is available on the interpretation of SARS-CoV-2 antibody tests after a previous infection with SARS-CoV-2 and on the dynamics of SARS-CoV-2 serology if a subsequent infection with another coronavirus occurs. In these two sets of circumstances interpretation of serology may be extremely challenging.

Viral isolation

Virus isolation is not recommended as a routine diagnostic procedure. All procedures involving viral isolation in cell culture require trained staff and BSL-3 facilities. A thorough risk assessment should be carried out when culturing specimens from potential SARS-CoV-2 patients for other respiratory viruses because SARS-CoV-2 has been shown to grow on a variety of cell lines [183].

Genomic sequencing for SARS-CoV-2

Genomic sequencing for SARS-CoV-2 can be used to investigate the dynamics of the outbreak, including changes in the size of an epidemic over time, its spatiotemporal spread, and testing hypotheses about transmission routes. In addition, genomic sequences can be used to decide which diagnostic assays, drugs and vaccines may be suitable candidates for further exploration. Analysis of SARS-CoV-2 virus genomes can, therefore, complement, augment and support strategies to reduce the disease burden of COVID-19. However, the potentially high cost and volume of the work required for genomic sequencing means that laboratories should have clarity about the expected returns from such investment and what is required to maximize the utility of such genomic sequence data. WHO guidance on SARS-CoV-2 genomic sequencing is currently being developed.

Quality assurance

Before introducing a new testing method, a new assay, new batches of materials, or a new PCR technician into the laboratory, a validation or verification should be carried out, to ensure that the laboratory testing system is performing adequately.

For manual PCR systems, each NAAT sample should include internal controls and ideally a specimen collection control (human gene target). Additionally, external controls are recommended for each test run. Laboratories that order their own primers and probes should carry out entry testing or validation looking at functionality and potential contaminants [184].

Laboratories are encouraged to define their assays' detection limits, and senior staff should recognize how disease prevalence alters the predictive value of their test results. Once the number of cases goes down, the positive predictive value will decrease, therefore the interpretation of tests should continue to be part of a stringent quality assurance scheme, with interpretation based on: timing of sampling, sample type, test specifics, clinical data and epidemiological data.

Laboratories should put measures in place to reduce the potential for false positive rRT-PCR results and have a strategy for the management of equivocal results. See Annex 4 for a checklist.

In general, laboratories should have a quality assurance system in place and are encouraged to participate in external quality assessment (EQA) schemes or perform result comparison between laboratories of a subset of samples.

WHO has previously advised national laboratories to ensure quality performance by confirmation of testing results for the first 5 positive specimens and the first 10 negative specimens (collected from patients that fit the case definition) by referring them to one of the WHO reference laboratories that provide confirmatory testing for SARS-CoV-2. WHO provided support to national laboratories to facilitate specimen shipment to one of the dedicated reference laboratories. For more information, consult the WHO website for the list of reference laboratories [185] and shipment instructions [135]. Strengthened national reference laboratories and growing access to EQA schemes for SARS-CoV-2 reduce the need to use this mechanism. If testing for SARS-CoV-2 is not yet available in a country, efforts should be made to establish national capacity.

Reporting of cases and test results

Rapid communication of test results is important for planning and design of public health and outbreak control interventions. Laboratories should follow national reporting requirements. In general, all test results, positive or negative, should be immediately reported to the national authorities. States Parties to the International Health Regulations (IHR) are reminded of their obligation to share with WHO relevant public health information for events for which they must notify WHO, using the decision instrument in Annex 2 of the IHR (2005) [186].

Regular interaction between public health experts, clinicians and local laboratory experts to discuss strategies, potential problems and solutions, should be considered to be an essential part of an adequate COVID-19 response. This response includes the development of guidance and (clinical-, epidemiological-, and trial) study protocols.

A rapid turnaround time of test results can, in turn, have a positive impact on the outbreak [187, 188]. More studies are needed to fine tune the maximum acceptable time from symptom onset to sample result to have impact on clinical management and outbreak control; currently a maximum of 24 hours is considered reasonable in most settings. As laboratories often have control only over the time between sample arrival and the test result, it is critical to ensure that samples arrive in the laboratory without delay.

Methods

This document was developed in consultation with experts from the SARS-CoV-2 laboratory expert network. Experts in the network completed a confidentiality agreement and declaration of interest. The declaration of interest forms were reviewed, and no conflicts regarding the support of this guidance document were identified. Relevant WHO guidance has been used in this document [136, 185, 189-194]. This is the sixth edition (version 2020.6) and was originally adapted from *Laboratory testing for Middle East Respiratory Syndrome Coronavirus* [189].

A broad spectrum of clinical laboratory experts from different regions were engaged in the development of this document. The internal experts involved in the development include WHO regional laboratory focal points, epidemiologists and clinical experts. This version of the guidance incorporates the novel understanding and characteristics of the virus and addresses questions and issues received from WHO's country and regional offices and other channels.

Contributors

WHO steering group: Amal Barakat, Céline Barnadas, Silvia Bertagnolio, Caroline Brown, Lisa Carter, Sebastian Cognat, Jane Cunningham, Varja Grabovac, Francis Inbanathan, Kazunobu Kojima, Juliana Leite, Marco Marklewitz, Jairo Mendez-Rico, Karen Nahapetyan, Chris Oxenford, Boris Pavlin, Mark Perkins, Anne Perrocheau, Jose Rovira, Maria Van Kerkhove, Karin von Eije, Joanna Zwetyenga,

External contributors:

Sarah Hill, Oxford University and Royal Veterinary College, United Kingdom; Maria Zambon, Public Health England, United Kingdom; Corine Geurts van Kessel, Richard Molenkamp and Marion Koopmans, Erasmus MC and Adam Meijer and Chantal Reusken, RIVM, The Netherlands; Antonino Di Caro, Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani, Italy; Anne von Gottberg, National Institute for Communicable Diseases, South Africa; Janejai Noppavan, National institute of Health, Thailand; Raymond Lin, National Public Health Laboratory, Singapore; Leo Poon and Malik Peiris, Hong Kong University, China, Hong Kong SAR; George Gao, Chinese CDC, China.

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WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance will expire 1 year after the date of publication.

WHO reference number: WHO/2019-nCoV-19/laboratory/2020.6

Annex 1: Specimen collection and storage

Specimen type	Collection materials	Recommended temperature for storage and/or shipment to the laboratory and until testing (from date of specimen collection) *
Nasopharyngeal and oropharyngeal swab	Dacron or polyester flocked swabs with VTM *	2-8 °C if ≤12 days* –70 °C (dry ice) if > 12 days
Bronchoalveolar lavage	Sterile container with viral transport medium **	2-8 °C if ≤ 2 days –70 °C (dry ice) if > 2 days
(Endo)tracheal aspirate, nasopharyngeal or nasal wash/aspirate	Sterile container with viral transport medium**	2-8 °C if ≤2 days –70 °C (dry ice) if > 2 days
Sputum	Sterile container	2-8 °C if ≤ 2 days –70 °C (dry ice) if > 2 days
Tissue from biopsy or autopsy including from lung	Sterile container with saline or VTM	2-8 °C if ≤ 24 hours –70 °C (dry ice) if > 24 hours
Serum	Serum separator tubes (adults: collect 3-5 ml whole blood)	2-8 °C if ≤ 5 days –70 °C (dry ice) if > 5 days
Whole blood	Collection tube	2-8 °C if ≤5 days –70 °C (dry ice) if > 5 days
Stool	Stool container	2-8 °C if ≤5 days –70 °C (dry ice) if > 5 days

* Avoid repeated freezing and thawing of specimens. If no access to –70 C consider storing at -20 C.

* For transport of specimens for viral detection, use preferentially viral transport medium (VTM) containing antifungal and antibiotic supplements. If VTM is not available, other solutions may be used after validation. Such solution may include phosphate buffered saline (PBS), 0.9% sterile saline, minimum essential medium (with storage at +4C up to 7 to 14 days) [195-197]. In case other viruses such as influenza should also be tested, do not store samples for more than 5 days at 4-8 degrees but –70 C or dry ice [194].

** If VTM is not available, sterile saline may be used [198]. Duration of specimen storage at 2-8 C may be different from what is indicated above.

Apart from specific collection materials indicated in the table, ensure that other materials and equipment are available: e.g. transport containers and specimen collection bags and packaging, coolers, and cold packs or dry ice, sterile blood-drawing equipment (e.g. needles, syringes and tubes), labels and permanent markers, PPE, materials for decontamination of surfaces, etc.

Annex 2: laboratory request form

SARS-CoV-2 LABORATORY TEST REQUEST FORM[1]

Submitter information				
NAME OF SUBMITTING HOSPITAL, LABORATORY, or OTHER FACILITY*				
Physician				
Address				
Phone number				
Case definition[2]:	☐ Suspected case ☐ Probable case ☐ Other:			
Patient info				
First name		**Last name**		
Patient ID number		**Date of Birth**		**Age:**
Address		**Sex**	☐ Male ☐ Female ☐ Unknown	
Phone number				
Specimen information				
Type	☐ Nasopharyngeal and oropharyngeal swab ☐ Bronchoalveolar lavage ☐ Endotracheal aspirate ☐ Nasopharyngeal aspirate ☐ Nasal wash ☐ Sputum ☐ Lung tissue ☐ Serum ☐ Whole blood ☐ Stool ☐ Other: ….			
All specimens collected should be regarded as potentially infectious **and you must contact the reference laboratory before sending specimens to them.** All specimens must be sent in accordance with category B transport requirements.				
Please tick the box if your clinical specimen is post mortem ☐				
Date of collection		**Time of collection**		
Priority status				
Clinical details				
Date of symptom onset:				
Has the patient had a recent history of travelling to an affected area?	☐ Yes ☐ No	**Country**		
		Return date		
Has the patient had contact with a confirmed case?		☐ Yes ☐ No ☐ Unknown ☐ Other exposure:		
Additional Comments (e.g. antimicrobial treatment, immunosuppressants)				

[1] Form in accordance with ISO 15189:2012 requirements
[2] Public health surveillance for COVID-19: interim guidance

Annex 3: Considerations when selecting the optimal NAAT for the use setting

Aspect	Considerations
Manufacturing quality	CE-IVD, WHO EUL, PQ, EU-FDA or other approval. Independent validation data. Manufacture under ISO.
Targets	Number of targets, specificity for SARS-CoV-2 or other sarbecoviruses.
Controls	For manual NAAT testing, a positive template control (PTC) and at least one negative template control (NTC) should be included. Use of an extraction control and an internal human housekeeping gene specimen adequacy control is also recommended.
Instrumentation	Is the assay compatible with available systems in the laboratory or country? Ease of use and operational utility. Opportunity to multiplex with other respiratory pathogens. Costing of platform and maintenance. Ease of access to maintenance provider/troubleshooting.
Workflow	Can the kit be implemented in the existing workflow of the laboratory, while assuring minimal disruption on other diagnostics?
Ease of use	Complexity of assay. Number of steps. Required training and staff.
Storage and shipment requirement	Many kits require cold chain conditions during shipment and storage, in some circumstances this might pose a challenge. Some kits contain lyophilized enzymes that do not require the kit to be shipped and sometimes stored cold. Shelf life: To be prepared for periods of intense testing stocks might be needed, a longer shelf life is needed to ensure adequate use of resources.
Training needs and access	Instructions for use (IFU) available, training available by company or others, troubleshooting options provided and accessible help line in local language.
Need for ancillary reagents	Complete kit for sampling/extraction/amplification or the PCR kit requires additional reagents or tools. Compatibility with laboratories' extraction method. Compatibility with procurable polymerases if needed. Special equipment needed (e.g. calibration panel before running the test, extraction platforms, heat block, vortex, magnetic stand or centrifuge).
Continuity of supply	Long term supply agreement. Secured routes of delivery if lockdowns occur. Assay and ancillary reagents costs.

Annex 4: Suggestions for checklist to reduce possible cases of false positive rRT-PCR results and handling of equivocal results

Laboratories should have a standard operating procedure in place to reduce the possible false positive rRT-PCR results and how to handle equivocal results. This checklist provides the laboratories with suggestions and considerations. The checklist is formulated for manual rRT-PCRs but many aspects can also be used for other NAATs.

CLERICAL

- ❑ Eliminate or reduce transcription
- ❑ If transcribe, method of checking
- ❑ Sorting, aliquoting and labelling
- ❑ Double identifiers
- ❑ Entering results

CROSS CONTAMINATION

- ❑ Preparation area
- ❑ Manipulation of tubes
- ❑ Aerosol generation
- ❑ Nucleic acid concentration and extraction setup
- ❑ PCR format and steps
- ❑ Check other positives in same run
- ❑ Environmental
- ❑ Contaminated reagents
- ❑ Disposal

EQUIPMENT and TEST KITS

- ❑ Calibration method
- ❑ Equipment validated for test kit
- ❑ Assess new equipment for contamination risk

PRACTICE

- ❑ For mass screening, separate high-prevalence from low-prevalence groups.
- ❑ Visual inspection of run
- ❑ Analytical – examination of raw data
- ❑ Extend run when necessary for late Ct

EQUIVOCAL RESULTS

- ❑ Follow manufacturer's instructions
- ❑ Laboratory policy for equivocal results
- ❑ Any additional laboratory criteria for equivocal category
- ❑ Communication of interpretation to users
- ❑ Criteria for repeat testing, if any
- ❑ Use of alternative test or PCR target
- ❑ Communication with clinical and public health staff

Privacy Office; Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

August 5, 2021

Sent via e-mail

Re: Full Disclosure – OUR FILE# NSHA-2021-092

On July 6, 2021 Nova Scotia Health (NSH) received your request under the *Freedom of Information and Protection of Privacy Act* (*FOIPOP Act*).

We understand your application to be for a copy of the following:
Membership (names) of the COVID-19 Therapeutics and Prophylactics Advisory Group, with their affiliations and voting status. (Date Range for Record Search: From 02/29/2020 To 07/04/2021).

Please find a copy of the records located in response to your request. We are providing these records to you in their entirety. We are now closing your file.

Should you have any questions, please do not hesitate to contact me.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review.

Sincerely,
Katie Smith
Freedom of Information Officer
Nova Scotia Health Authority
Halifax, Nova Scotia

Membership (names) of the COVID-19 Therapeutics and Prophylactics Advisory Group, with their affiliations and voting status. (Date Range for Record Search: From 02/29/2020 To 07/04/2021).

Name	**Affiliation**	**Voting Status**
Lisa Barrett (Co-Chair)	NS HEALTH Infectious Diseases Physician	Voting Member
Tasha Ramsey (Co-Chair)	NS HEALTH Infectious Diseases Pharmacist	Voting Member
Glenn Cox	NS HEALTH Pharmacy Director	Voting Member
Kathleen Coleman	DHW Formulary and Clinical Practice Director	Voting Member
Gabrielle Richard	DHW Pharmacist Consultant	Voting Member
Lisa Grandy-Allen	NS HEALTH Drug Information Pharmacist	Voting Member
Emma Reid	NS HEALTH Covid Unit Pharmacist	Voting Member
TBD	NS HEALTH Critical Care Physician/Pharmacist	Voting Member
Ken Rockwood	NS Health Medical Co-lead Director, Frailty/Elder Care Network	Voting Member
Kathy Slayter	IWK Infectious Diseases Pharmacist	Voting Member
Robert Strang	Chief Medical Officer of Health	Non-Voting Member
Shelly McNeil	COVID Network (Co-Chair)	Non-Voting Member
Shelly McNeil	NS Covid Vaccine Expertise (Vaccine Expert Panel Co-Chair and C-19 COVID vaccine workstream member)	Non-Voting Member
Barbara Goodall	COVID Research	Non-Voting Member
Karina Top	IWK Physician	Non-Voting Member
TBD	NS HEALTH Finance	Non-Voting Member
TBD	DHW Finance	Non-Voting Member
Amanda Porter	Ethics	Non-Voting Member
TBD	Epidemiologic Data Modeler	Non-Voting Member
TBD	Patient and Family Advisor	Non-Voting Member

Privacy Office; Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

August 4, 2021

Sent via e-mail

Re: Full Disclosure – OUR FILES# NSHA-2021-095 and 2021-099

On July 12, 2021 Nova Scotia Health (NSH) received your request under the *Freedom of Information and Protection of Privacy Act* (*FOIPOP Act*).

We understand your applications to be for a copy of the following:

File 2021-095:
How many cycles were used to amplify the proteins for the tests for the presence of COV-19 from swab tests? Were the # of cycles ever altered, and if so what were the cycle numbers in the amplification protocol PCR as a function of time? What is the genome of the protein that was being identified in the test? What is the genome for the virus that infected Nova Scotians?
(Date Range for Record Search: From 12/31/2019 To 07/06/2021)

File 2021-099:
How many cycles were used to amplify the proteins for the tests for the presence of COV-19 from swab tests? Were the # of cycles ever altered, and if so what were the cycle numbers in the amplification protocol PCR as a function of time? What is the genome of the protein that was being identified in the test? What is the genome for the virus that infected Nova Scotians?
(Date Range for Record Search: From 12/31/2019 To 07/14/2021)

Please find a copy of the records located in response to your request. We are providing these records to you in their entirety. We are now closing your files.

Should you have any questions, please do not hesitate to contact me.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review.

Sincerely,
Katie Smith
Freedom of Information Officer
Nova Scotia Health Authority
Halifax, Nova Scotia

FOIPOP 2021-095:

1) *How many cycles were used to amplify the proteins for the tests for the presence of COV-19 from swab tests?*

Proteins do not get amplified. The genes that encode the proteins are amplified are outlined in the table below which included the number of cycles used (where available). The attached primer on CT values also describes the thresholds used for reporting.

Laboratory	SARS CoV 2 Test	Ct value
QEII	In house assay based on BCCDC primers for RdRp on ABI 7500 fast	Total cycles – 45 RdRp CT <35 = positive RdRp CT 35 -38 = indeterminate
	Hologic Panther Aptima SARS CoV 2 assay	Total cycles – not described by manufacturer Positive based on manufacturer's criteria. Assay does not produce a Ct value
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	Roche 6800 – Cobas SARS CoV 2 assay	Total cycles – not described by manufacturer Ct<38 = positive Ct ≥ 38 = indeterminate
IWK	Biofire Respiratory 2.1 panel	Total cycles – not described by manufacturer Positive based on manufacturer's criteria - Ct value not reported by the instrument and cut off not defined by manufacturer
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
Cape Breton Regional	Hologic Panther Aptima SARS CoV 2 assay	Total cycles – not described by manufacturer Positive based on manufacturer's criteria. Assay does not produce a Ct value
	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate

	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	Biofire Respiratory 2.1 panel	Positive based on manufacturer's criteria - Ct value not reported by the instrument and cut off not defined by manufacturer
St Martha's Hospital	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
Aberdeen Hospital	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
Colchester Regional	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
Cumberland Regional Health Care Center	Biofire Respiratory 2.1 panel	Positive based on manufacturer's criteria - Ct value not reported by the instrument and cut off not defined by manufacturer
	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
Valley Regional Hospital	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate
	Biofire Respiratory 2.1 panel	Positive based on manufacturer's criteria - Ct value not reported by the instrument and cut off not defined by manufacturer
Yarmouth Regional Hospital	GeneXpert Xpert Xpress SARS-COV-2/Flu/RSV	Total cycles – 45 Ct<37 = positive

		Ct ≥ 37 = indeterminate
	GeneXpert Xpert Xpress SARS-COV-2	Total cycles – 45 Ct<37 = positive Ct ≥ 37 = indeterminate

2) *Were the # of cycles ever altered, and if so what were the cycle numbers in the amplification protocol PCR as a function of time?*

The number of cycles was never altered.

3) *What is the genome of the protein that was being identified in the test?*

The gene segments corresponding the target proteins are described in the attached document. The portions of the gene amplified are directed by the primers used in the assay. For any commercial assay the primers used are proprietary and not available. The primers used to amplify the RdRp target in the LDT are:

Name	Sequence (5'-3')
RdRP_Lee_F	TGCCGATAAGTATGTCCGCA
RdRP_Lee_R	CAGCATCGTCAGAGAGTATCATCATT

4) *What is the genome for the virus that infected Nova Scotians?*

The genomes have identified these as SARS CoV-2 viruses of various lineages including a number of SARS CoV-2 variants of concern (VOCs). The sequencing data we have to date for VOCs is outlined below. Note: not all of the viruses from the second wave have been sequenced.

Lineage	WHO designation	Variant status	# of samples
B.1.1.7	Alpha (B.1.1.7-like)	VOC	36
B.1.617.2	Delta (B.1.617.2-like)	VOC	20
P.1	Gamma (P.1-like)	VOC	1
B.1.525	Eta (B.1.525-like)	VOI	9
B.1.429	Epsilon (B.1.427/429-like)	VOI	1
B.1	n/a	n/a	1
None	n/a	n/a	1
Grand Total			**69**

nova scotia health authority

Primer on cycle threshold (Ct) values for the QEII laboratory, Central Zone Nova Scotia Health

The QEII Microbiology Laboratory has received multiple requests for how our polymerase chain reaction (PCR) tests are interpreted based on cycle threshold (Ct) values. The following is a brief FAQ on Ct values used in our laboratory for the detection of the virus that causes COVID-19, SARS-CoV-2. For a full discussion on interpretation of Ct values, please refer to the Public Health Ontario's excellent document Ct(Public Health Ontario)

What is a Ct value? Most nucleic acid amplification tests (NAAT) (like Reverse transcriptase PCR (RT-PCR) detect viral RNA through a process of amplifying targeted, specific strands of viral RNA The presence of the virus in a clinical specimen is determined by copying it in an exponential fashion through a temperature cycling reaction of up to 45 times. The presence of the viral copies are detected by a florescent signal produced during the reaction, which increases with the product. The number of amplification cycles required to create enough copies of the viral RNA to be detected is called the cycle threshold or Ct value.

How are Ct values used? The fewer amplification steps it takes to pass this threshold (a low Ct value) the more viral RNA is likely to have been present in the initial specimen; conversely more cycles required to amplify the viral RNA above the threshold (a high Ct value) suggests a lower amount of virus present in the initial sample. There can be up to 45 total number of cycles for many NAATs, and non-specific reactions can occur near the end of the cycling process that can mistakenly be flagged as positive by the instrument. The Ct value cutoff for positivity is defined by the vendor or the laboratory during the validation process to ensure that PCR is correctly detecting the presence of the virus.

Below is a table outlining how the different testing methods used at the QEII use Ct values to define positive results:

	Lab Developed Test[@]	GeneXpert SARS-CoV-2	Roche 6800 SARS-CoV-2	Panther
Total cycles	45	45	Not described	Not described
Genetic Targets	RdRp gene	E gene N2 gene	E gene ORF1 gene	ORF 1a/b gene
Definition of positive	RdRp Ct <35	Dual gene positive: E POS and Ct ≤ 37* N2 POS and Ct ≤ 37*	Dual gene positive: E POS and Ct ≤ 38* ORF1 POS and Ct ≤ 38*	As per instrument (does not produce a Ct value)
Definition of negative	RdRp Ct ≥38	E Neg N2 Neg	ORF1 Neg E Neg	As per instrument (does not

				produce a Ct value)
Definition of indeterminate**	RdRp Ct 35 - 38	Single gene positive: E POS and Ct ≤ 37* N2 Neg E Neg N2 POS and Ct ≤ 37*	Single gene positive: E POS and Ct ≤ 38* ORF1 Neg E Neg ORF1 POS and Ct ≤ 38*	As per instrument (does not produce a Ct value)

* Positive results with Ct above this value needs to be discussed with director who examines the amplification curve to help determine if this is a true or non-specific amplification

****Indeterminate report phrase:** SARS-CoV-2 (COVID 19) result indeterminate. This may represent early disease, late disease, or a false positive result. Please recollect once after 24 hrs if clinically warranted. If indeterminate result persist, please discuss with public health

¥ While RdRp is used for interpretation of the SARS-CoV-2 result in the LDT, the RT-PCR reaction also include a second target, the E gene (Corman et al) to increase specificity, and helps with the interpretation of specimens with high RdRp Ct values. A microbiologist would be notified of result where a single target detection with E gene only is observed, and the result would be interpreted using the same Ct value cutoffs as RdRp.

Important factors to consider in interpreting Ct values:

1) *Ct values will depend on the stage of infection* - During pre-symptomatic and early infection, the baseline viral load can be initially low which is associated with high Ct values i.e. >30 and above. This period may last hours to days. Ct value interpretation is further complicated by asymptomatic infections where the time of infection onset may be unknown. **Therefore, if clinically indicated, patients should undergo repeat testing within 24 to 48 hrs to determine if the Ct value is stable, rising or declining**.

2) *Individuals can shed detectable SARS-CoV-2 RNA for a prolonged period* – RT-PCR can be positive for over 100 days or more after infection, but in most cases are unlikely to transmit to others beyond 10 days post symptom onset.

3) *Ct values are affected by the type AND quality of the specimen* - Nasopharyngeal swabs (NPs) are the most sensitive specimen type in the outpatient setting; throat/nares swabs, and gargles may be less sensitive. Also in patient with lower tract infection (e.g. pneumonias), lower tract specimens are preferred as upper tract specimens may be negative. The quality of the sample collection directly impacts the amount of respiratory material collected and this directly affects the generated Ct value i.e., poorly collected samples can yield an artificially high Ct value (low RNA levels).

4) *Ct values are not comparable between different testing platforms* - The Ct ranges and distributions differ by the PCR technology used. There is no international standard to allow for comparison. Results of proficiency panels used in in other provinces where identical specimens were tested by different laboratories have seen variation of upto 8 Cts.

5) The impact of new variants on Ct values is not clear – While our current tests can detect the current SARS-CoV-2 variants identified in the UK and South Africa, ongoing surveillance is underway to identify novel variants and their potential impacts on diagnostic testing.

Does a certain Ct value predict who is infectious? This is a complex issue. There is good evidence that when more than 24 to 30 cycles are required to detect virus the virus concentration is so low that it becomes difficult to grow the virus in the laboratory (Bullard et al., 2020; Baslie et al., 2020; Singanayagam et al., 2020). However the cells used in the laboratory to grow the virus are different that cells in the back of the throat and nose (nasopharynx) or the lungs in people. So just because one can't grow the virus in a laboratory that does not mean that it won't transmit. Many

believe that with low copy numbers (high CT) values the virus is not likely to be transmitted. But we do not know how much virus is actually required to cause an infection in someone and there are other important factors that may influence infectiousness including the health of the person exposed and the type of exposure that has happened.

How does Public Health use Ct values? Considering the Ct values can be helpful when reviewing people with positive test results that are asymptomatic or in situations where there are concerns about potential false positive results.

References:

1. Basile K, McPhie K, Carter I, Alderson S, Rahman H, Donovan L, Kumar S, Tran T, Ko D, Sivaruban T, Ngo C, Toi C, O'Sullivan MV, Sintchenko V, Chen SC, Maddocks S, Dwyer DE, Kok J. Cell-based culture of SARS-CoV-2 informs infectivity and safe de-isolation assessments during COVID-19. Clin Infect Dis. 2020 Oct 24:ciaa1579. doi: 10.1093/cid/ciaa1579. Epub ahead of print. PMID: 33098412; PMCID: PMC7665383.
2. Bullard J, Dust K, Funk D, Strong JE, Alexander D, Garnett L, Boodman C, Bello A, Hedley A, Schiffman Z, Doan K, Bastien N, Li Y, Van Caeseele PG, Poliquin G. Predicting infectious **SARS**-**CoV**-2 from diagnostic samples. Clin Infect Dis. 2020 May 22:ciaa638. doi: 10.1093/cid/ciaa638. Online ahead of print.
3. Singanayagam A, Patel M, Charlett A, Lopez Bernal J, Saliba V, Ellis J, Ladhani S, Zambon M, Gopal R .Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of **COVID**-**19**, England, January to May 2020. Euro Surveill. 2020 Aug;25(32):2001483. doi: 10.2807/1560-7917.ES.2020.25.32.2001483

Privacy Office; Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

August 6, 2021

Sent via e-mail

Re: Partial Access – OUR FILES# NSHA-2021-095 and 2021-099

On July 12, 2021 Nova Scotia Health (NSH) received your request under the *Freedom of Information and Protection of Privacy Act* (*FOIPOP Act*).

We understand your application to be for a copy of the following:

File 2021-095:
What is the genome for the virus that infected Nova Scotians?
(Date Range for Record Search: From 12/31/2019 To 07/06/2021).

File 2021-099:
What is the genome for the virus that infected Nova Scotians?
(Date Range for Record Search: From 12/31/2019 To 07/14/2021).

Please find a copy of the records located in response to your request. The records are the same for both files. We have withheld the variant and the count when fewer than five cases occurred under sections 20(1) and 20(3)(a) of the *FOIPOP Act* because the variant and the count could be traced to reveal an identifiable third party's medical diagnosis and condition.

Section 20(1) of the *FOIPOP Act* states: *The head of a public body shall refuse to disclose personal information to an applicant if the disclosure would be an unreasonable invasion of a third party's personal privacy.*

Section 20(3) *FOIPOP Act* states: *A disclosure of personal information is presumed to be an unreasonable invasion of a third party's personal privacy if*

> *a) the personal information relates to a medical history, diagnosis, condition, treatment or evaluation.*

Should you have any questions, please do not hesitate to contact me.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review.

Sincerely,
Katie Smith
Freedom of Information Officer
Nova Scotia Health Authority
Halifax, Nova Scotia

4) What is the genome for the virus that infected Nova Scotians?

There are genetic variations of SARS COV 2, there is not one Nova Scotia genome. Each virus has a genetic code consisting of 30 000 base pairs. We send our genomes to the National Microbiology Lab. We get the lineage of the virus when we get the results back, the genetic relatedness to other COVID strains as they continually evolve and can vary depending on where Canada or the world they were introduced. Each of the virus would have different sequences. We do not have the actual sequences for each of the viruses in the table below. They are all at the National Microbiology Lab in Winnipeg, Manitoba.

COVID-19 Lineage	Count
<5	<5
<5	<5
<5	<5
<5	<5
A.3	5
B	7
B.1	163
B.1.1	5
B.1.1.1	22
B.1.1.10	14
<5	<5
B.1.1.127	5
B.1.1.130	5
<5	<5
<5	<5
B.1.1.157	220
<5	<5
<5	<5
B.1.1.162	5
B.1.1.176	5
<5	<5
<5	<5
<5	<5
<5	<5
<5	<5
B.1.1.247	5
<5	<5
<5	<5
B.1.1.29	12
B.1.1.291	5
<5	<5
<5	<5
<5	<5

<5	<5
<5	<5
<5	<5
<5	<5
B.1.1.7 (alpha variant)	234
<5	<5
<5	<5
<5	<5
<5	<5
<5	<5
<5	<5
<5	<5
B.1.177	10
B.1.2	32
<5	<5
B.1.22	6
<5	<5
<5	<5
<5	<5
B.1.280	5
<5	<5
<5	<5
<5	<5
<5	<5
B.1.332	6
B.1.351 (beta variant)	12
B.1.36	15
B.1.36.18	12
B.1.36.26	16
<5	<5
<5	<5
B.1.369	7
<5	<5
B.1.413	6
<5	<5
<5	<5
B.1.438	54
<5	<5
<5	<5
B.1.517	8
<5	<5
B.1.525	11

<5	<5
B.1.617.2 (delta variant)	25
<5	<5
B.1.98	6
<5	<5
<5	<5
<5	<5
L.1	549
<5	<5
Grand Total	**1580**

List 2

COVID-19 Lineage	Count
<5	<5
<5	<5
<5	<5
<5	<5
A.3	5
B	7
B.1	163
B.1.1	5
B.1.1.1	22
B.1.1.10	14
<5	<5
B.1.1.127	5
B.1.1.130	5
<5	<5
<5	<5
B.1.1.157	220
<5	<5
<5	<5
B.1.1.162	5
B.1.1.176	5
<5	<5
<5	<5
<5	<5
<5	<5
<5	<5
B.1.1.247	5
<5	<5
<5	<5
B.1.1.29	12

B.1.1.291	5
<5	<5
<5	<5
B.1.1.317	4
<5	<5
<5	<5
<5	<5
<5	<5
B.1.1.7 (alpha variant)	234
<5	<5
<5	<5
<5	<5
<5	<5
<5	<5
<5	<5
<5	<5
B.1.177	10
B.1.2	32
<5	<5
B.1.22	6
<5	<5
<5	<5
<5	<5
B.1.280	5
<5	<5
<5	<5
<5	<5
<5	<5
B.1.332	6
B.1.351 (beta variant)	12
B.1.36	15
B.1.36.18	12
B.1.36.26	16
<5	<5
<5	<5
B.1.369	7
<5	<5
B.1.413	6
<5	<5
<5	<5
B.1.438	54
<5	<5

B.1.509	3
B.1.517	8
<5	<5
B.1.525	11
<5	<5
B.1.617.2 (delta variant)	25
<5	<5
B.1.98	6
<5	<5
<5	<5
<5	<5
L.1	549
<5	<5
No lineage assigned	105
NO SEQUENCE PROVIDED	202
NOT SEQUENCED	317
pending review for sequencing	4159
Grand Total	**6363**

Aptima™ SARS-CoV-2 Assay (Panther™ System)

This test has not been reviewed by the FDA. This test is being distributed in accordance with Section IV.C. of the FDA's policy for diagnostic tests for Coronavirus disease – 2019 during the public health emergency at *https://www.fda.gov/media/135659/download [fda.gov]*.

CONTENTS

General Information

Intended Use

The Aptima™ SARS-CoV-2 assay is a nucleic acid amplification *in vitro* diagnostic test intended for the qualitative detection of RNA from SARS-CoV-2 isolated and purified from nasopharyngeal (NP), nasal, mid-turbinate and oropharyngeal (OP) swab specimens, nasopharyngeal wash/ aspirate or nasal aspirates obtained from individuals meeting COVID-19 clinical and/or epidemiological criteria.

Results are for the identification of SARS-CoV-2 RNA. The SARS-CoV-2 RNA is generally detectable in upper respiratory specimens during the acute phase of infection. Positive results are indicative of the presence of SARS-CoV-2 RNA, clinical correlation with patient history and other diagnostic information is necessary to determine patient infection status. Positive results do not rule out bacterial infection or co-infection with other viruses.

Negative results do not preclude SARS-CoV-2 infection and should not be used as the sole basis for patient management decisions. Negative results must be combined with clinical observations, patient history, and epidemiological information.

The Aptima SARS-CoV-2 assay on the Panther™ and Panther Fusion™ system is intended for use by clinical laboratory personnel specifically instructed and trained in the operation of the Panther and Panther Fusion systems and in vitro diagnostic procedures.

Summary and Explanation of the Test

Coronaviruses are a large family of viruses which may cause illness in animals or humans. In humans, several coronaviruses are known to cause respiratory infections ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). The most recently discovered coronavirus, SARS-CoV-2, causes the associated coronavirus disease COVID-19. This new virus and disease were unknown before the outbreak began in Wuhan, China, in December 2019.[1]

The most common symptoms of COVID-19 are fever, tiredness, and dry cough. Some patients may have aches and pains, nasal congestion, runny nose, sore throat, or diarrhea. These symptoms are usually mild and begin gradually. Some people become infected but don't develop any symptoms and don't feel unwell. The disease can spread through respiratory droplets produced when an infected person coughs or sneezes. These droplets land on objects and surfaces around the person. Other people may acquire SARS-CoV-2 by touching these objects or surfaces, then touching their eyes, nose, or mouth.

The virus that causes COVID-19 is infecting people and spreading easily from person to person. On March 11, 2020, the COVID-19 outbreak was characterized as a pandemic by the World Health Organization (WHO).[3,4]

Principles of the Procedure

The Aptima SARS-CoV-2 assay combines the technologies of target capture, Transcription Mediated Amplification (TMA), and Dual Kinetic Assay (DKA).

Specimens are collected and transferred into their respective specimen transport tubes. The transport solutions in these tubes release the RNA target and protect them from degradation

during storage. When the Aptima SARS-CoV-2 assay is performed in the laboratory, the target RNA molecules are isolated from specimens by use of capture oligomers via target capture that utilizes magnetic microparticles. The capture oligomers contain sequences complementary to specific regions of the target molecules as well as a string of deoxyadenosine residues. A separate capture oligomer is used for each target. During the hybridization step, the sequence specific regions of the capture oligomers bind to specific regions of the target molecules. The capture oligomer:target complex is then captured out of solution by decreasing the temperature of the reaction to room temperature. This temperature reduction allows hybridization to occur between the deoxyadenosine region on the capture oligomer and the poly-deoxythymidine molecules that are covalently attached to the magnetic particles. The microparticles, including the captured target molecules bound to them, are pulled to the side of the reaction vessel using magnets and the supernatant is aspirated. The particles are washed to remove residual specimen matrix that may contain amplification reaction inhibitors. After the target capture steps are completed, the specimens are ready for amplification.

Target amplification assays are based on the ability of complementary oligonucleotide primers to specifically anneal and allow enzymatic amplification of the target nucleic acid strands. The Aptima SARS-CoV-2 assay replicates specific regions of the RNA from SARS-CoV-2 virus. Detection of the RNA amplification product sequences (amplicon) is achieved using nucleic acid hybridization. Single-stranded chemiluminescent nucleic acid probes, which are unique and complementary to a region of each target amplicon and Internal Control (IC) amplicon, are labeled with different acridinium ester (AE) molecules. The AE labeled probes combine with amplicon to form stable hybrids. The Selection Reagent differentiates hybridized from unhybridized probe, eliminating the generation of signal from unhybridized probe. During the detection step, light emitted from the labeled hybrids is measured as photon signals in a luminometer, and are reported as Relative Light Units (RLU). In DKA, differences in the kinetic profiles of the labeled probes allow for the differentiation of signal; kinetic profiles are derived from measurements of photon output during the detection read time. The chemiluminescent detection reaction for the IC signal has very rapid kinetics and has the “flasher” kinetic type. The chemiluminescent detection reaction for the SARS-CoV-2 signal is relatively slower and has the “glower” kinetic type. Assay results are determined by a cut-off based on the total RLU and the kinetic curve type.

Warnings and Precautions

A. Carefully read this entire package insert and the *Panther/Panther Fusion System Operator’s Manual*.

B. Only personnel adequately trained on the use of this assay and in handling potentially infectious materials should perform these procedures. If a spill occurs, immediately disinfect using appropriate site procedures.

C. Handle all specimens as if infectious using safe laboratory procedures. Refer to Interim Laboratory Biosafety Guidelines for Handling and Processing Specimens Associated with 2019-nCoV. https://www.cdc.gov/coronavirus/2019-ncov/lab/lab-biosafety-guidelines.html.

D. Specimens may be infectious. Use Universal Precautions when performing this assay. Proper handling and disposal methods should be established by the laboratory director. Only personnel adequately trained in handling infectious materials should be permitted to perform this diagnostic procedure.[5]

E. If infection with SARS-CoV-2 is suspected based on current clinical screening criteria recommended by public health authorities, specimens should be collected with appropriate infection control precautions.

F. Use only supplied or specified disposable laboratory ware.

G. Use appropriate personal protective equipment when collecting and handling specimens from individuals suspected of being infected with SARS-CoV-2 as outlined in CDC Interim Laboratory Biosafety Guidelines for Handling and Processing Specimens Associated with 2019 Novel Coronavirus (2019-nCoV).

H. Wear disposable, powderless gloves, protective eye wear, and laboratory coats when handling specimens and reagents. Wash hands thoroughly after handling specimens and reagents.

I. Dispose of all material that has come into contact with specimens and reagents in accordance with applicable national, international, and regional regulations.

J. Expiration dates listed on the Panther Fusion Specimen Lysis Tubes and Multitest Collection Kit pertain to the transfer of sample into the tube and not to testing of the sample. Specimens collected/transferred any time prior to these expiration dates are valid for testing provided they are transported and stored in accordance with the appropriate package insert, even if these expiration dates have passed.

K. Maintain proper storage conditions during specimen shipping to ensure the integrity of the specimen. Specimen stability under shipping conditions other than those recommended has not been evaluated.

L. Avoid cross-contamination during the specimen handling steps. Specimens can contain extremely high levels of virus or other organisms. Ensure that specimen containers do not come in contact with one another, and discard used materials without passing them over any open containers. Change gloves if they come in contact with specimens.

M. Do not use the reagents and controls after the expiration date.

N. Store assay components at the recommended storage condition. See *Reagent Storage and Handling Requirements (*page 5), and *Panther System Test Procedure* (page 10) for more information.

O. Do not combine any assay reagents or fluids. Do not top off reagents or fluids; the Panther system verifies reagent levels.

P. Avoid microbial and ribonuclease contamination of reagents.

Q. Quality control requirements must be performed in conformance with local, state, and/or federal regulations or accreditation requirements and your laboratory's standard quality control procedures.

R. Do not use material that may contain Guanidinium thiocyanate or any guanidine-containing materials on the instrument. Highly reactive and/or toxic compounds may form if combined with sodium hypochlorite.

S. A reagent in this kit is labeled with risk and safety symbols.

Note: *For information on any hazard and precautionary statements that may be associated with reagents, refer to the Safety Data Sheet Library at www.hologicsds.com.*

Selection Reagent
BORIC ACID 1-5%
WARNING
H315 - Causes skin irritation
H319 - Causes serious eye irritation
P264 - Wash face, hands and any exposed skin thoroughly after handling
P280 - Wear protective gloves/protective clothing/eye protection/face protection
P305 + P351 + P338 - IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing
P337 + P313 - If eye irritation persists: Get medical advice/attention
P302 + P352 - IF ON SKIN: Wash with plenty of soap and water
P332 + P313 - If skin irritation occurs: Get medical advice/attention
P362 - Take off contaminated clothing and wash before reuse

Reagent Storage and Handling Requirements

A. The following reagents are stable when stored at 2°C to 8°C (refrigerated):
   Aptima SARS-CoV-2 Amplification Reagent
   Aptima SARS-CoV-2 Enzyme Reagent
   Aptima SARS-CoV-2 Probe Reagent
   Aptima SARS-CoV-2 Internal Control
   Aptima SARS-CoV-2 Positive Control
   Aptima SARS-CoV-2 Negative Control

B. The following reagents are stable when stored at 2°C to 30°C:
   Aptima SARS-CoV-2 Amplification Reconstitution Solution
   Aptima SARS-CoV-2 Enzyme Reconstitution Solution
   Aptima SARS-CoV-2 Probe Reconstitution Solution
   Aptima SARS-CoV-2 Selection Reagent

C. The following reagents are stable when stored at 15°C to 30°C (room temperature):
   Aptima SARS-CoV-2 Target Capture Reagent
   Aptima Wash Solution

Aptima Buffer for Deactivation Fluid

Aptima Oil Reagent

D. Working Target Capture Reagent (wTCR) is stable for 30 days when stored at 15°C to 30°C. Do not refrigerate.

E. After reconstitution, the Enzyme Reagent, Amplification Reagent, and Probe Reagent are stable for 30 days when stored at 2°C to 8°C.

F. Discard any unused reconstituted reagents and wTCR after 30 days or after the Master Lot expiration date, whichever comes first.

G. Controls are stable until the date indicated on the vials.

H. Reagents stored on-board the Panther System have 72 hours of on-board stability.

I. The Probe Reagent and Reconstituted Probe Reagent are photosensitive. Store the reagents protected from light. The specified reconstituted stability is based on 12 hours exposure of the Reconstituted Probe Reagent to two 60W fluorescent bulbs, at a distance of 17 inches (43 cm), and temperature less than 30°C. Light exposure of the Reconstituted Probe Reagent should be limited accordingly.

J. Upon warming to room temperature, some control tubes may appear cloudy or contain precipitates. Cloudiness or precipitation associated with controls does not affect control performance. The controls may be used whether they are clear or cloudy/precipitated. If clear controls are desired, solubilization may be expedited by incubating them at the upper end of the room temperature range (15°C to 30°C).

K. Do not freeze the reagents.

Specimen Collection and Storage

Specimens - Clinical material collected from patient placed in an appropriate transport system. For the Aptima SARS-CoV-2 assay, this includes NP, nasal and OP swab specimens in viral transport medium (VTM/UTM), saline, Liquid Amies, or specimen transport medium (STM).

Samples - Represents a more generic term to describe any material for testing on the Panther System including specimens, specimens transferred into a Panther Fusion Specimen Lysis Tube and controls.

Note: *Handle all specimens as if they contain potentially infectious agents. Use Universal Precautions.*

Note: *Take care to avoid cross-contamination during specimen handling steps. For example, discard used material without passing over open tubes.*

A. Swab Specimen collection

Collect NP swab, nasal swab, and OP swab specimens according to standard technique using a polyester-, rayon-, or nylon-tipped swab. Immediately place the swab specimen into 3mL of VTM or UTM. Swab specimens may alternatively be added to saline, Liquid Amies or STM. The Aptima Multitest Swab Specimen Collection Kit may be used for the collection of OP and nasal swab samples.

The following types of VTM/UTM were verified for use.

- Remel MicroTest M4, M4RT, M5 or M6 formulations
- Copan Universal Transport Medium
- BD Universal Viral Transport Medium

B. Specimen processing

1. Prior to testing on the Panther system, transfer specimen* to a Panther Fusion Specimen Lysis Tube, except for specimens collected in the Aptima Multitest Tube which require no additional processing.
   - Transfer 500 µL of the collected specimen to a Panther Fusion Specimen Lysis Tube.

   ***Note:** When testing frozen specimen, allow specimen to reach room temperature prior to processing.*
2. Storing specimens before testing
   a. After collection, specimens collected in VTM/UTM can be stored at 2°C to 8°C up to 96 hours before transferred to the Panther Fusion Specimen Lysis Tube. Remaining specimen volumes can be stored at ≤-70°C. Refer to vendor instructions for specimen stability in Liquid Amies.
   b. Specimens in the Panther Fusion Specimen Lysis Tube or Aptima Multitest Tube may be stored under one of the following conditions:
      - 15°C to 30°C up to 6 days or
      - 2°C to 8°C up to 3 months.

      ***Note:** It is recommended that specimens transferred to the Panther Fusion Specimen Lysis Tube and specimens in the Aptima Multitest Tube are stored capped and upright in a rack.*

C. Samples on board the Panther system may be archived for additional testing at a later time.

D. Storing samples after testing

1. Samples that have been assayed should be stored upright in the rack under one of the following conditions:
   - 15°C to 30°C up to 6 days or
   - 2°C to 8°C up to 3 months.
2. The samples should be covered with a new, clean plastic film or foil barrier.
3. If assayed samples need to be frozen or shipped, remove the penetrable cap and place a new non-penetrable cap on the specimen tubes. If samples need to be shipped for testing at another facility, recommended temperatures must be maintained. Prior to uncapping previously tested and recapped samples, specimen transport tubes must be centrifuged for 5 minutes at 420 Relative Centrifugal Force (RCF) to bring all of the liquid down to the bottom of the tube. Avoid splashing and cross-contamination.

Specimen Transport

Maintain specimen storage conditions as described in the *Specimen Collection and Storage section on* page 6.

***Note:** Specimens must be shipped in accordance with applicable national, international, and regional transportation regulations.*

Panther System

Reagents for the Aptima SARS-CoV-2 assay are listed below for the Panther System. Reagent Identification Symbols are also listed next to the reagent name.

Reagents and Materials Provided

Aptima SARS-CoV-2 Assay Kit PRD-06495

250 tests (2 boxes)

Aptima SARS-CoV-2 Refrigerated Box (Box 1 of 2)
(store at 2°C to 8°C upon receipt)

Symbol	Component	Quantity 250 test kit
A	**Aptima SARS-CoV-2 Amplification Reagent** *Non-infectious nucleic acids dried in buffered solution containing < 5% bulking agent.*	1 vial
E	**Aptima SARS-CoV-2 Enzyme Reagent** *Reverse transcriptase and RNA polymerase dried in HEPES buffered solution containing < 10% bulking reagent.*	1 vial
P	**Aptima SARS-CoV-2 Probe Reagent** *Non-infectious chemiluminescent DNA probes dried in succinate buffered solution containing < 5% detergent.*	1 vial
IC	**Aptima SARS-CoV-2 Internal Control**	1 vial

Aptima SARS-CoV-2 Room Temperature Box (Box 2 of 2)
(store at 15°C to 30°C upon receipt)

Symbol	Component	Quantity 250 test kit
AR	**Aptima SARS-CoV-2 Amplification Reconstitution Solution** *Aqueous solution containing preservatives.*	1 x 27.7 mL
ER	**Aptima SARS-CoV-2 Enzyme Reconstitution Solution** *HEPES buffered solution containing a surfactant and glycerol.*	1 x 11.1 mL
PR	**Aptima SARS-CoV-2 Probe Reconstitution Solution** *Succinate buffered solution containing < 5% detergent.*	1 x 35.4 mL
S	**Aptima SARS-CoV-2 Selection Reagent** *600 mM borate buffered solution containing surfactant.*	1 x 108 mL
TCR	**Aptima SARS-CoV-2 Target Capture Reagent** *Buffered salt solution containing solid phase and capture oligomers.*	1 x 54 mL
	Reconstitution Collars	3
	Master Lot Barcode Sheet	1 sheet

Aptima SARS-CoV-2 Controls Kit (Cat. No. PRD-06496)
(store at 2°C to 8°C upon receipt)

Symbol	Component	Quantity
PC	**Aptima SARS-CoV-2 Positive Control** *Non-infectious nucleic acid in a buffered solution containing < 5% detergent.*	5 x 1.7 mL
NC	**Aptima SARS-CoV-2 Negative Control** *A buffered solution containing < 5% detergent.*	5 x 1.7 mL

Materials Required and Available Separately

Note: *Materials available from Hologic have catalog numbers listed, unless otherwise specified.*

	Cat. No.
Panther System	303095
Aptima Assay Fluids Kit *(Aptima Wash Solution, Aptima Buffer for Deactivation Fluid, and Aptima Oil Reagent)*	303014 (1000 tests)
Aptima Auto Detect Kit	303013 (1000 tests)
Multi-tube units (MTUs)	104772-02
Panther Waste Bag Kit	902731
Panther Waste Bin Cover	504405
Or Panther Run Kit *contains MTUs, waste bags, waste bin covers, assay fluids, and auto detects*	303096 (5000 tests)
Tips, 1000 µL conductive, liquid sensing	10612513 (Tecan)
Aptima Multitest Swab Specimen Collection Kit	PRD-03546
Panther Fusion Specimen Lysis Tubes, 100 per bag	PRD-04339
Bleach, 5% to 7% (0.7M to 1.0M) sodium hypochlorite solution	—
Disposable gloves	—
Aptima penetrable caps	105668
Replacement non-penetrable caps	103036A
Replacement Caps for the 250-test kits	—
Amplification and Probe reagent reconstitution solutions	*CL0041 (100 caps)*
Enzyme Reagent reconstitution solution	*501616 (100 caps)*
TCR and Selection reagent	*CL0040 (100 caps)*

Optional Materials

	Cat. No.
Hologic Bleach Enhancer for Cleaning *for routine cleaning of surfaces and equipment*	302101
Tube rocker	—

Panther System Test Procedure

Note: *Refer to the Panther/Panther System Operator's Manual for additional procedural information.*

A. Work Area Preparation

Clean work surfaces where reagents and samples will be prepared. Wipe down work surfaces with 2.5% to 3.5% (0.35M to 0.5M) sodium hypochlorite solution. Allow the sodium hypochlorite solution to contact surfaces for at least 1 minute and then follow with a water rinse. Do not allow the sodium hypochlorite solution to dry. Cover the bench surface on which the reagents and samples will be prepared with clean, plastic-backed absorbent laboratory bench covers.

B. Reagent Reconstitution/Preparation of a New Kit

Note: *Reagent reconstitution should be performed prior to beginning any work on the Panther System.*

1. To reconstitute Amplification, Enzyme, and Probe Reagents, combine the bottles of lyophilized reagent with the reconstitution solution. If refrigerated, allow the reconstitution solutions to reach room temperature before use.
   a. Pair each reconstitution solution with its lyophilized reagent. Ensure that the reconstitution solution and reagent have matching label colors before attaching the reconstitution collar.
   b. Check the lot numbers on the Master Lot Barcode Sheet to ensure that the appropriate reagents are paired.
   c. Open the lyophilized reagent vial and firmly insert the notched end of the reconstitution collar into the vial opening (Figure , Step 1).
   d. Open the matching reconstitution solution, and set the cap on a clean, covered work surface.
   e. While holding the reconstitution solution bottle on the bench, firmly insert the other end of the reconstitution collar into the bottle opening (Figure , Step 2).
   f. Slowly invert the assembled bottles. Allow the solution to drain from the bottle into the glass vial (Figure , Step 3).
   g. Thoroughly mix the solution in the glass vial by swirling (Figure , Step 4).
   h. Wait for the lyophilized reagent to go into solution, then invert the assembled bottles again, tilting at a 45° angle to minimize foaming (Figure , Step 5). Allow all of the liquid to drain back into the plastic bottle.
   i. Remove the reconstitution collar and glass vial (Figure , Step 6).

j. Recap the plastic bottle. Record operator initials and reconstitution date on the label (Figure , Step 7).

k. Discard the reconstitution collar and glass vial (Figure , Step 8).

Option: Additional mixing of the Amplification, Enzyme, and Probe Reagents using a tube rocker is allowed. The reagents may be mixed by placing the recapped plastic bottle on a tube rocker set to 20 RPM (or equivalent) for a minimum of 5 minutes.

Warning: *Avoid creating foam when reconstituting reagents. Foam compromises the level-sensing in the Panther System.*

Warning: *Adequate mixing of the reagents is necessary to achieve expected assay results.*

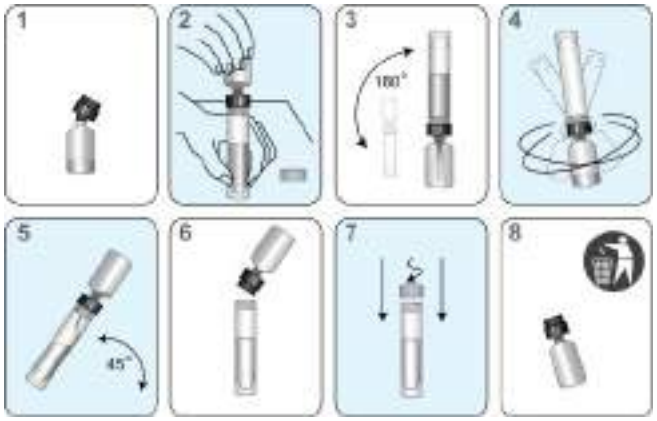

Figure 1. Panther System Reconstitution Process

2. Prepare Working Target Capture Reagent (wTCR)
   a. Pair the appropriate bottles of TCR and IC.
   b. Check the reagent lot numbers on the Master Lot Barcode Sheet to make sure that the appropriate reagents in the kit are paired.
   c. Open the bottle of TCR, and set the cap on a clean, covered work surface.
   d. Open the IC bottle and pour the entire contents into the bottle of TCR. Expect a small amount of liquid to remain in the IC bottle.
   e. Cap the bottle of TCR and gently swirl the solution to mix the contents. Avoid creating foam during this step.
   f. Record operator initials and the current date on the label.
   g. Discard the IC bottle and cap.
3. Prepare Selection Reagent
   a. Check the lot number on the reagent bottle to make sure it matches the lot number on the Master Lot Barcode Sheet.
   b. Record operator initials and the current date on the label.

Note: *Thoroughly mix by gently inverting all reagents prior to loading on the system. Avoid creating foam during inversion of reagents.*

C. Reagent Preparation for Previously Reconstituted Reagents

1. Previously reconstituted Amplification, Enzyme, and Probe Reagents must reach room temperature (15°C to 30°C) prior to the start of the assay.

   Option: The reagents may be brought to room temperature by placing the reconstituted Amplification, Enzyme, and Probe Reagents on a tube rocker set to 20 RPM (or equivalent) for a minimum of 25 minutes.

2. If reconstituted Probe Reagent contains precipitate that does not return to solution at room temperature, heat the capped bottle at a temperature that does not exceed 62°C for 1 to 2 minutes. After this heat step, the Probe Reagent may be used even if residual precipitate remains. Mix Probe Reagent by inversion, being careful not to induce foam, prior to loading onto the system.
3. Thoroughly mix each reagent by gently inverting prior to loading on the system. Avoid creating foam during inversion of reagents. This step is not required if reagents are loaded onto the system directly after mixing on the tube rocker.
4. Do not top off reagent bottles. The Panther System will recognize and reject bottles that have been topped off.
5. *Adequate mixing of the reagents is necessary to achieve expected assay results.*

D. Specimen Handling

Note: *Prepare specimens per the Specimen Processing instructions in the Specimen Collection and Storage section before loading specimens onto the Panther system.*

1. **Do not vortex samples.**
2. Inspect sample tubes before loading into the rack. If a sample tube contains bubbles or has a lower volume than is typically observed, gently tap the bottom of the tube to bring contents to the bottom.

Note: *To avoid a processing error, ensure adequate specimen volume is added to the Panther Fusion Specimen Lysis Tube. When 500 µL of collected specimen is added to the Panther Fusion Specimen Lysis Tube, there is sufficient volume to perform 3 nucleic acid extractions.*

E. System Preparation

1. Set up the system according to the instructions in the *Panther/Panther Fusion System Operator's Manual* and *Procedural Notes*. Make sure that the appropriately sized reagent racks and TCR adapters are used.
2. Load samples.

Procedural Notes

A. Controls

1. To work properly with the Aptima Assay software for the Panther System, one pair of controls is required. The Aptima SARS-CoV-2 positive and negative controls can be loaded in any rack position or in any Sample Bay Lane on the Panther System. Patient specimen pipetting will begin when one of the following two conditions has been met:
   a. A pair of controls is currently being processed by the system.
   b. Valid results for the controls are registered on the system.
2. Once the control tubes have been pipetted and are processing for a specific reagent kit, patient specimens can be run with the associated kit up to 24 hours unless:
   a. Controls results are invalid.
   b. The associated assay reagent kit is removed from the system.
   c. The associated assay reagent kit has exceeded stability limits.
3. Each Aptima control tube can be tested once. Attempts to pipette more than once from the tube can lead to processing errors.
4. Patient specimen pipetting begins when one of the following two conditions is met:
   a. Valid results for the controls are registered on the system.
   b. A pair of controls is currently in process on the system.

B. Temperature

Room temperature is defined as 15°C to 30°C.

C. Glove Powder

As in any reagent system, excess powder on some gloves may cause contamination of opened tubes. Powderless gloves are recommended.

D. Lab Contamination Monitoring Protocol for the Panther System

There are many laboratory-specific factors that may contribute to contamination, including testing volume, workflow, disease prevalence and various other laboratory activities. These factors should be taken into consideration when contamination monitoring frequency is being established. Intervals for contamination monitoring should be established based on each laboratory's practices and procedures.

To monitor for laboratory contamination, the following procedure may be performed using the Aptima Unisex Swab Specimen Collection Kit for Endocervical and Male Urethral Swab Specimens:

1. Label swab transport tubes with numbers corresponding to the areas to be tested.
2. Remove the specimen collection swab (blue shaft swab with green printing) from its packaging, wet the swab in the specimen transport medium (STM), and swab the designated area using a circular motion.
3. Immediately insert the swab into transport tube.
4. Carefully break the swab shaft at the score line; use care to avoid splashing of the contents.
5. Recap the swab transport tube tightly.
6. Repeat Steps 2 to 5 for each area to be swabbed.

E. If the results are positive, see *Interpretation of Results*. For additional Panther System-specific contamination monitoring information, contact Hologic Technical Support.

Quality Control

A run or specimen result may be invalidated by the Panther System if problems occur while performing the assay. Specimens with invalid results must be retested.

Negative and Positive Controls

To generate valid results, a set of assay controls must be tested. One replicate of the negative assay control and positive assay control must be tested each time a new kit lot is loaded on the Panther system or when the current set of valid controls have expired.

The Panther system is configured to require assay controls run at an administrator-specified interval of up to 24 hours. Software on the Panther system alerts the operator when assay controls are required and does not start new tests until the assay controls are loaded and have started processing.

During processing, criteria for acceptance of the assay controls are automatically verified by the Panther system. To generate valid results, the assay controls must pass a series of validity checks performed by the Panther system.

If the assay controls pass all validity checks, they are considered valid for the administrator-specified time interval. When the time interval has passed, the assay controls are expired by the Panther system which requires a new set of assay controls be tested prior to starting any new samples.

If any one of the assay controls fails the validity checks, the Panther system automatically invalidates the affected samples and requires a new set of assay controls be tested prior to starting any new samples.

Internal Control

An internal control is added to each sample with the wTCR. During processing, the internal control acceptance criteria are automatically verified by the Panther system software. Detection of the internal control is not required for samples that are positive for SARS-CoV-2. The internal control must be detected in all samples that are negative for SARS-CoV-2 targets; samples that fail to meet that criteria will be reported as Invalid. Each sample with an Invalid result must be retested.

The Panther system is designed to accurately verify processes when procedures are performed following the instructions provided in this package insert and the *Panther/Panther Fusion System Operator's Manual.*

Interpretation of Results

The Panther system automatically determines the test results for samples and controls. A test result may be negative, positive, or invalid.

Table1 shows the possible results reported in a valid run with result interpretations.

Table 1: Result Interpretation

SARS-CoV-2 Result	IC Result	Interpretation
Neg	Valid	SARS-CoV-2 not detected.
POS	Valid	SARS-CoV-2 detected.
Invalid	Invalid	Invalid. There was an error in the generation of the result; retest sample.

Note: Detection of internal control is not required for samples that are positive for SARS-CoV-2.

Limitations

A. Use of this assay is limited to personnel who are trained in the procedure. Failure to follow these instructions may result in erroneous results.

B. Reliable results are dependent on adequate specimen collection, transport, storage, and processing.

C. Avoid contamination by adhering to good laboratory practices and to the procedures specified in this package insert.

D. A positive result indicates the detection of nucleic acid from the relevant virus. Nucleic acid may persist even after the virus is no longer viable.

E. Nasopharyngeal wash/aspirate or nasal aspirates and self-collected or healthcare provider collected nasal and midturbinate nasal swabs are additional acceptable upper respiratory specimens that can be tested with the Aptima SARS-CoV-2 assay; however, performance with these specimen types have not been determined.

Panther SARS-CoV-2 Assay Performance

Analytical Sensitivity

The analytical sensitivity (limit of detection or LoD) of the Aptima SARS-CoV-2 assay was determined by testing serial dilutions of pooled negative clinical nasopharyngeal swab specimens spiked with inactivated cultured SARS-CoV-2 virus (USA-WA1/2020; BEI Resources; NR-52281). Ten replicates of each serial dilution were evaluated using each of two assay reagent lots across two Panther systems. The LoD was determined to be 0.01 $TCID_{50}$/mL and verified by testing an additional 20 replicates with one assay reagent lot. The LoD was also confirmed using saline, Liquid Amies and specimen transport medium (STM) swab collection media.

Inclusivity

The inclusivity of the Aptima SARS-CoV-2 assay was evaluated using *in silico* analysis of the assay target capture oligos, amplification primers, and detection probes in relation to 9,896 SARS-CoV-2 sequences available in the NCBI and GISAID gene databases. Any sequence with missing or ambiguous sequence information was removed from the analysis, resulting in 9,879 sequences evaluated for the first target region of the assay and 9,880 for the second target region. The *in silico* analysis showed 100% homology to the assay oligos of both target systems for 9,749 (98.5%) of the evaluated sequences and 100% homology to the assay oligos of at least one target system for all 9,896 sequences. There were no evaluated sequences with identified mismatches predicted to impact binding or performance of both target systems, indicating 100% inclusivity.

Analytical Specificity and Microbial Interference

The analytical specificity of the Aptima SARS-CoV-2 assay was evaluated by testing 30 microorganisms representing common respiratory pathogens or closely related species (Table 2). Bacteria were tested at 10^6 CFU/mL and viruses were tested at 10^5 $TCID_{50}$/mL, except where noted. Microorganisms were tested with and without the presence of SARS-CoV-2 inactivated virus at 3x LoD. Analytical specificity of the Aptima SARS-CoV-2 assay was 100% with no evidence of microbial interference.

In addition to microorganism testing, *in silico* analysis was performed to assess the specificity of the assay in relation to the microorganisms listed in Table 2. The *in silico* analysis showed no probable cross reactivity to any of the 112 GenBank sequences evaluated.

Table 2: Aptima SARS-CoV-2 Analytical Specificity and Microbial Interference Microorganisms

Microorganism	Concentration	Microorganism	Concentration
Human coronavirus 229E	1E+5 $TCID_{50}$/mL	Parainfluenza virus 1	1E+5 $TCID_{50}$/mL
Human coronavirus OC43	1E+5 $TCID_{50}$/mL	Parainfluenza virus 2	1E+5 $TCID_{50}$/mL
Human coronavirus HKU1[1]	1E+6 copies/mL	Parainfluenza virus 3	1E+5 $TCID_{50}$/mL
Human coronavirus NL63	1E+4 $TCID_{50}$/mL	Parainfluenza virus 4	1E+3 $TCID_{50}$/mL
SARS-coronavirus[1]	1E+6 copies/mL	Influenza A	1E+5 $TCID_{50}$/mL
MERS-coronavirus	1E+4 $TCID_{50}$/mL	Influenza B	2E+3 $TCID_{50}$/mL
Adenovirus (e.g. C1 Ad. 71)	1E+5 $TCID_{50}$/mL	Enterovirus (e.g. EV68)	1E+5 $TCID_{50}$/mL
Human Metapneumovirus (hMPV)	1E+6 $TCID_{50}$/mL	Rhinovirus	1E+4 $TCID_{50}$/mL
Respiratory syncytial virus	1E+5 $TCID_{50}$/mL	*Legionella pneumophila*	1E+6 CFU/mL
Chlamydia pneumoniae	1E+6 IFU/mL	*Mycobacterium tuberculosis*	1E+6 $TCID_{50}$/mL
Haemophilus influenzae	1E+6 CFU/mL	*Streptococcus pneumoniae*	1E+6 CFU/mL
Bordetella pertussis	1E+6 CFU/mL	*Streptococcus pyogenes*	1E+6 CFU/mL
Pneumocystis jirovecii (PJP)	1E+6 nuc/mL	*Streptococcus salivarius*	1E+6 CFU/mL
Candida albicans	1E+6 CFU/mL	*Mycoplasma pneumoniae*	1E+6 CFU/mL
Staphylococcus epidermidis	1E+6 CFU/mL	*Pseudomonas aeruginosa*	1E+6 CFU/mL
Pooled human nasal wash[2] - *to represent diverse microbial flora in human respiratory tract*	N/A		

[1] Cultured virus and whole genome purified nucleic acid for Human coronavirus HKU1 and SARS-coronavirus are not readily available. HKU1 and SARS-coronavirus IVTs corresponding to the ORF1ab gene regions targeted by the assay were used to evaluate cross-reactivity and microbial interference.

[2] In place of evaluating pooled human nasal wash, testing of 30 individual negative clinical NP swab specimens was performed to represent diverse microbial flora in the human respiratory tract.

Clinical Performance

The clinical performance of the Aptima SARS-CoV-2 assay was evaluated in comparison to the Panther Fusion SARS-CoV-2 assay (Hologic, Inc.) using a panel of remnant clinical specimens. For the study, 105 remnant clinical nasopharyngeal specimens were collected from US patients with signs and symptoms of respiratory infection. One replicate from 55 negative and 50 positive specimens for SARS-CoV-2 were tested with both the Aptima and Panther Fusion assays.

The Positive Percent Agreement (PPA) and Negative Percent Agreement (NPA) was calculated in relation to the Panther Fusion assay as the reference result, as shown in Table 3. The Aptima SARS-CoV-2 assay showed positive and negative agreements of 100% and 98.2%, respectively.

Table 3: Aptima SARS-CoV-2 Clinical Agreement

		Panther Fusion SARS-CoV-2 Assay	
		Positive	Negative
Aptima SARS-CoV-2 Assay	Positive	50	1
	Negative	0	54

Positive Percent Agreement: (95% CI): 100% (92.9% – 100%)
Negative Percent Agreement: (95% CI): 98.2% (90.4% – 99.7%)
Overall Agreement: (95% CI): 99.0% (94.8% – 99.8%)

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Hologic, Inc.
10210 Genetic Center Drive
San Diego, CA 92121 USA

Customer Support: +1 800 442 9892
customersupport@hologic.com

Technical Support: +1 888 484 4747
molecularsupport@hologic.com

For more contact information visit www.hologic.com.

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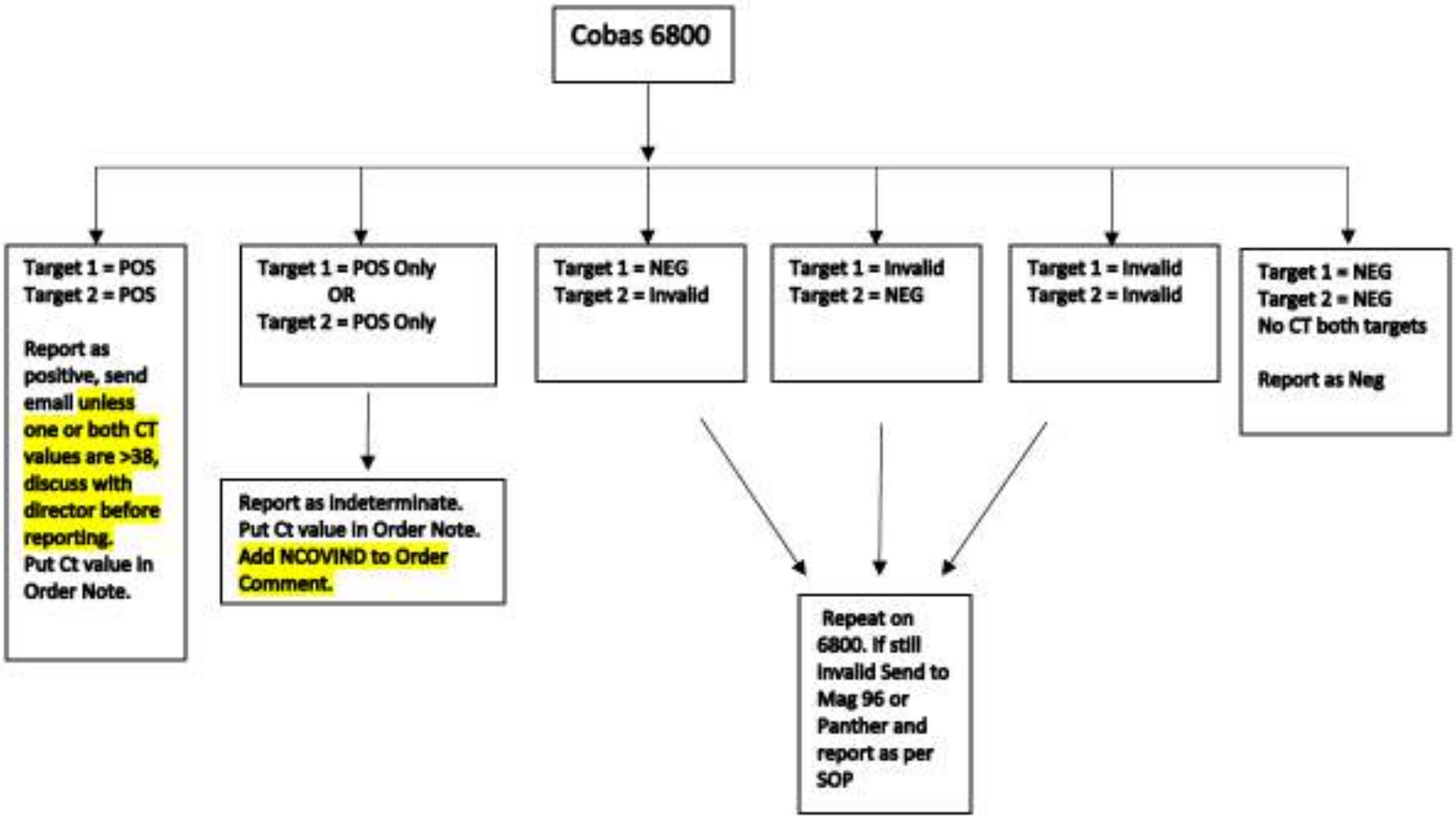
2020-05

Cobas 6800 COVID Reporting Process

Final Approval: Dr. Jason Leblanc



TITLE: Cobas 6800 COVID-19 SARS-CoV-2 Procedure	**Doc #:** 86124
Section: Management System\PLM\Microbiology\5-VIM 6800\	**Version:** 1.6 Current
Document Owner: MB1 Immunology Virology Technical Specialist	**Effective Date:** 2020/12/18
Final Approval: Dr. Jason Leblanc	**Review Date:**

Purpose

The purpose of this assay is to use RT-Real Time PCR technology to qualitatively detect the SARS-CoV-2 virus that will aid in patient treatment and isolation.

Abbreviations and Definitions

SARS-CoV-2	2019 novel coronavirus
MGP	Magnetic Glass Particles
UTM	Universal Transport Media
RFID	Radio Frequency ID
IC	Internal Control
PCR	Polymerase Chain Reaction
RT	Reverse Transcriptase
dUTP	deoxyuridine triphosphate
dTTP	deoxythimidine triphosphate

Safety Precautions

1. Do not pipette by mouth
2. Do not eat, drink or smoke in designated work areas
3. Wear laboratory gloves, laboratory coats and eye protection when handling specimens and reagents. Gloves must be changed between handling reagents/controls and specimens
4. Wash hands thoroughly after handling reagents/controls and specimens and after removing gloves
5. Thoroughly clean and disinfect laboratory work surfaces with freshly prepared 0.5% sodium hypochlorite (dilute house-hold bleach 1:10). Follow by wiping with 70% ethanol.
6. If spill occurs on the cobas 6800 refer to document Cobas 6800 Spill Clean-up procedure Doc # 87107
7. All specimens should be treated as infectious and should be handled using universal precautions. If a spill occurs follow PLM Spills-Biological-Requiring Routine Practices Procedure Document # 54002
8. Safety Data Sheets (SDS) can be found online on the Central Zone intranet and in the WHMIS binder in the fourth floor office
9. Cobas omni Lysis reagent contains guanidine thiocyanate, a potentially hazardous chemical. Avoid contact with skin, eyes and mucous membranes. If contact does occur immediately rinse with water or burns may result.

10. Cobas®SARS-CoV-2 kit, cobas®SARS-CoV-2 control kit, cobas®Buffer Negative Control kit, cobas omni MGP kit, and cobas omni Specimen Diluent contain sodium azide as a preservative. Avoid contact with skin, eyes and mucous membranes. If contact does occur immediately rinse with water or burns may result.
11. Do not allow cobas omni Lysis reagent, contains guanidium thiocyanate, to come into contact with sodium hypochlorite (bleach solution). This mixture results in a toxic gas.

Materials

Reagents	Storage Temp.	Open-Kit stability	On-board stability (outside fridge)	Number of Runs/kit	Preparation (Y/N)
cobas® SARS-CoV-2 reagent kit	2-8˚C	90 days from first usage	40 hours	40 Runs	N
cobas omni Lysis Reagent	2-8˚C	30 days from loading	NA	NA	N
cobas omni MGP Reagent	2-8˚C	30 days from loading	NA	NA	N
cobas omni Specimen Diluent	2-8˚C	30 days from loading	NA	NA	N
cobas omni Wash Reagent	15-30˚C	30 days from loading	NA	NA	N

Supplies
cobas omni Processing Plate
cobas omni Amplification Plate
cobas omni Pipette Tips
cobas omni Liquid Waste Container
Solid Waste Bag
Solid Waste Container

Equipment
cobas®6800(Option Moveable)
Sample Supply Module

Sample

Sample type	Amount required	Transport and Storage	Stability
Nasopharyngeal swab in UTM	Minimum 600 uL (no dilution necessary)	2-25˚C	48 hrs
Throat/Nose Roche swab in UTM	Minimum 600 uL (no dilution required)	2-25˚C	48 hrs
Throat gargle	Minimum 600 uL (no dilution necessary)	2-25˚C	48 hrs
Throat/Nose Aptima swab	Minimum 200 µL (dilution required, see step 2.1)	2-25˚C	48 hrs

Sample retention: Positives indefinitely. Negatives are stored at 2-8˚C for 4 days then discarded.

Maintenance

Step	Action
	Refer to periodic maintenance document # 84412

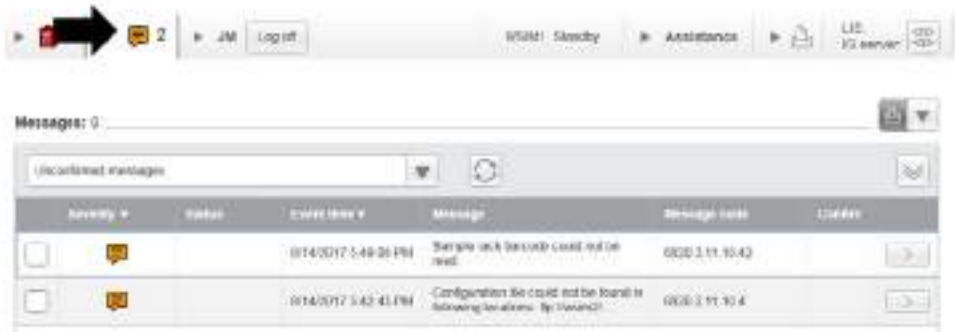
Quality Control

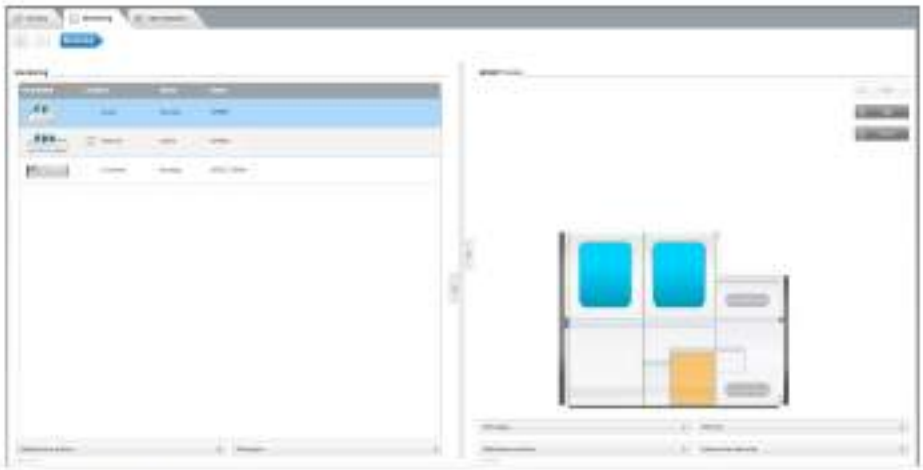
Control	Stability	Frequency	Preparation (y/n)
SARS-CoV-2 Positive Control (SARS-CoV-2 (+)C)	2-8˚C, 8hrs onboard outside	Once per batch/unopened kit	N
cobas® Buffer Negative Control (BUF (-)C)	2-8˚C, 10hrs outside fridge	Once per batch/unopened kit	N

Procedure

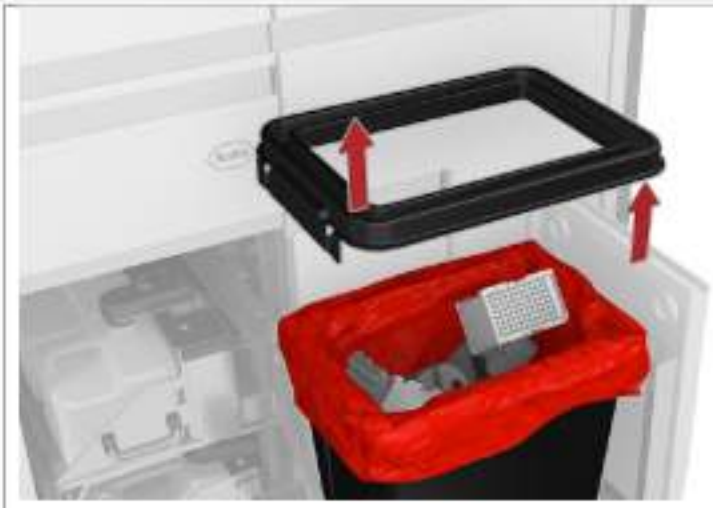
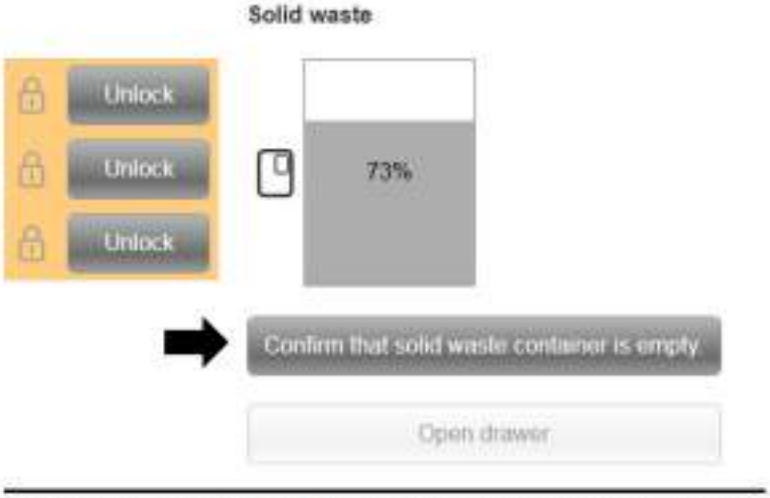
1. Cobas 6800 Instrument

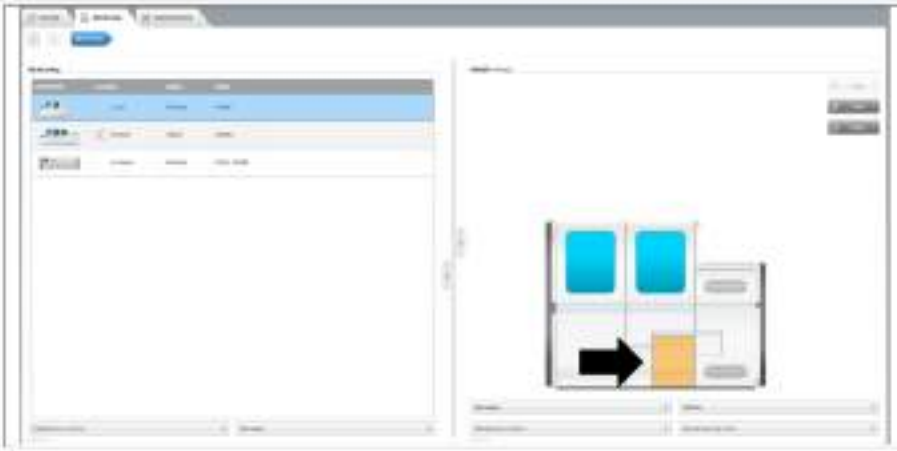
Step	Action
1.1	If the cobas 6800 analyzer is in **Standby** status continue on to step 2.2 to start up the sample supply module. To start the system from hibernation status: If the system is in Hibernation status.Press the  button below the monitor. The instrument changes to an initializing status which takes approximately 15 mins.
1.2	If racks of specimens are present on the input and output buffer lanes of the Sample Module remove them and discard/archive. Specimens may not be in the on the input tray. To move them to the output tray push the green  . Place the empty output tray back on the output lane of the Sample Module.
1.3	 on button on the IM screen have an RFID tag swipe over
1.4	Check the status light on top of the instrument. If the light is green no immediate tasks or maintenance needs to be completed.
1.5	If the status light is orange the tasks are medium priority and will soon need to be addressed. If the light is red perform the tasks immediately. To view the task click the Task Indicator button on the top left of the IM screen. **Note: do not do maintenance until the task is OVERDUE.**

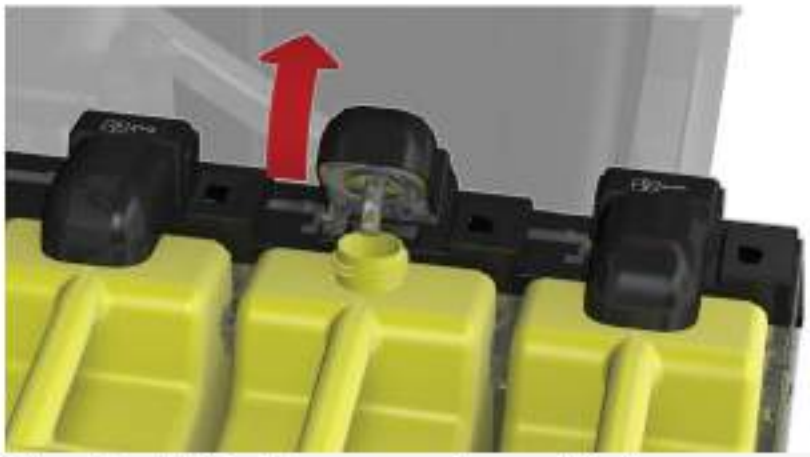
1.6	Check the Message Indicator message if there are pending messages. Three types of messages are possible ERROR, WARNING and INFORMATION. ERROR messages must be immediately resolved before resuming operation See COBAS 6800 Error procedure Doc #84413. Notify a technical specialist of all errors. If the severity level is a WARNING then the warning must be resolved soon. INFORMATION severity level messages do not require immediate attention. 
1.7	After the messages have been read and resolved choose the **Confirm Button** to archive the messages. The messages must be confirmed so the indicator light on top of the instrument is orange (Standby)
1.8	Wearing gloves and starting at the right of the instrument empty the amplification drawer. The amplification drawer can hold up to 12 amplification plates and if the drawer is full the instrument requires that the drawer be emptied. To do this under the Monitoring tab click the amplification drawer and choose the Open Drawer button.

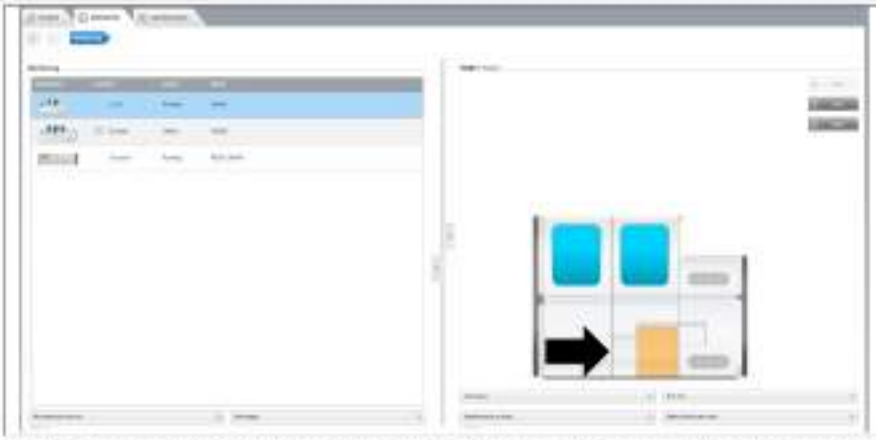
	
1.9	Remove all **sealed amplification plates** from the drawer and discard into a yellow bucket. Do Not Reach Inside the Analytic Module due to moving parts.
1.10	Manually close the amplification cassette drawer until it clicks into place.
1.11	Check to see if the solid or liquid waste needs to be changed. The solid waste contains used processing plates, tip racks, waste inserts, and empty reagent and MGP cassettes. Change the solid waste **after 3 runs of 96** (the solid waste can hold more runs if the runs have less than <49 tests) or **75% full or greater**. If the solid fills during a run, the next run will start and the waste will remain on the processing module. A high priority task will prompt you to change the solid waste.
1.12	Under the **Monitoring tab**, choose the wash/waste drawer. 
1.13	If the **solid waste** needs to be changed choose the **Open drawer** button.

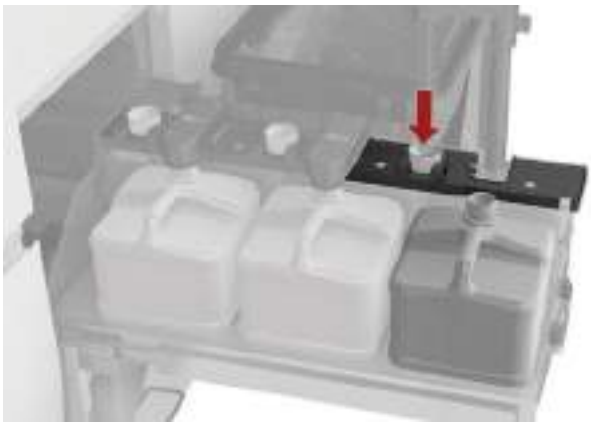
1.14	Wait for the wash/waste door to open automatically and then manually open it completely. Turn the solid container to the right until it clicks into place.
1.15	Remove the solid waste fastener.

	
1.16	Remove and tie the red waste bag and place in a yellow bag for disposal. **CAUTION** The red waste bag may be pierced by sharp objects check for perforations and check for liquid inside the solid waste container and if present follow the decontamination procedure. Place the red bag in a cardboard box and dispose of as per lab policy. **Change gloves**. Get a new red waste bag containing a folded up cardboard box. Open up the bag, unfold the box, and place inside the waste container making sure the bag and the unfolded box go to the very bottom.
1.17	Place the waste bag fastener back on the top of the waste container.
1.18	Choose Confirm the solid waste container is empty button and close the drawer. If the liquid waste and/or wash reagent needs to be changed. If not close the drawer. 
1.19	To change the **liquid waste/wash reagent** on the Monitoring screen select the wash/waste drawer.

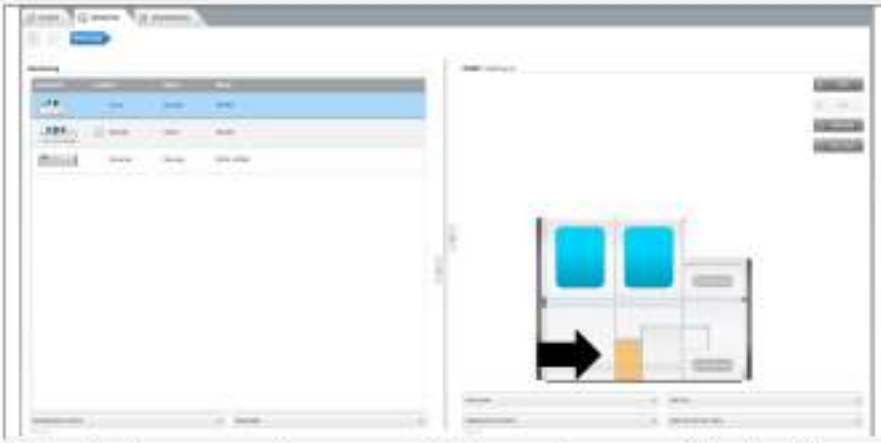
	
1.20	Choose the **Open drawer.** Wait for the wash/waste drawer to automatically open slightly then manually open it fully then turn the solid waste container to the right side until it clicks. Pull out the liquid waste drawer. 
1.21	Check the fill levels to find the liquid waste containers that need to be exchanged. Choose the **Unlock** button to unlock the waste dispense caps. Once **Unlock** button has been pressed a completely empty waste container must replace the removed waste container. Do not put a partially filled waste container on the instrument.

	
1.22	Wait for the click sound and check whether the status indicator next to the waste dispense cap has turned off and lift the waste dispense cap. 
1.23	Close the full liquid waste containers with the cap screw cap (stored on the inner part of the liquid waste drawer). Remove the full liquid waste container from the drawer. Never remove all waste containers at one time. Inspect the liquid waste drawer for salt residues and wipe using a lint-free cloth with water followed by 70% ethanol. Load empty liquid waste containers. Remove the screw cap and place it on the inside part of the liquid waste drawer for storage then close the waste dispense cap. Push the liquid waste drawer back in. Dump the waste down the sink and let the water fun for 5 mins. Rinse the waste container out with water and place upside down on an empty tip box that is lined with a blue absorpant pad to dry. **NEVER put a wet waste container on the instrument. Change gloves.**
1.24	If the liquid/waste drawer is not already open from changing the waste on the **Monitoring** tab choose the wash/waste drawer.

	
1.25	Choose which wash bottles need to be changed (bottles showing 0%) and choose the **Open drawer** button the wash/waste drawer unlocks and automatically opens slightly. Pull the wash drawer out fully and clicks into place.  
1.26	In the software, check the fill levels and choose the **Unlock** button for the container that needs to be replaced.
1.27	Wait for the click sound and the status indicator to turn off. Pull out the reagent aspiration arm and turn it into the reagent aspiration arm park position. **Do not**

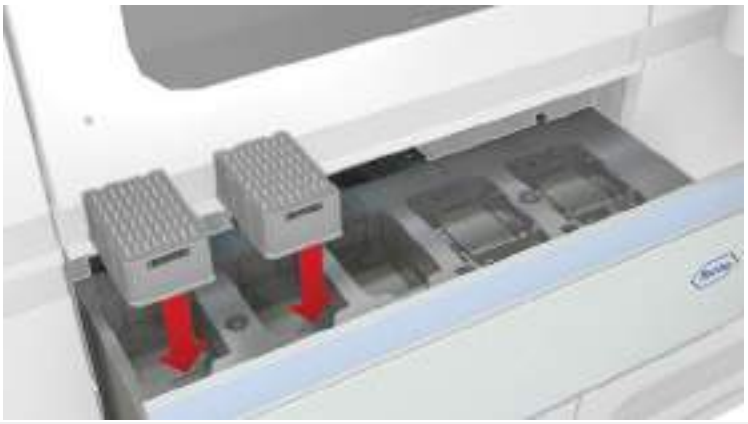
	touch the reagent aspiration arm where it comes into contact with the wash buffer. 
1.28	Close the empty container with a screw cap and remove the container. Inspect the wash reagent drawer for salt residues. If present wipe with a lint-free moistened with dH2O. Repeat with 70% ethanol. Install a new wash container. Always replace an empty wash container with a full wash container.
1.29	Remove the cap and place it in the reagent arm aspiration park position. Close the reagent aspiration arm. Push down until the status indicator lights up again. 

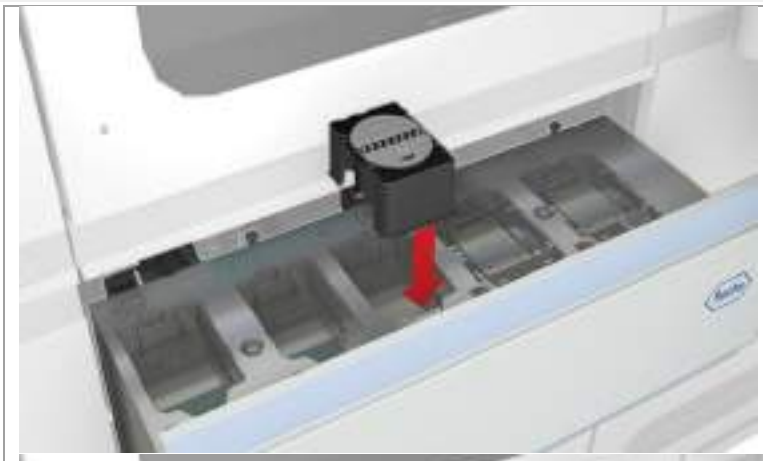
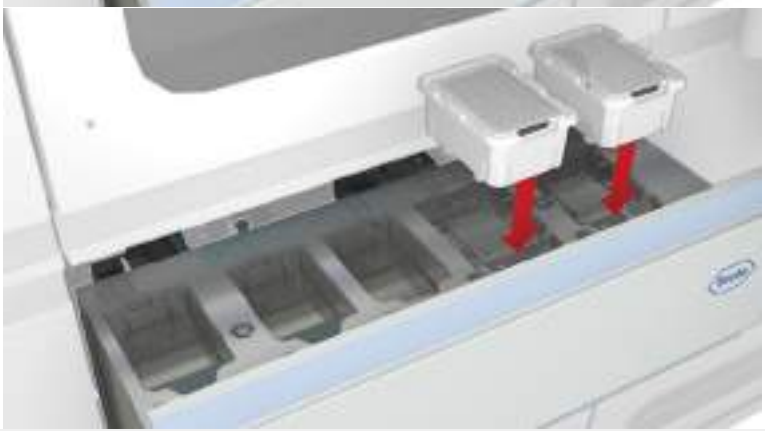
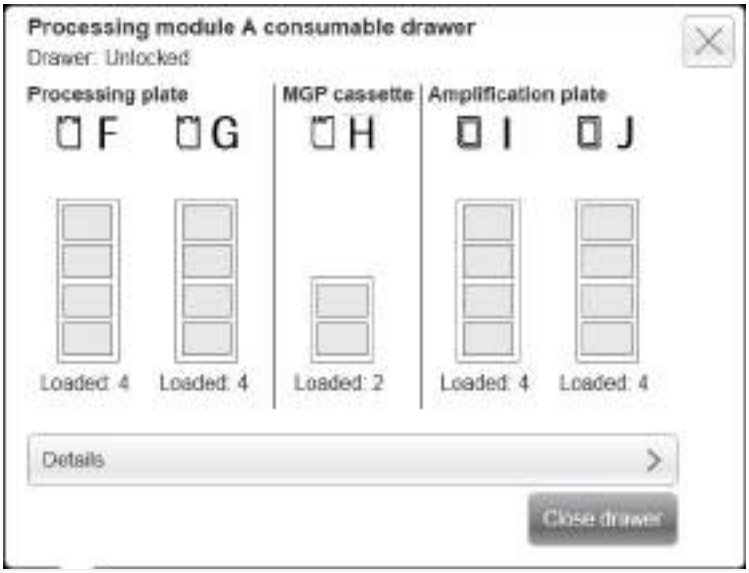
	
1.30	In the software verify that the fill levels show 100% 
1.31	Push the wash reagent drawer back in and close the wash waste drawer fully. **Change Gloves**. 
1.32	To load **Diluent and Lysis** reagent on the **Monitoring tab** choose the bulk reagent drawer and then choose the **Open drawer button**.

	
1.33	The bulk reagent drawer unlocks and opens slightly. Manually pull the drawer open. 
1.34	Check the fill levels of the lysis and diluent in their respective bottles. To unlock a reagent aspiration arm, choose the **Unlock** button of the respective bottles and then wait for the status indicator light to turn off. Lysis bottles are black and diluent bottles are white.

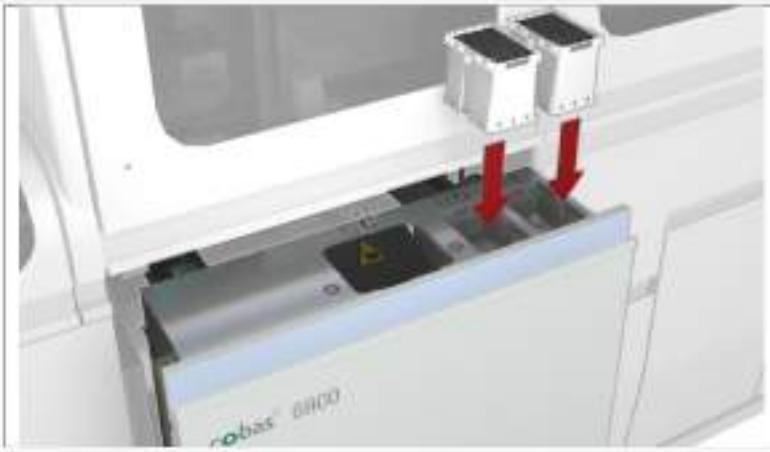
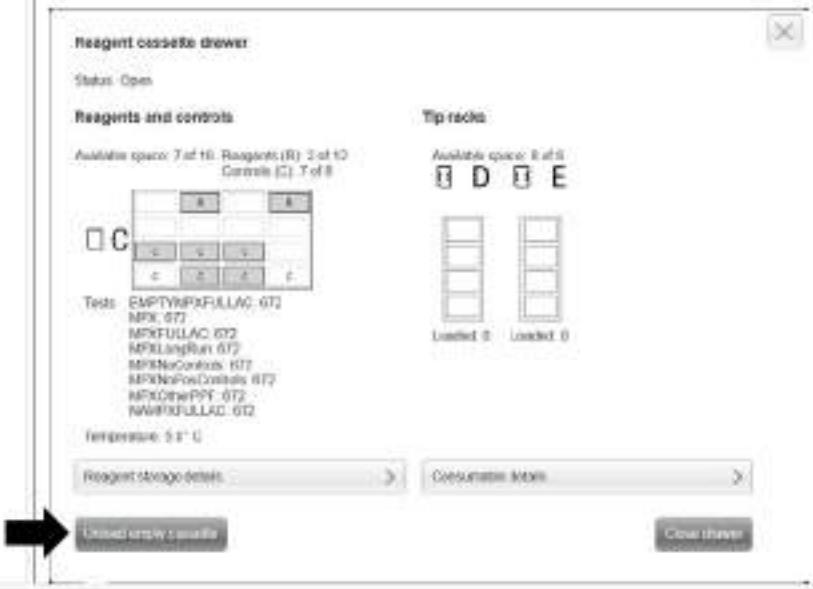
	
1.35	If the status indicator light is turned off for the respective bottle pull up the reagent aspiration arm and turn it to the reagent arm aspiration park position. Never touch the park of the reagent aspiration arm that is in contact with the reagent. 
1.36	Close the empty bottle with its screw cap and remove the bottle from the drawer. Inspect the bulk reagent drawer surface for salt residues and if present wipe with a lint-free cloth soaked with dH2O followed by 70% ethanol.

1.37	Load a new bottle. Never remove a bottle without replacing it with a new one. Remove the cap and place it into the reagent aspiration park position.

	
1.38	Close the reagent aspiration arm. Push it down until the status indicator lights up again. It should now be green. **Change gloves**. 
1.39	Load processing cartridges, amplification plates and MGP cassettes as necessary. Make sure enough consumables are loaded to run the days test batches. MGPs are only loaded if the magazine is empty. If a partially used MGP must be loaded the instrument must be in **Stand By** mode. 

	 
1.40	In the call out check the loading status. If all supplies are added choose **Close drawer**. 
1.41	Wait for the click sound, and then push the consumables drawer back until it clicks in to place.

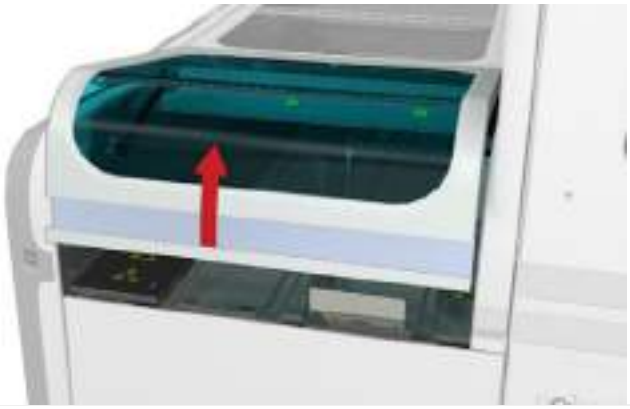
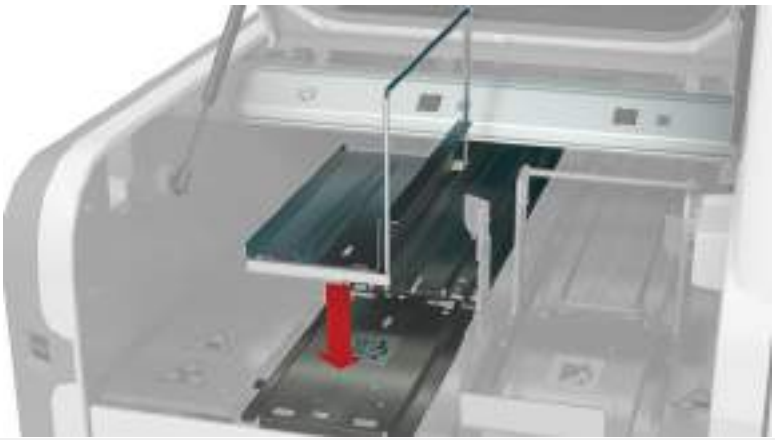
	
1.42	To load **tips, reagents and controls**, on the **Monitoring tab** choose the reagent cassette drawer, and then choose **Open drawer** button. The reagent cassette drawer unlocks and automatically opens slightly. Manually open the reagent cassette drawer.  
1.43	Refill tip racks as needed one after another in magazines D and E. Do not stack multiple racks on top of one another. Wait until the barcode is read and the callout is updated.

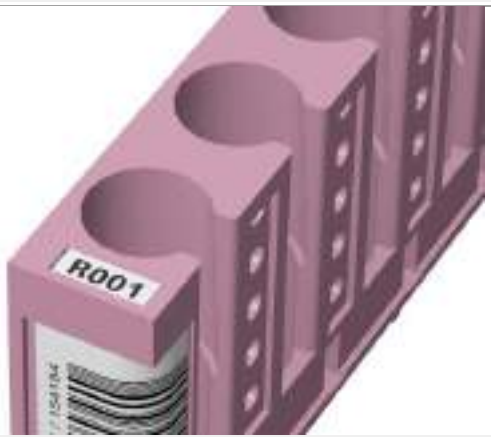
	
1.44	In the callout check to see if there are any empty or expired control cassettes and unload them if necessary. Empty/expired control cassettes appear as white "C" rectangles and empty reagent cassettes appear as white "R" rectangles. Empty reagent cassettes are unloaded automatically to the solid waste when they are completely used or if they have less than 5 tests remaining. If reagent cassettes have expired they must be unloaded in the same manner as the controls. The unload button will be present if there is empty cassettes to unload. Do reach inside the magazine when loading controls and reagents. 
1.45	Once the reagents have been moved into reagent storage load the control cassettes. Make sure the mini racks are flat and placed correctly.

	
1.46	If all reagent and consumables are loaded, in the callout, choose the **Close drawer** button. Wait for the click sound and push the reagent drawer back in manually until it is fully closed. 
1.47	If the system is in **Standby status,** it requires priming before use to ensure air bubbles are not in the Lysis, Diluent or Wash lines. On the **Monitoring** tab, choose the **Start** button. The system switches to **Preparing** status. Priming takes approximately 10 minutes. The system then moves into **Ready** status and specimens can now be loaded.

2. Specimen Loading

Step	Action
2.1	Create a Worklist using the VGMB COVID Holding list. Transfer the specimens saved on the worklist from VGMB COVID-19 Holding Bench to VGMB Cobas 6800 using Pending Inquiry. Log transferred specimens to MBVG from VGMB Cobas 6800 pending list. See Job Aid - Genlab LIS COVID document # 90523 for details.
2.2	600 uL of UTM (Nasopharyngeal), 600 µL of Gargle (throat) or 200 uL of Hologic Aptima buffer (Nose/Throat) + 1 mL cobas omni Diluent are loaded into 12x75mm aliquot tubes. The 200 uL of Hologic Aptima specimen must be mixed with the cobas diluent by pipetting at least 5 times. Be careful not to

	generate bubbles while aliquoting and mixing. Once Aptima specimen is added to the cobas diluent it is stable for 2 hrs prior to processing.
2.3	In order for the cobas 6800 to run it requires racks for clotted tips. The system has the capacity to load 2 racks containing 5 tubes each. If a clot/bubble is detected the tip is discarded into one of the tubes in the clotted tip rack. If not enough tubes are available for clotted tip discard then the analyzer will stop processing.
2.4	To load the clotted tip racks and specimens open the front cover of the sample supply module and ensure the output buffer is ↑ status. 
2.5	Load an empty rack tray on the output buffer if not already present. If the rack is placed correctly the status indicator changes to ■ status. 
2.6	The clotted tip racks are PINK and the rack ID starts with “R”.

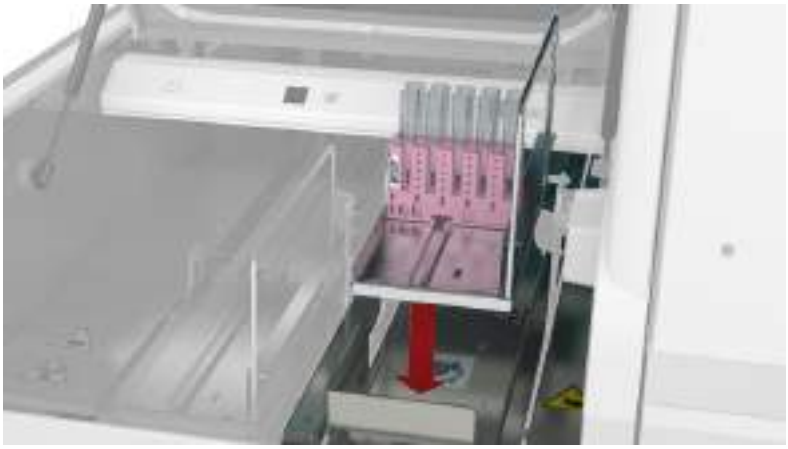
	
2.7	Insert 5 empty sample tubes in the pink clotted tip rack. These tubes are 16x100mm, are clear and lack a barcode. Repeat loading for the other clotted tip rack. If the tubes in the clotted tip rack from the previous day have not been used by the instrument the same clotted tip rack (s) can be reloaded onto the instrument. 
2.8	To load onto the sample supply module the 2 clotted tip racks can be loaded alone or with specimens. The specimen RD racks are grey and the barcode must be facing outwards for the instrument to be able to scan them.

2.9

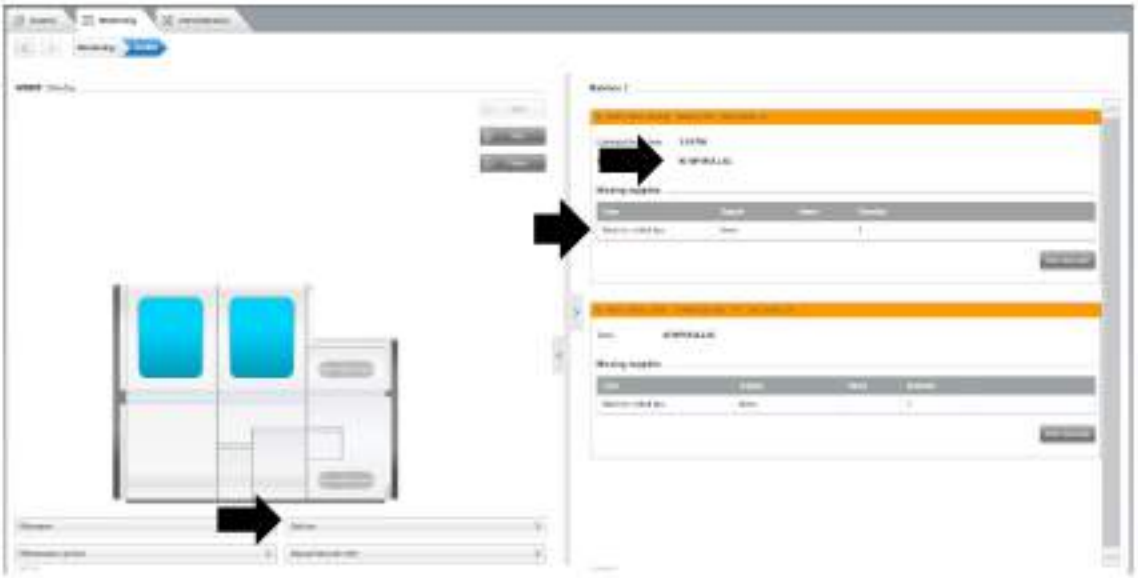
Ensure the input buffer status is ↑ status.

2.10

Load the rack tray on the input buffer.



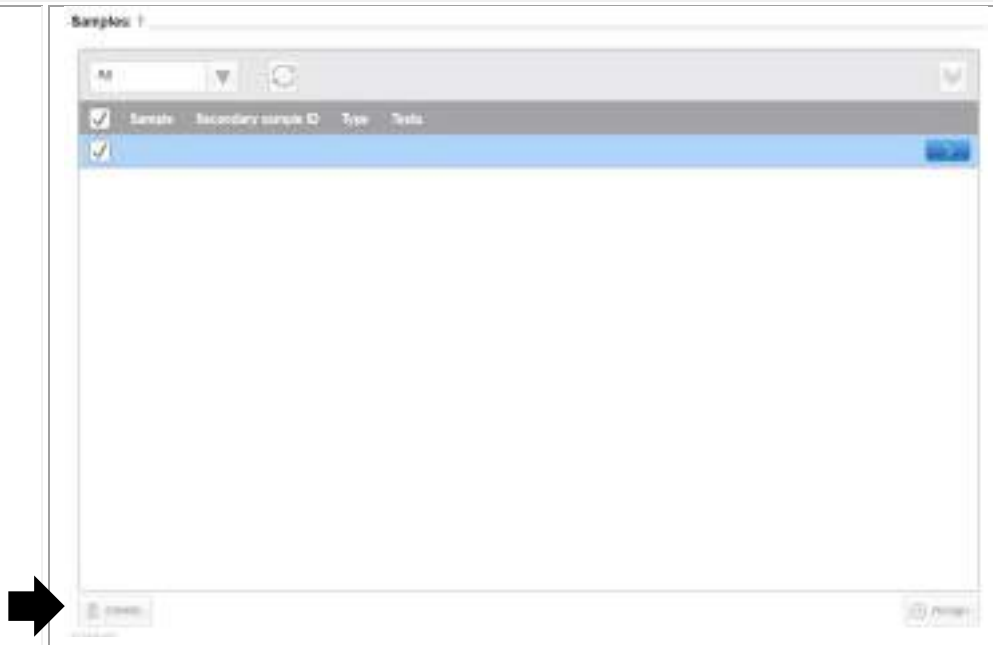
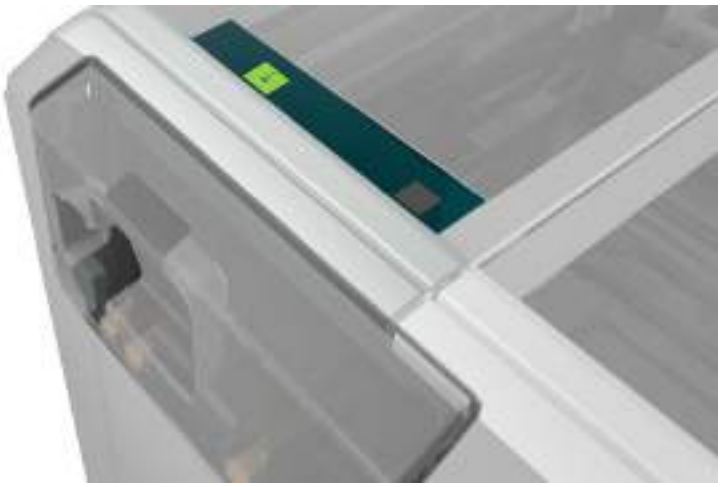
After loading the tray keep your hands out of the loading area. Do not remove the rack tray until loading has been completed and status indicator is green again.

2.11	Once the specimens are loaded and taken into Transfer module they are placed into a batch. A batch consists of a group of specimens that are run with one set of controls. A full kit of 192 reactions will run 94 SARS-CoV-2 plus 2 controls to fill a 96 well plate. If a batch needs to use reagent from another kit 2 additional controls will be used minus and reserved wells that are required.
2.12	To view the current Batch, choose Monitoring, then Batches.  The number of specimens in the batch and any missing supplies appears on the right. Load any missing supplies.
2.13	As soon as all specimens and supplies are loaded the **Start manually** button becomes active.  If the run is not a full batch and you need to start it you can choose the **Start manually** button and the instrument changes to **Running** status. If a full batch is loaded the system will automatically start the batch and if the batch is not completely filled it will automatically start after 2 hours. If too many specimens

	are loaded for a batch they will get bumped to the next batch. At this point, you have 2 hours to add more to this batch before it automatically starts. If you don't want to process these specimens and cancel the run you can chose the **Stop button**. Once the specimens are removed from the Transfer module and sent to the output lane of the Sample Supply module the **Resume** button must be chosen to resume the current run. 
2.14	When the control batch is complete print the batch report. Highlight all of the specimens on the control batch and click the release button at the bottom of the screen.
2.15	All negative results will autoverify in LIS. Any results with one or both targets positive will hold in LIS. Follow the result interpretation section below.

3. System and specimen/rack errors

Step	Action
3.1	If there is a malfunction causing a run to abort the system will go into **Stopping then Error status**. Note that the system will not get to Error status until the Analytical module has completed processing the current run. See Error procedure for instructions on how to reset the 6800 after an error. Specimen test orders that were scheduled or processing must be deleted or the system will not process them when they are reloaded. Choose the Routine tab, then Sample orders. Check off all sample orders that need to be repeated and then choose the Delete button. Now the specimens can be reloaded.

	
3.2	Specimens/racks that have errors go to the error output lane. The error output lane receives specimen racks with specimen tubes that could not be processed by the system. Check the status indicator to see if the light is green, red or orange. If so the rack is ready to be unloaded. 

	
3.3	To identify the error associated with the specimen go to Routine, choose test orders status and filter the test batch by flags. Note this specimen cannot be retested until its batch has been totally processed and finished thermocycling.

Result Interpretations

The SARS-CoV-2 assay detects two targets. Target 1 (ORF1) is specific to the SARS-CoV-2 virus while Target 2 (E gene) is specific to the Sarbecoviruses which also include the SARS and MERS viruses.

Positive for SARS-CoV-2 Virus:

Target 1 and **Target 2** must have a Ct value. If either or both targets have a CT >38 discuss with a director before reporting.
Report as positive, send email.
Record Ct values in Order Note.
Report result in ARE using the drop down list of results.

Negative for SARS-CoV-2 Virus:

No CT both targets and the IC is Valid: **report as negative**. Note the IC values vary however the instrument software validates the efficiency of the PCR/extraction.
Negative results autoverify in LIS upon release from the instrument.

Indeterminate for SARS-CoV-2:

Single target positives are considered indeterminate on the 6800. Report as indeterminate in ARE, using the drop down list of results. Add NCOVIND in an Order Comment.

Invalids

Invalids off the 6800 do not yield a result for the corresponding target. If **target 1** and/or **target 2** are invalid the specimen needs to be repeated on the 6800. If it repeats as invalid run on the Magnapure 96 or Panther.

Reporting

Public health needs to be notified about all positives and indeterminates. This can be done by sending an email to PHProvincialCOVID@nshealth.ca (also copy Dr. Hatchette, Dr. Leblanc, Janice Pettipas and the DHW Epi team surveillancedhw@novascotia.ca) and including the following information for each patient:

Name:
HCN:
Accession #:
Result:

For **inpatients**, the floors must also be phoned and the **CR template** must be completed in the order comment.

Capture QC units using **VLQC3** for each QC run.

Principle

The cobas®SARS-CoV-2 assay is a fully automated extraction and Real-Time PCR amplification and detection process. SARS-CoV-2 nucleic acid is released from the viral capsid using lysis buffer and proteinase. The nucleic acid then binds the MGP along with IC RNA in the reagent. The nucleic acid is extensively washed getting rid of cellular debris and PCR inhibitors and eluted at an elevated temperature. The resulting eluate, in combination with primer probes for the ORF1 a/b gene which is specific for SARS-CoV-2 and the E gene which is pan-Sarbecovirus specific are used in a Real-Time RT PCR reaction. The IC is also amplified in a similar manner validating both the extraction and amplification processes. If SARS-CoV-2 RNA is present an RT reaction creates a DNA template. During PCR amplification the probes bind to the target DNA sequence and the 5' to 3' exonuclease of the DNA polymerase results in the separation of the reporter dye and quencher. This results in detectable fluorescence which increases with each PCR cycle. The master mix contains dUTP instead of dTTP which is incorporated in the newly synthesized amplicon. Any amplicon from previous PCR reactions will be destroyed by the AmpErase enzyme (uracil-N-Glycosylase) included in the reaction mix.

Related Procedures and Documents

Document Name	Document #	Location
Cobas 6800 Error procedure	84413	PCR Bench Manual
Cobas 6800 Periodic Maintenance procedure	84412	PCR Bench Manual.

Job Aid

Document Name	Document #	Location
Cobas 6800 COVID Reporting Process	87343	Paradigm
Job Aid - Genlab LIS COVID document	90523	Paradigm

Reference

Cobas® 6800/8800 User Assistance Guide: Publication version 4.1

Rx Only

cobas® SARS-CoV-2

Qualitative assay for use on the cobas® 6800/8800 Systems

For in vitro diagnostic use

cobas® SARS-CoV-2	P/N: 09175431190
cobas® SARS-CoV-2 Control Kit	P/N: 09175440190
cobas® 6800/8800 Buffer Negative Control Kit	P/N: 07002238190

Table of Contents

Intended use

cobas® SARS-CoV-2 for use on the **cobas**® 6800/8800 Systems is a real-time RT-PCR test intended for the qualitative detection of nucleic acids from SARS-CoV-2 in nasopharyngeal and oropharyngeal swab samples from patients with signs and symptoms suggestive of COVID-19 (e.g., fever and/or symptoms of acute respiratory illness).

Results are for the detection of SARS-CoV-2 RNA that are detectable in nasopharyngeal and oropharyngeal swab samples during infection. Positive results are indicative of SARS-CoV-2 RNA detection, but may not represent the presence of transmissible virus.

Negative results do not preclude SARS-CoV-2 infection and should not be used as the sole basis for patient management decisions. Negative results must be combined with clinical observations, patient history, and epidemiological information.

cobas® SARS-CoV-2 is intended for use by trained clinical laboratory personnel specifically instructed and trained in the techniques of real-time PCR and in vitro diagnostic procedures.

Summary and explanation of the test

Explanation of the test

cobas® SARS-CoV-2 is a qualitative test on the **cobas**® 6800 System and **cobas**® 8800 System for the detection of the 2019 novel coronavirus (SARS-CoV-2) RNA in nasopharyngeal and oropharyngeal swab samples collected in Copan Universal Transport Medium System (UTM-RT) or BD™ Universal Viral Transport System (UVT). The RNA Internal Control, used to monitor the entire sample preparation and PCR amplification process, is introduced into each specimen during sample processing. In addition, the test utilizes external controls (low titer positive control and a negative control).

Principles of the procedure

cobas® SARS-CoV-2 is based on fully automated sample preparation (nucleic acid extraction and purification) followed by PCR amplification and detection. The **cobas**® 6800/8800 Systems consist of the sample supply module, the transfer module, the processing module, and the analytic module. Automated data management is performed by the **cobas**® 6800/8800 software, which assigns test results for all tests. Results can be reviewed directly on the system screen, and printed as a report.

Nucleic acid from patient samples and added internal control RNA (RNA IC) molecules are simultaneously extracted. Nucleic acid is released by addition of proteinase and lysis reagent to the sample. The released nucleic acid binds to the silica surface of the added magnetic glass particles. Unbound substances and impurities, such as denatured protein, cellular debris and potential PCR inhibitors, are removed with subsequent wash steps and purified nucleic acid is eluted from the magnetic glass particles with elution buffer at elevated temperature. External controls (positive and negative) are processed in the same way with each **cobas**® SARS-CoV-2 run.

Selective amplification of target nucleic acid from the sample is achieved by the use of target-specific forward and reverse primers for ORF1/a non-structural region that is unique to SARS-CoV-2. Additionally, a conserved region in the structural protein envelope E-gene were chosen for pan-Sarbecovirus detection. The pan-Sarbecovirus detection sets will also detect SARS-CoV-2 virus.

Selective amplification of RNA Internal Control is achieved by the use of non-competitive sequence specific forward and reverse primers which have no homology with the coronavirus genome. A thermostable DNA polymerase enzyme is used for amplification.

The **cobas**® SARS-CoV-2 master mix contains detection probes which are specific for the coronavirus type SARS-CoV-2, members of the Sarbecovirus subgenus, and the RNA Internal Control nucleic acid. The coronavirus and RNA Internal Control detection probes are each labeled with unique fluorescent dyes that act as a reporter. Each probe also has a second dye which acts as a quencher. When not bound to the target sequence, the fluorescent signals of the intact probes are suppressed by the quencher dye. During the PCR amplification step, hybridization of the probes to the specific single-stranded DNA template results in cleavage of the probe by the 5' to 3' exonuclease activity of the DNA polymerase resulting in separation of the reporter and quencher dyes and the generation of a fluorescent signal. With each PCR cycle, increasing amounts of cleaved probes are generated and the cumulative signal of the reporter dye increases concomitantly. Each reporter dye is measured at defined wavelengths, which enables simultaneous detection and discrimination of the amplified coronavirus target and the RNA Internal Control. The master mix includes deoxyuridine triphosphate (dUTP), instead of deoxythimidine triphosphate (dTTP), which is incorporated into the newly synthesized DNA (amplicon). Any contaminating amplicons from previous PCR runs are destroyed by the AmpErase enzyme [uracil-N-glycosylase], which is included in the PCR mix, when heated in the first thermal cycling step. However, newly formed amplicons are not destroyed since the AmpErase enzyme is inactivated once exposed to temperatures above 55°C.

Reagents and materials

The materials provided for **cobas**® SARS-CoV-2 can be found in Table 1 and Table 2. Materials required, but not provided can be found in Table 3, Table 4, Table 7, and Table 8.

Refer to the **Reagents and materials** section and **Precautions and handling requirements** section for the hazard information for the product.

cobas® SARS-CoV-2 reagents and controls

All unopened reagents and controls shall be stored as recommended in Table 1 to Table 4.

Table 1 cobas® SARS-CoV-2

cobas® SARS-CoV-2 Store at 2-8°C 192 test cassette (P/N 09175431190)		
Kit components	**Reagent ingredients**	**Quantity per kit 192 tests**
Proteinase Solution (PASE)	Tris buffer, < 0.05% EDTA, calcium chloride, calcium acetate, 8% proteinase EUH210: Safety data sheet available on request. EUH208: Contains Subtilisin. May produce an allergic reaction.	22.3 mL
RNA Internal Control (RNA IC)	Tris buffer, <0.05% EDTA, <0.001% non-Sarbecovirus related armored RNA construct containing primer and probe specific primer sequence regions (non-infectious RNA in MS2 bacteriophage), <0.1% sodium azide	21.2 mL
Elution Buffer (EB)	Tris buffer, 0.2% methyl-4 hydroxybenzoate	21.2 mL
Master Mix Reagent 1 (MMX-R1)	Manganese acetate, potassium hydroxide, <0.1% sodium azide	7.5 mL
SARS-CoV-2 Master Mix Reagent 2 (SARS-CoV-2 MMX-R2)	Tricine buffer, potassium acetate, < 18% dimethyl sulfoxide, glycerol, < 0.1% Tween 20, EDTA, < 0.12% dATP, dCTP, dGTP, dUTPs, < 0.01% upstream and downstream SARS-CoV-2 and Sarbecovirus primers, < 0.01% Internal Control forward and reverse primers, < 0.01% fluorescent-labeled oligonucleotide probes specific for SARS-CoV-2, Sarbecovirus, and the RNA Internal Control, < 0.01% oligonucleotide aptamer, < 0.1% Z05D DNA polymerase, < 0.10% AmpErase (uracil-N-glycosylase) enzyme (microbial), < 0.1% sodium azide	9.7 mL

Table 2 cobas® SARS-CoV-2 Control Kit

cobas® SARS-CoV-2 Control Kit Store at 2–8°C (P/N 09175440190)		
Kit components	**Reagent ingredients**	**Quantity per kit**
SARS-CoV-2 Positive Control **(SARS-CoV-2 (+)C)**	Tris buffer, < 0.05% Sodium azide, < 0.005% EDTA, < 0.003% Poly rA, < 0.01% Non-infectious plasmid DNA (microbial) containing SARS-CoV-2 sequence, < 0.01% Non-infectious plasmid DNA (microbial) containing pan-Sarbecovirus 1 sequence, < 0.01% Non-infectious plasmid DNA (microbial) containing pan-Sarbecovirus sequence	16 mL (16 x 1 mL)

Table 3 cobas® Buffer Negative Control Kit

cobas® Buffer Negative Control Kit Store at 2-8°C (P/N 07002238190)		
Kit components	**Reagent ingredients**	**Quantity per kit**
cobas® Buffer Negative Control **(BUF (-) C)**	Tris buffer, < 0.1% sodium azide, EDTA, < 0.002% Poly rA RNA (synthetic)	16 mL (16 x 1 mL)

cobas omni reagents for sample preparation

Table 4 cobas omni reagents for sample preparation*

Reagents	Reagent ingredients	Quantity per kit	Safety symbol and warning**
cobas omni MGP Reagent (MGP) Store at 2–8°C (P/N 06997546190)	Magnetic glass particles, Tris buffer, 0.1% methyl-4 hydroxybenzoate, < 0.1% sodium azide	480 tests	Not applicable
cobas omni Specimen Diluent (SPEC DIL) Store at 2–8°C (P/N 06997511190)	Tris buffer, 0.1% methyl-4 hydroxybenzoate, < 0.1% sodium azide	4 x 875 mL	Not applicable
cobas omni Lysis Reagent (LYS) Store at 2–8°C (P/N 06997538190)	43% (w/w) guanidine thiocyanate***, 5% (w/v) polydocanol***, 2% (w/v) dithiothreitol***, dihydro sodium citrate	4 x 875 mL	  **DANGER** H302 + H332: Harmful if swallowed or if inhaled. H314: Causes severe burns and eye damage. H412: Harmful to aquatic life with long lasting effects. EUH032: Contact with acids liberates very toxic gas. P261: Avoid breathing dust/fume/gas/mist/vapours/ spray. P273: Avoid release to the environment. P280: Wear protective gloves/ protective clothing/ eye protection/ face protection. P303 + P361 + P353: IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water. P304 + P340 + P310: IF INHALED: Remove person to fresh air and keep comfortable for breathing. Immediately call a POISON CENTER/doctor. P305 + P351 + P338 + P310: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a POISON CENTER/ doctor. 593-84-0 Guanidinium thiocyanate 9002-92-0 Polidocanol 3483-12-3 (R*,R*)-1,4-dimercaptobutane-2,3-diol
cobas omni Wash Reagent (WASH) Store at 15–30°C (P/N 06997503190)	Sodium citrate dihydrate, 0.1% methyl-4 hydroxybenzoate	4.2 L	Not applicable

* These reagents are not included in the **cobas**® SARS-CoV-2 test kit. See listing of additional materials required (Table 7).

** Product safety labeling primarily follows EU GHS guidance

***Hazardous substance

Reagent storage and handling requirements

Reagents shall be stored and will be handled as specified in Table 5 and Table 6.

When reagents are not loaded on the **cobas**® 6800/8800 Systems, store them at the corresponding temperature specified in Table 5.

Table 5 Reagent storage (when reagent is not on the system)

Reagent	Storage temperature
cobas® SARS-CoV-2 -192	2–8°C
cobas® SARS-CoV-2 Control Kit	2–8°C
cobas® Buffer Negative Control Kit	2–8°C
cobas omni Lysis Reagent	2–8°C
cobas omni MGP Reagent	2–8°C
cobas omni Specimen Diluent	2–8°C
cobas omni Wash Reagent	15–30°C

Reagents loaded onto the **cobas**® 6800/8800 Systems are stored at appropriate temperatures and their expiration is monitored by the system. The **cobas**® 6800/8800 Systems allow reagents to be used only if all of the conditions shown in Table 6 are met. The system automatically prevents use of expired reagents. Table 6 allows the user to understand the reagent handling conditions enforced by the **cobas**® 6800/8800 Systems.

Table 6 Reagent expiry conditions enforced by the **cobas**® 6800/8800 Systems

Reagent	Kit expiration date	Open-kit stability	Number of runs for which this kit can be used	On-board stability (cumulative time on board outside refrigerator)
cobas® SARS-CoV-2 – 192	Date not passed[1]	90 days from first usage[1,2]	Max 40 runs[1]	Max 40 hours[1]
cobas® SARS-CoV-2 Control Kit	Date not passed[1]	Not applicable[3]	Not applicable	Max 8 hours[1]
cobas® Buffer Negative Control Kit	Date not passed	Not applicable[3]	Not applicable	Max 10 hours
cobas omni Lysis Reagent	Date not passed	30 days from loading[2]	Not applicable	Not applicable
cobas omni MGP Reagent	Date not passed	30 days from loading[2]	Not applicable	Not applicable
cobas omni Specimen Diluent	Date not passed	30 days from loading[2]	Not applicable	Not applicable
cobas omni Wash Reagent	Date not passed	30 days from loading[2]	Not applicable	Not applicable

[1] The performance has not been established for suggested use cycles and time, but is based on similar reagents used on the same system.

[2] Time is measured from the first time that reagent is loaded onto the **cobas**® 6800/8800 Systems.

[3] Single use reagents

Additional materials required

Table 7 Materials and consumables for use on **cobas**® 6800/8800 Systems

Material	P/N
cobas omni Processing Plate	05534917001
cobas omni Amplification Plate	05534941001
cobas omni Pipette Tips	05534925001
cobas omni Liquid Waste Container	07094388001
cobas omni Lysis Reagent	06997538190
cobas omni MGP Reagent	06997546190
cobas omni Specimen Diluent	06997511190
cobas omni Wash Reagent	06997503190
Solid Waste Bag	07435967001
Solid Waste Bag and Solid Waste Container or Solid Waste Bag With Insert and Kit Drawer	07435967001 and 07094361001 or 08030073001 and 08387281001
Solid Waste Container	07094361001
cobas omni Secondary Tubes 13x75 (optional)	06438776001

Instrumentation and software required

The **cobas**® 6800/8800 software and **cobas**® SARS-CoV-2 analysis package must be installed on the instrument(s). The Instrument Gateway (IG) server will be provided with the system.

Table 8 Instrumentation

Equipment	P/N
cobas® 6800 System (Moveable Platform)	05524245001 and 06379672001
cobas® 6800 System (Fixed Platform)	05524245001 and 06379664001
cobas® 8800 System	05412722001
Sample Supply Module	06301037001
Instrument Gateway	06349595001

For additional information, please refer to the **cobas**® 6800/8800 Systems – User Assistance and/or User Guide.

Note: Contact your local Roche representative for a detailed order list for sample racks, racks for clotted tips and rack trays accepted on the instruments.

Precautions and handling requirements

Warnings and precautions

As with any test procedure, good laboratory practice is essential to the proper performance of this assay. Due to the high sensitivity of this test, care should be taken to keep reagents and amplification mixtures free of contamination.

- For *in vitro* diagnostic use.
- Positive results are indicative of active infection.
- All patient samples should be handled as if infectious, using good laboratory procedures as outlined in Biosafety in Microbiological and Biomedical Laboratories and in the CLSI Document M29-A4.[1,2] Only personnel proficient in handling infectious materials and the use of **cobas**® SARS-CoV-2 and **cobas**® 6800/8800 Systems should perform this procedure.
- All human-sourced materials should be considered potentially infectious and should be handled with universal precautions. If spillage occurs, immediately disinfect with a freshly prepared solution of 0.5% sodium hypochlorite in distilled or deionized water (dilute household bleach 1:10) or follow appropriate site procedures.
- The use of sterile disposable pipettes and nuclease-free pipette tips is recommended. Use only supplied or specified required consumables to ensure optimal test performance.
- Safety Data Sheets (SDS) are available on request from your local Roche representative.
- Closely follow procedures and guidelines provided to ensure that the test is performed correctly. Any deviation from the procedures and guidelines may affect optimal test performance.
- False positive results may occur if carryover of samples is not adequately controlled during sample handling and processing.

Reagent handling

- Handle all reagents, controls, and samples according to good laboratory practice in order to prevent carryover of samples or controls.
- Before use, visually inspect each reagent cassette, diluent, lysis reagent, and wash reagent to ensure that there are no signs of leakage. If there is any evidence of leakage, do not use that material for testing.
- **cobas omni** Lysis Reagent contains guanidine thiocyanate, a potentially hazardous chemical. Avoid contact of reagents with the skin, eyes, or mucous membranes. If contact does occur, immediately wash with generous amounts of water; otherwise, burns can occur.
- **cobas**® SARS-CoV-2 test kit, **cobas**® SARS-CoV-2 Control kit, **cobas**® Buffer Negative Control kit, **cobas omni** MGP Reagent, and **cobas omni** Specimen Diluent contain sodium azide as a preservative. Avoid contact of reagents with the skin, eyes, or mucous membranes. If contact does occur, immediately wash with generous amounts of water; otherwise, burns can occur. If these reagents are spilled, dilute with water before wiping dry.
- Do not allow **cobas omni** Lysis Reagent, which contains guanidine thiocyanate, to contact sodium hypochlorite (bleach) solution. This mixture can produce a highly toxic gas.
- Dispose of all materials that have come in contact with samples and reagents in accordance with country, state, and local regulations.

Good laboratory practice

- Do not pipette by mouth.
- Do not eat, drink, or smoke in designated work areas.
- Wear laboratory gloves, laboratory coats, and eye protection when handling samples and reagents. Gloves must be changed between handling samples and **cobas**® SARS-CoV-2 kits, **cobas**® SARS-CoV-2 Control kit, **cobas**® Buffer Negative Control kit and **cobas omni** reagents to prevent contamination. Avoid contaminating gloves when handling samples and controls.
- Wash hands thoroughly after handling samples and kit reagents, and after removing the gloves.
- Thoroughly clean and disinfect all laboratory work surfaces with a freshly prepared solution of 0.5% sodium hypochlorite in distilled or deionized water (dilute household bleach 1:10). Follow by wiping the surface with 70% ethanol.
- If spills occur on the **cobas**® 6800/8800 instrument, follow the instructions in the **cobas**® 6800/8800 Systems – User Assistance and/or User Guide to properly clean and decontaminate the surface of instrument(s).

Sample collection, transport, and storage

Note: Handle all samples and controls as if they are capable of transmitting infectious agents.

Samples

- Follow manufacturer's instructions for collection, transport and storage of samples in Copan UTM-RT System (UTM-RT) or BD™ Universal Viral Transport System (UVT).
- Sample stability when using **cobas**® SARS-CoV-2 has not been established for suggested temperatures and time, but is based on viability data from testing similar viruses in the UTM-RT or UVT Systems as stated in Copan UTM-RT System Instructions For Use and shown below:
    - After collection, the specimen should be stored at 2-25 °C and processed within 48 hours.
    - If delivery and processing exceed 48 hours, specimens should be transported in dry ice and once in laboratory frozen at -70 °C or colder.

Instructions for use

Procedural notes

- Do not use **cobas**® SARS-CoV-2 reagents, **cobas**® SARS-CoV-2 Control Kit, **cobas**® Buffer Negative Control Kit, or **cobas omni** reagents after their expiry dates.
- Do not reuse consumables. They are for one-time use only.
- Refer to the **cobas**® 6800/8800 Systems – User Assistance and/or User Guide for proper maintenance of instruments.

Running cobas® SARS-CoV-2

cobas® SARS-CoV-2 can be run with a minimum required sample volume of 0.6 mL.

Always use caution when transferring specimens from primary containers to secondary tube.

Use pipettes with aerosol-barrier or positive-displacement tips to handle specimens.

Always use a new pipette tip for each specimen.

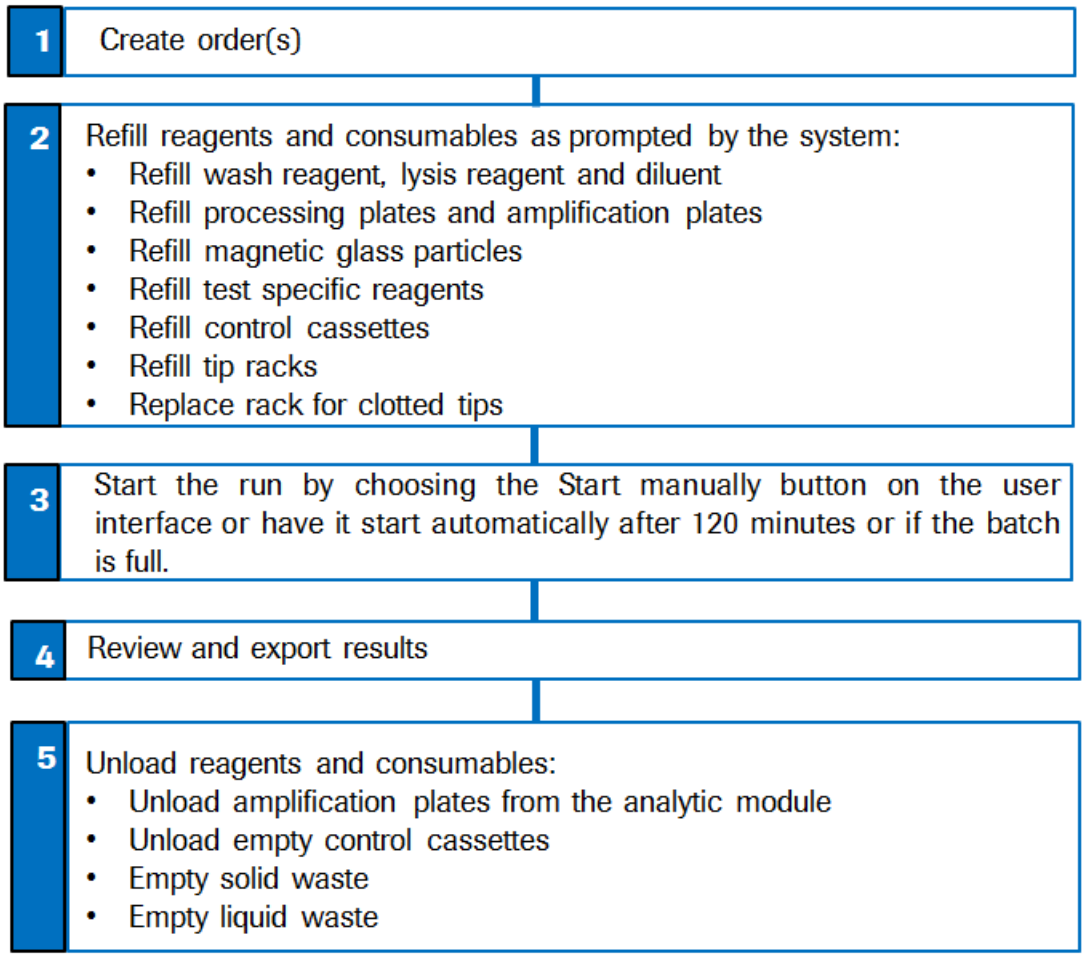
Ensure samples are equilibrated to room temperature prior to transfer into a cobas omni Secondary Tube.

Follow the steps below to transfer patient sample from a UTM-RT or UVT tube into a **cobas omni** Secondary Tube:

- Unscrew the primary sample tube cap.
- Lift the cap and any attached swab to allow a pipette to be inserted into the sample tube. Avoid lifting the swab completely out of the sample tube.
- Transfer 0.6 mL into the prepared barcoded secondary tube.
- Transfer secondary tube to a rack. Close the primary sample tube cap.

The test procedure is described in detail in the **cobas**® 6800/8800 Systems – User Assistance and/or User Guide. Figure 1 below summarizes the procedure.

Figure 1 **cobas**® SARS-CoV-2 procedure



Results

The **cobas**® 6800/8800 Systems automatically detects the SARS-CoV-2 , for each individually processed sample and control, displaying individual target results for samples as well as test validity and overall results for controls.

Quality control and validity of results

- One **cobas**® Buffer Negative Control [(-) Ctrl] and one [SARS-CoV-2 (+)C] are processed with each batch.
- In the **cobas**® 6800/8800 software and/or report, check for flags and their associated results to ensure the batch validity.
- All flags are described in the **cobas**® 6800/8800 Systems User Guide.
- The batch is valid if no flags appear for any controls. If the batch is invalid, repeat testing of the entire batch.

Validation of results is performed automatically by the **cobas**® 6800/8800 software based on negative and positive control performance.

Interpretation of results

cobas® SARS-CoV-2 for System Software v1.2

Display examples for **cobas®** SARS-CoV-2 for System Software v1.2 or higher are shown in Figure 2.

Figure 2 Example of **cobas®** SARS-CoV-2 results display for System Software v1.2

Test	Sample ID	Valid*	Flags	Sample type	Overall result*	Target 1	Target 2
SARS-CoV-2 400 µL	Swab_01	Yes		Swab	**Negative**	Negative	Negative
SARS-CoV-2 400 µL	Swab _C1	No	Y40T	Swab	**Invalid**	Invalid	Invalid
SARS-CoV-2 400 µL	Swab _B1	Yes		Swab	**Reactive**	Negative	Positive
SARS-CoV-2 400 µL	Swab _B2	Yes		Swab	**Positive**	Positive	Positive
SARS-CoV-2 400 µL	Swab _D1	Yes		Swab	**Negative**	Negative	Negative
SARS-CoV-2 400 µL	Swab _A6	Yes		Swab	**Reactive**	Positive	Negative
SARS-CoV-2 400 µL	Swab _E1	No	C01H2	Swab	**Invalid**	Positive	Invalid
SARS-CoV-2 400 µL	Swab _A2	No	C01H1	Swab	**Invalid**	Invalid	Positive
SARS-CoV-2	C16142028409042882840 4	Yes		(-) Ctrl	**Valid**	Valid	Valid
SARS-CoV-2	C16142028409300958026 4	Yes		SARS-CoV-2 (+) C	**Valid**	Valid	Valid

* The "Valid" and "Overall Result" columns are not applicable to sample results for the **cobas®** SARS-CoV-2. Values reported in these columns are not applicable and do not impact the validity of results reported within individual Target Result columns. Refer to Table 9, **cobas®** SARS-CoV-2 results interpretation, for specific instructions on test results interpretation.

cobas® SARS-CoV-2 for System Software v1.3 or higher

Display examples for **cobas®** SARS-CoV-2 for System Software v1.3 or higher are shown in Figure 3.

Figure 3 Example of **cobas®** SARS-CoV-2 results display for System Software v1.3 or higher

Test	Sample ID	Valid*	Flags	Sample type	Overall result*	Target 1	Target 2
SARS-CoV-2 400 µL	Swab_01	NA		Swab	**NA**	Negative	Negative
SARS-CoV-2 400 µL	Swab _C1	NA	Y40T	Swab	**NA**	Invalid	Invalid
SARS-CoV-2 400 µL	Swab _B1	NA		Swab	**NA**	Negative	Positive
SARS-CoV-2 400 µL	Swab _B2	NA		Swab	**NA**	Positive	Positive
SARS-CoV-2 400 µL	Swab _D1	NA		Swab	**NA**	Negative	Negative
SARS-CoV-2 400 µL	Swab _A6	NA		Swab	**NA**	Positive	Negative
SARS-CoV-2 400 µL	Swab _E1	NA	C01H2	Swab	**NA**	Positive	Invalid
SARS-CoV-2 400 µL	Swab _A2	NA	C01H1	Swab	**NA**	Invalid	Positive
SARS-CoV-2	C16142028409042882840 4	Yes		(-) Ctrl	**Valid**	Valid	Valid
SARS-CoV-2	C16142028409300958026 4	Yes		SARS-CoV-2 (+) C	**Valid**	Valid	Valid

* The "Valid" and "Overall Result" columns are not applicable to sample results for the **cobas®** SARS-CoV-2. Values reported in these columns are not applicable and do not impact the validity of results reported within individual Target Result columns. Refer to Table 9, **cobas®** SARS-CoV-2 results interpretation, for specific instructions on test results interpretation.

Interpretation of results

The following result interpretation applies to both **cobas**® 6800/8800 software version 1.2 and **cobas**® 6800/8800 software version 1.3 and higher.

For a valid batch, check each individual sample for flags in the **cobas**® 6800/8800 software and/or report. The result interpretation should be as follows:

- A valid batch may include both valid and invalid sample results.
- **The "Valid" and "Overall Result" columns are not applicable to sample results for the cobas® SARS-CoV-2. Values reported in these columns are not applicable and do not impact the validity of results reported within individual Target Result columns.**
- Invalid results for one or more target combinations are possible and are reported out specifically for each channel.
- Results of this test should only be interpreted in conjunction with information available from clinical evaluation of the patient and patient history.

Results and their corresponding interpretation for detecting SARS-CoV-2 are shown below (Table 9).

Table 9 **cobas®** SARS-CoV-2 results interpretation

Target 1	Target 2	Interpretation
Positive	**Positive**	All Target Results were valid. Result for SARS-CoV-2 RNA is Detected.
Positive	**Negative**	All Target Results were valid. Result for SARS-CoV-2 RNA is Detected. A positive Target 1 result and a negative Target 2 result is suggestive of 1) a sample at concentrations near or below the limit of detection of the test, 2) a mutation in the Target 2, target region, or 3) other factors.
Negative	**Positive**	All Target Results were valid. Result for SARS-CoV-2 RNA is Presumptive Positive. A negative Target 1 result and a positive Target 2 result is suggestive of 1) a sample at concentrations near or below the limit of detection of the test, 2) a mutation in the Target 1 target region in the oligo binding sites, or 3) infection with some other Sarbecovirus (e.g., SARS-CoV or some other Sarbecovirus previously unknown to infect humans), or 4) other factors. Sample should be retested. For samples with a repeated Presumptive Positive result, additional confirmatory testing may be conducted, if it is necessary to differentiate between SARS-CoV-2 and SARS-CoV-1 or other Sarbecovirus currently unknown to infect humans, for epidemiological purposes or clinical management.
Negative	**Negative**	All Target Results were valid. Result for SARS-CoV-2 RNA is Not Detected.
Positive	**Invalid**	Not all Target Results were valid. Result for SARS-CoV-2 RNA is Detected.
Invalid	**Positive**	Not all Target Results were valid. Result for SARS-CoV-2 RNA is Presumptive Positive. Sample should be retested. For samples with a repeated Presumptive Positive result, additional confirmatory testing may be conducted, if it is necessary to differentiate between SARS-CoV-2 and SARS-CoV-1 or other Sarbecovirus currently unknown to infect humans, for epidemiological purposes or clinical management.
Negative	**Invalid**	Not all Target Results were valid. Sample should be retested. If the result is still invalid, a new specimen should be obtained.
Invalid	**Negative**	Not all Target Results were valid. Sample should be retested. If the result is still invalid, a new specimen should be obtained.
Invalid	**Invalid**	All Target Results were invalid. Sample should be retested. If the result is still invalid, a new specimen should be obtained.

Procedural limitations

- **cobas**® SARS-CoV-2 has been evaluated only for use in combination with the **cobas**® SARS-CoV-2 Control Kit, **cobas**® Buffer Negative Control Kit, **cobas omni** MGP Reagent, **cobas omni** Lysis Reagent, **cobas omni** Specimen Diluent, and **cobas omni** Wash Reagent for use on the **cobas**® 6800/8800 Systems.
- Reliable results depend on proper sample collection, storage and handling procedures.
- This test is intended to be used for the detection of SARS-CoV-2 RNA in nasopharyngeal and oropharyngeal swab samples collected in a Copan UTM-RT System (UTM-RT) or BD™ Universal Viral Transport System (UVT). Testing of other sample types with **cobas**® SARS-CoV-2 may result in inaccurate results.
- Detection of SARS-CoV-2 RNA may be affected by sample collection methods, patient factors (e.g., presence of symptoms), and/or stage of infection.
- As with any molecular test, mutations within the target regions of **cobas**® SARS-CoV-2 could affect primer and/or probe binding resulting in failure to detect the presence of virus.
- Due to inherent differences between technologies, it is recommended that, prior to switching from one technology to the next, users perform method correlation studies in their laboratory to qualify technology differences. One hundred percent agreement between the results should not be expected due to aforementioned differences between technologies. Users should follow their own specific policies/procedures.
- False negative or invalid results may occur due to interference. The Internal Control is included in **cobas**® SARS-CoV-2 to help identify the specimens containing substances that may interfere with nucleic acid isolation and PCR amplification.
- The addition of AmpErase enzyme into the **cobas**® SARS-CoV-2 Master Mix reagent enables selective amplification of target RNA; however, good laboratory practices and careful adherence to the procedures specified in this Instructions For Use document are necessary to avoid contamination of reagents.

Non-clinical performance evaluation

Analytical sensitivity

Limit of detection (LoD) studies determine the lowest detectable concentration of SARS-CoV-2 at which greater or equal to 95% of all (true positive) replicates test positive.

To determine the LoD, a cultured virus of an isolate from a US patient (USA-WA1/2020, catalog number NR-52281, lot number 70033175, 2.8E+05 $TCID_{50}$/mL^) was serially diluted in simulated clinical matrix. A total of 7 concentration levels, with 3-fold serial dilutions between the levels, were tested with a total of 21 replicates per concentration, with an additional 10 replicates of a blank sample (i.e, simulated clinical matrix).

As shown in Table 10, the concentration level with observed hit rates greater than or equal to 95% were 0.009 and 0.003 $TCID_{50}$/mL for SARS-CoV-2 (Target 1) and pan-Sarbecovirus (Target 2), respectively. As shown in Table 11, the Probit predicted 95% hit rates were 0.007 and 0.004 $TCID_{50}$/mL for SARS-CoV-2 (Target 1) and pan-Sarbecovirus (Target 2), respectively.

Table 10 LoD determination using USA-WA1/2020 strain

Strain	Concentration [$TCID_{50}$/mL]	Total valid results	Hit rate [%]^		Mean Ct*	
			Target 1	Target 2	Target 1	Target 2
USA-WA1/2020§ (stock concentration 2.8E+05 $TCID_{50}$/mL)	0.084	21	100	100	31.0	33.0
	0.028	21	100	100	31.8	34.1
	0.009	21	100	100	32.7	35.2
	0.003	21	38.1	100	33.5	36.4
	0.001	21	0	52.4	n/a	37.9
	0.0003	21	0	14.3	n/a	37.2
	0.0001	21	0	9.5	n/a	38.5
	0 (blank)	10	0	0	n/a	n/a

§ Reagent was deposited by the Centers for Disease Control and Prevention and obtained through BEI Resources, NIAID, NIH: SARS-Related Coronavirus 2, Isolate USA-WA1/2020, NR-52281

^ All replicates where Target 1 was positive were also positive for Target 2.

* Calculations only include positive results.

Table 11 Probit predicted 95% hit rates using USA-WA1/2020 strain

Strain	Probit Predicted 95% Hit Rate [$TCID_{50}$/mL]	
	Target 1	Target 2
USA-WA1/2020 (stock concentration 2.8E+05 $TCID_{50}$/mL)	0.007 (95% CI: 0.005 – 0.036)	0.004 (95% CI: 0.002 – 0.009)

Cross-reactivity

In silico analysis

The *in silico* analysis for possible cross-reactions with all the organisms listed in Table 12 was conducted by mapping primers in **cobas**® SARS-CoV-2 individually to the sequences downloaded from NCBI and GISAID databases. If any two of the primers were mapped to a sequence on opposite strands with short distance apart, potential amplifications were flagged. No potential unintended cross reactivity is expected based on this *in silico* analysis.

Table 12 In silico analysis for SARS-CoV-2

Strain	*In Silico* Analysis for % Identity to Target 1 (nCoV)	*In Silico* Analysis for % Identity to Target 2 (Pan-Sarbecovirus 1)
CoV 229E	74.47	No alignment was found*
CoV OC43	72.26	No alignment was found*
CoV HKU1	76.52	No alignment was found*
CoV NL63	71.32	No alignment was found*
SARS-CoV	95.04	100
MERS	No alignment was found*	No alignment was found*
AdV	No alignment was found*	No alignment was found*
HMPV	No alignment was found*	No alignment was found*
HPIV1	No alignment was found*	No alignment was found*
HPIV2	No alignment was found*	No alignment was found*
HPIV3	No alignment was found*	No alignment was found*
HPIV4	No alignment was found*	No alignment was found*
Flu A	No alignment was found*	No alignment was found*
Flu B	No alignment was found*	No alignment was found*
EV	No alignment was found*	No alignment was found*
RSV	No alignment was found*	No alignment was found*
RV	No alignment was found*	No alignment was found*
Chlamydia pneumoniae	No alignment was found*	No alignment was found*
Haemophilus influenzae	No alignment was found*	No alignment was found*

Strain	***In Silico* Analysis for % Identity to Target 1 (nCoV)**	***In Silico* Analysis for % Identity to Target 2 (Pan-Sarbecovirus 1)**
Legionella pneumophila	No alignment was found*	No alignment was found*
MTB Mycobacterium bovis subsp. Bovis	No alignment was found*	No alignment was found*
Streptococcus pneumoniae	No alignment was found*	No alignment was found*
Streptococcus pyrogenes	No alignment was found*	No alignment was found*
Bordetella pertussis	No alignment was found*	No alignment was found*
Mycoplasma pneumoniae	No alignment was found*	No alignment was found*
Pneumocystis jirovecii	No alignment was found*	No alignment was found*
Influenza C	No alignment was found*	No alignment was found*
Parechovirus	No alignment was found*	No alignment was found*
Candida albicans	No alignment was found*	No alignment was found*
Corynebacterium diphtheriae	No alignment was found*	No alignment was found*
Legionella non-pneumophila	No alignment was found*	No alignment was found*
Bacillus anthracosis (Anthrax)	No alignment was found*	No alignment was found*
Moraxella cararrhalis	No alignment was found*	No alignment was found*
Neisseria elongate and meningitides	No alignment was found*	No alignment was found*
Pseudomonas aeruginosa	No alignment was found*	No alignment was found*
Staphylococcus epidermis	No alignment was found*	No alignment was found*
Staphylococcus salivarius	No alignment was found*	No alignment was found*
Leptospirosis	No alignment was found*	No alignment was found*
Chlamydia psittaci	No alignment was found*	No alignment was found*
Coxiella burneti (Q-Fever)	No alignment was found*	No alignment was found*
Streptococcus aureus	No alignment was found*	No alignment was found*

Note: * The amplicon sequences were blasted against all the exclusive sequences with very low stringency cutoff (50% and 100bp). No alignment were found passing the cutoff and no concerns for cross-reactivity were observed.

Cross reactivity testing

Cross-reactivity of **cobas**® SARS-CoV-2 was evaluated by testing whole organisms. As listed in Table13, a panel of multiple unique sub-species of microorganisms were tested. High titer stocks of the potentially cross-reacting microorganisms were spiked into negative simulated clinical matrix to a concentration level of 1.0E+05 units/mL for viruses and 1.0E+06 units/mL for other microorganisms, unless otherwise noted.

None of the organisms tested interfered with **cobas**® SARS-CoV-2 performance by generating false positive results.

Table13 Cross-reactivity test results

Microorganism	Concentration	Target 1 Result	Target 2 Result
Human coronavirus 229E	1.0E+05 $TCID_{50}$/mL	Negative	Negative
Human coronavirus OC43	1.0E+05 $TCID_{50}$/mL	Negative	Negative
Human coronavirus HKU1	1.0E+05 cp/mL	Negative	Negative
Human coronavirus NL63	1.0E+05 $TCID_{50}$/mL	Negative	Negative
MERS coronavirus	1.0E+05 genomic equivalent/mL	Negative	Negative
SARS coronavirus	1.0E+05 PFU/mL	Negative	Positive
Adenovirus B (Type 34)	1.0E+05 $TCID_{50}$/mL	Negative	Negative
Human Metapneumovirus (hMPV)	1.0E+05 $TCID_{50}$/mL	Negative	Negative
Parainfluenza virus Type 1	1.0E+05 $TCID_{50}$/mL	Negative	Negative
Parainfluenza virus Type 2	1.0E+05 $TCID_{50}$/mL	Negative	Negative
Parainfluenza virus Type 3	1.0E+05 $TCID_{50}$/mL	Negative	Negative
Parainfluenza virus Type 4	1.0E+05 $TCID_{50}$/mL	Negative	Negative
Influenza A (H1N1)	1.0E+05 $TCID_{50}$/mL	Negative	Negative
Influenza B	1.0E+05 $TCID_{50}$/mL	Negative	Negative
Enterovirus E (Type 1)	1.0E+05 $TCID_{50}$/mL	Negative	Negative
Respiratory syncytial virus	1.0E+05 PFU/mL	Negative	Negative
Rhinovirus	1.0E+05 $TCID_{50}$/mL	Negative	Negative
Chlamydia pneumonia	1.0E+06 $TCID_{50}$/mL	Negative	Negative
Haemophilus influenzae	1.0E+06 CFU/mL	Negative	Negative
Legionella pneumophila	1.0E+06 CFU/mL	Negative	Negative
Mycobacterium tuberculosis	1.0E+06 cells/mL	Negative	Negative
Streptococcus pneumonia	1.0E+06 CFU/mL	Negative	Negative
Streptococcus pyrogenes	1.0E+06 CFU/mL	Negative	Negative
Bordetella pertussis	1.0E+06 CFU/mL	Negative	Negative
Mycoplasma pneumoniae	1.0E+06 CFU/mL	Negative	Negative
Pooled human nasal wash	5 - 50%	Negative	Negative

Sample type equivalency

Equivalence between nasopharyngeal swab (NPS) and oropharyngeal swab (OPS) sample types was evaluated using cultured virus (USA-WA1/2020 strain) spiked into paired negative samples (individual samples, not pooled) to prepare contrived low positive (approximately 1.5x Target 1 LoD) and moderate positive (approximately 4x Target 1 LoD) samples for each sample type. A total of 21 low positive paired samples, 11 moderate positive paired samples, and 11 negative paired samples were tested.

As shown in Table14, all low positive and moderate positive paired samples were positive in both sample matrices. All negative paired samples were negative in both sample types. The observed Ct values for contrived positive samples were comparable in both sample types.

Table14 Nasopharyngeal vs oropharyngeal sample type comparison

Sample Type	Sample Concentration	N	Target 1		Target 2	
			% Positive	Mean Ct (95% CI)	% Positive	Mean Ct (95% CI)
NPS	~1.5x LoD (Target 1)	21	100	31.9 (31.7 – 32.0)	100	33.6 (33.5 – 33.7)
OPS			100	32.2 (31.8 – 32.6)	100	33.7 (33.4 – 34.1)
NPS	~4x LoD (Target 1)	11	100	30.9 (30.3 – 31.5)	100	32.2 (31.6 – 32.9)
OPS			100	31.5 (31.2 – 31.9)	100	32.7 (32.4 – 33.0)
NPS	Negative	11	0	n/a	0	n/a
OPS			0	n/a	0	n/a

Clinical evaluation

The performance of **cobas**® SARS-CoV-2 with prospectively collected nasopharyngeal swab clinical samples was evaluated using 100 individual negative clinical samples and 50 contrived positive clinical samples collected from patients with signs and symptoms of an upper respiratory infection.

Clinical samples were collected by qualified personnel according to the package insert of the collection device. Samples were handled as described in the package insert of the collection devise and stored frozen until use. Samples were tested to be negative by a commercially available nucleic acid test for the qualitative detection of microorganisms associated with common upper respiratory tract infections.

Low positive and moderate positive contrived positive clinical samples were prepared by spiking cultured virus (USA-WA1/2020 strain) into individual negative clinical samples to approximately ~1.5x LoD (Target 1) (25 samples) and ~4x LoD (Target 1) (25 samples), respectively.

As shown in Table15 all low positive and moderate positive samples were positive and all negative samples were negative in the background of individual clinical sample matrix.

Table15 Clinical evaluation with nasopharyngeal swab samples

Sample Concentration	N	Target 1		Target 2	
		% positive (two-sided 95% CI)	Mean Ct	% positive (two-sided 95% CI	Mean Ct
~1.5x LoD	25	100 (86.7 – 100)	31.6	100 (89 – 100)	33.2
~4x LoD	25	100 (86.7 – 100)	31.1	100 (89 – 100)	32.4
Negative	100	0 (n/a)	n/a	0 (n/a)	n/a

Performance against the expected results are:

Positive Percent Agreement 100% (50/50; 95% CI: 86.7% - 100%)
Negative Percent Agreement 100% (100/100; 95% CI: 96.3% - 100%)

Additional information

Key test features

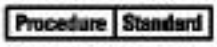
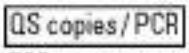
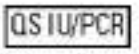
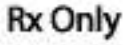
Sample type	Nasopharyngeal and oropharyngeal swab samples collected in the Copan UTM-RT System or the BD™ UVT System
Minimum amount of sample required	0.6 mL*
Sample processing volume	0.4 mL
Test duration	Results are available within less than 3.5 hours after loading the sample on the system.

*Dead volume of 0.2 mL is identified for the **cobas omni** Secondary tubes. Other tubes compatible with **cobas**® 6800/8800 Systems (consult User Assistance Guide) may have different dead volume and require more or less minimum volume.

Symbols

The following symbols are used in labeling for Roche PCR diagnostic products.

Table 16 Symbols used in labeling for Roche PCR diagnostics products

	Ancillary Software		Lower Limit of Assigned Range		Negative Control
	Authorized representative in the European community		Upper Limit of Assigned Range		Positive Control
	Barcode Data Sheet		Store in the dark		Control
	Batch code		Contains sufficient for <*n*> tests		Assigned Range (copies/mL)
	Biological risks		Temperature limit		Assigned Range (IU/mL)
	Catalogue number		Test Definition File		Standard Procedure
	Consult instructions for use		Manufacturer		Ultrasensitive Procedure
	Contents of kit		Use-by date		QS copies per PCR reaction, use the QS copies per PCR reaction in calculation of the results.
	Distributed by		Global Trade Item Number		QS IU per PCR reaction, use the QS International Units (IU) per PCR reaction in calculation of the results.
	For IVD performance evaluation only		Serial number		This product fulfills the requirements of the European Directive 98/79 EC for *in vitro* diagnostic medical devices.
	US Only: Federal law restricts this device to sale by or on the order of a physician.		Date of manufacture		
	*In Vitro* diagnostic medical device		Do not reuse		

US Customer Technical Support 1-800-526-1247

Manufacturer and distributors

Table 17 Manufacturer and distributors

Roche Molecular Systems, Inc.
1080 US Highway 202 South
Branchburg, NJ 08876 USA
www.roche.com

Roche Diagnostics GmbH
Sandhofer Strasse 116
68305 Mannheim, Germany

Roche Diagnostics
9115 Hague Road
Indianapolis, IN 46250-0457 USA
(For Technical Assistance call the
Roche Response Center
toll-free: 1-800-526-1247)

Trademarks and patents

See http://www.roche-diagnostics.us/patents

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References

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2. Clinical and Laboratory Standards Institute (CLSI). Protection of laboratory workers from occupationally acquired infections. Approved Guideline-Fourth Edition. CLSI Document M29-A4:Wayne, PA;CLSI, 2014.

Document revision

Document Revision Information	
Doc Rev. 1.0 03/2020	First Publishing.

LabSpecimenCollectionDate1	LabTestResult1	Ct Value RdRP for LDT
		34.9
20-Mar-20	Positive	27.652
13-Mar-20	Positive	
28-Mar-20	Positive	27.74
14-Mar-20	Positive	UNK
23-Mar-20	Positive	33.09
13-Mar-20	Positive	
15-Mar-20	Positive	21.102
16-Mar-20	Positive	22.328
16-Mar-20	Positive	25.905
		32.5
14-Mar-20	Positive	
22-Mar-20	Positive	34.7
17-Mar-20	Positive	22.92
31-Mar-20	Positive	34.7
28-Mar-20	Positive	23.77
19-Mar-20	Positive	26.284
17-Mar-20	Positive	
14-Mar-20	Positive	20.519
15-Mar-20	Positive	15.943
15-Mar-20	Positive	24.441
22-Mar-20	Positive	33.3
18-Mar-20	Positive	18.954
15-Mar-20	Positive	22.526
19-Mar-20	Positive	21.5
21-Mar-20	Positive	25.2
3-Apr-20	Positive	38.2
31-Mar-20	Positive	
19-Mar-20	Positive	24.4
21-Mar-20	Positive	20.27
23-Mar-20	Positive	27.375
23-Mar-20	Positive	33.67
26-Mar-20	Positive	30.574
29-Mar-20	Positive	29.048
23-Mar-20	Positive	21.912
22-Mar-20	Positive	24.94
22-Mar-20	Positive	23.94
28-Mar-20	Positive	30.471
28-Mar-20	Positive	20.75
29-Mar-20	Positive	32.29
23-Mar-20	Positive	18.53
20-Mar-20	Positive	35.886
22-Mar-20	Positive	21.9
24-Mar-20	Positive	32.014
29-Mar-20	Positive	33.96
20-Mar-20	Positive	22.357

31-Mar-20	Positive	32.21
23-Mar-20	Positive	30.064
3-Apr-20	Positive	
20-Mar-20	Positive	
20-Mar-20	Positive	29.691
23-Mar-20	Positive	18.912
20-Mar-20	Positive	37.8
19-Mar-20	Positive	20.1
23-Mar-20	Positive	25.806
21-Mar-20	Positive	28.057
27-Mar-20	Positive	25.186
25-Mar-20	Positive	25.254
25-Mar-20	Positive	24.418
21-Mar-20	Positive	22.603
18-Mar-20	Positive	20.738
19-Mar-20	Positive	20.2
21-Mar-20	Positive	29.104
20-Mar-20	Positive	20.503
29-Mar-20	Positive	26.113
21-Mar-20	Positive	26.67
25-Mar-20	Positive	24.85
23-Mar-20	Positive	30.9
22-Mar-20	Positive	24.361
27-Mar-20	Positive	33.589
22-Mar-20	Positive	22.372
25-Mar-20	Positive	
22-Mar-20	Positive	16.94
26-Mar-20	Positive	34.93
20-Mar-20	Positive	24.881
21-Mar-20	Positive	23.839
24-Mar-20	Positive	20.012
22-Mar-20	Positive	27.909
25-Mar-20	Positive	31.8
21-Mar-20	Positive	18.034
25-Mar-20	Positive	25.673
20-Mar-20	Positive	34.4
2-Apr-20	Positive	
23-Mar-20	Positive	35.385
25-Mar-20	Positive	24.482
23-Mar-20	Positive	25.594
26-Mar-20	Positive	27.34
21-Mar-20	Positive	25.4
26-Mar-20	Positive	30.2
22-Mar-20	Positive	21.41
25-Mar-20	Positive	16.39
22-Mar-20	Positive	23.1

2-Apr-20	Positive	29.1
22-Mar-20	Positive	19.2
26-Mar-20	Positive	32.83
26-Mar-20	Positive	21.43
25-Mar-20	Positive	24.71
23-Feb-20	Positive	22.72
22-Mar-20	Positive	31.21
23-Mar-20	Positive	22.61
29-Mar-20	Positive	31.843
29-Mar-20	Positive	28.965
25-Mar-20	Positive	31.62
25-Mar-20	Positive	31.19
21-Mar-20	Positive	27.199
26-Mar-20	Positive	26.5
7-Apr-20	Positive	
31-Mar-20	Positive	30.457
26-Mar-20	Positive	30.9
2-Apr-20	Positive	27.22
26-Mar-20	Positive	26.236
4-Apr-20	Positive	30.564
3-Apr-20	Positive	39.785
7-Apr-20	Positive	34.797
28-Mar-20	Positive	27.938
23-Mar-20	Positive	28.304
22-Mar-20	Positive	18.25
1-Apr-20	Positive	21.2
23-Mar-20	Positive	31.21
4-Apr-20	Positive	34.96
27-Mar-20	Positive	25.16
28-Mar-20	Positive	24.88
27-Mar-20	Positive	30.635
31-Mar-20	Positive	
31-Mar-20	Positive	
4-Apr-20	Positive	26.084
4-Apr-20	Positive	28.614
30-Mar-20	Positive	
27-Mar-20	Positive	30.311
26-Mar-20	Positive	18.82
27-Mar-20	Positive	19.315
26-Mar-20	Positive	26.104
31-Mar-20	Positive	38.127
9-Apr-20	Positive	35.1
24-Mar-20	Positive	17.794
25-Mar-20	Positive	28.87
25-Mar-20	Positive	18.27
1-Apr-20	Positive	
4-Apr-20	Positive	32.739

25-Mar-20	Positive	19.858
28-Mar-20	Positive	16.85
12-Apr-20	Positive	37.79
29-Mar-20	Positive	
25-Mar-20	Positive	22.509
25-Mar-20	Positive	25.202
27-Mar-20	Positive	23.8
8-Apr-20	Positive	
26-Mar-20	Positive	25.329
26-Mar-20	Positive	23.65
29-Mar-20	Positive	27.778
26-Mar-20	Positive	22.573
26-Mar-20	Positive	34.34
30-Mar-20	Positive	
26-Mar-20	Positive	22.811
25-Mar-20	Positive	32.79
27-Mar-20	Positive	20.51
1-Apr-20	Positive	31.508
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31-Mar-20	Positive	22.587
27-Mar-20	Positive	28.324
27-Mar-20	Positive	32.9
27-Mar-20	Positive	20.59
31-Mar-20	Positive	
27-Mar-20	Positive	22.9
1-Apr-20	Positive	
27-Mar-20	Positive	20.939
7-Apr-20	Positive	
30-Mar-20	Positive	
29-Mar-20	Positive	22.015
27-Mar-20	Positive	25.638
29-Mar-20	Positive	15.305
25-Mar-20	Positive	23.6
28-Mar-20	Positive	25.49
30-Mar-20	Positive	24.8
28-Mar-20	Positive	32.898
2-Apr-20	Positive	
2-Apr-20	Positive	
31-Mar-20	Positive	
28-Mar-20	Positive	26.2
3-Apr-20	Positive	31.942
1-Apr-20	Positive	29.7
28-Mar-20	Positive	33.4
17-Apr-20	Positive	
28-Mar-20	Positive	22.662
3-Apr-20	Positive	29.172
1-Apr-20	Positive	

28-Mar-20	Positive	19.513
1-Apr-20	Positive	
29-Mar-20	Positive	33.21
29-Mar-20	Positive	27.117
29-Mar-20	Positive	26.842
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10-Apr-20	Positive	
8-Apr-20	Positive	32.8
4-Apr-20	Positive	
31-Mar-20	Positive	24.337
29-Mar-20	Positive	32.509
31-Mar-20	Positive	23
28-Mar-20	Positive	24.29
29-Mar-20	Positive	
29-Mar-20	Positive	24.751
29-Mar-20	Positive	30.95
9-Apr-20	Positive	32.995
29-Mar-20	Positive	
29-Mar-20	Positive	32.18
28-Mar-20	Positive	26.799
2-Apr-20	Positive	22.8
31-Mar-20	Positive	28.4
6-Apr-20	Positive	
3-Apr-20	Positive	25.6
2-Apr-20	Positive	29.952
5-Apr-20	Positive	
5-Apr-20	Positive	25.92
4-Apr-20	Positive	27.96
30-Mar-20	Positive	
30-Mar-20	Positive	34.458
31-Mar-20	Positive	
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3-Apr-20	Positive	27.643
30-Mar-20	Positive	30.9
31-Mar-20	Positive	30.2
2-Apr-20	Positive	27.853
5-Apr-20	Positive	26.7
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29-Mar-20	Positive	26.429
30-Mar-20	Positive	
30-Mar-20	Positive	23.3
2-Apr-20	Positive	18.9
30-Mar-20	Positive	
22-Apr-20	Positive	
6-Apr-20	Positive	24.789
9-Apr-20	Positive	28.114
31-Mar-20	Positive	26.7

3-Apr-20	Positive	
2-Apr-20	Positive	
31-Mar-20	Positive	35.9
9-Apr-20	Positive	24.511
4-Apr-20	Positive	30.29
8-Apr-20	Positive	30.4
6-Apr-20	Positive	25.92
31-Mar-20	Positive	26.7
1-Apr-20	Positive	27.88
3-Apr-20	Positive	
31-Mar-20	Positive	19.9
31-Mar-20	Positive	35.4
3-Apr-20	Positive	
3-Apr-20	Positive	22.5
5-Apr-20	Positive	18.47
10-Apr-20	Positive	35.304
7-Apr-20	Positive	32.6
2-Apr-20	Positive	29.173
8-Apr-20	Positive	34.314
7-May-20	Positive	
4-Apr-20	Positive	21.373
5-Apr-20	Positive	
30-Mar-20	Positive	
15-Apr-20	Positive	
4-Apr-20	Positive	28.003
8-Apr-20	Positive	25.153
6-Apr-20	Positive	35.5
3-Apr-20	Positive	24.6
2-Apr-20	Positive	
1-Apr-20	Positive	32.389
1-Apr-20	Positive	31.619
2-Apr-20	Positive	
2-Apr-20	Positive	24.148
3-Apr-20	Positive	23.8
3-Apr-20	Positive	36.449
6-Apr-20	Positive	27.693
2-Apr-20	Positive	
2-Apr-20	Positive	33.381
2-Apr-20	Positive	33.83
4-Apr-20	Positive	27.44
4-Apr-20	Positive	25.952
2-Apr-20	Positive	
2-Apr-20	Positive	35.622
4-Apr-20	Positive	
2-Apr-20	Positive	
2-Apr-20	Positive	28.899
4-Apr-20	Positive	33.861

4-Apr-20	Positive	24.415
2-Apr-20	Positive	32.9
3-Apr-20	Positive	35.476
6-Apr-20	Positive	23.3
7-Apr-20	Positive	24.8
12-Apr-20	Positive	
6-Apr-20	Positive	
6-Apr-20	Positive	31.241
6-Apr-20	Positive	
2-Apr-20	Positive	17.394
4-Apr-20	Positive	
2-Apr-20	Positive	24.194
2-Apr-20	Positive	30.97
7-Apr-20	Positive	
2-Apr-20	Positive	28.4
2-Apr-20	Positive	
2-Apr-20	Positive	
12-Apr-20	Positive	
6-Apr-20	Positive	27.04
7-Apr-20	Positive	21.8
3-Apr-20	Positive	
3-Apr-20	Positive	
7-Apr-20	Positive	24.7
5-Apr-20	Positive	29.24
8-Apr-20	Positive	33.227
3-Apr-20	Positive	
3-Apr-20	Positive	
3-Apr-20	Positive	
3-Apr-20	Positive	29.314
3-Apr-20	Positive	
3-Apr-20	Positive	
9-Apr-20	Positive	26.62
3-Apr-20	Positive	
3-Apr-20	Positive	27.951
2-Apr-20	Positive	25.581
3-Apr-20	Positive	
2-Apr-20	Positive	31.7
3-Apr-20	Positive	
18-Apr-20	Positive	27.564
3-Apr-20	Positive	
3-Apr-20	Positive	29.817
5-Apr-20	Positive	21.67
3-Apr-20	Positive	
4-Apr-20	Positive	21.177
9-Apr-20	Positive	
3-Apr-20	Positive	
3-Apr-20	Positive	

4-Apr-20	Positive	
9-Apr-20	Positive	31.6
5-Apr-20	Positive	25.61
4-Apr-20	Positive	22.799
8-Apr-20	Positive	
4-Apr-20	Positive	33.77
7-Apr-20	Positive	20.328
8-Apr-20	Positive	27.122
9-Apr-20	Positive	24.97
13-Apr-20	Positive	
8-Apr-20	Positive	
13-Apr-20	Positive	
9-Apr-20	Positive	
3-Apr-20	Positive	39.691
4-Apr-20	Positive	25.325
4-Apr-20	Positive	32.697
7-Apr-20	Positive	29.2
7-Apr-20	Positive	27.731
5-Apr-20	Positive	18.88
5-Apr-20	Positive	
5-Apr-20	Positive	24.479
11-Apr-20	Positive	
13-Apr-20	Positive	
18-Apr-20	Positive	34.392
6-Apr-20	Positive	29.119
13-Apr-20	Positive	
5-Apr-20	Positive	28.52
6-Apr-20	Positive	24.6
6-Apr-20	Positive	
7-Apr-20	Positive	23.598
5-Apr-20	Positive	
4-Apr-20	Positive	
7-Apr-20	Positive	34.995
6-Apr-20	Positive	
3-Apr-20	Positive	
5-Apr-20	Positive	
6-Apr-20	Positive	
7-Apr-20	Positive	33.131
7-Apr-20	Positive	30.212
8-Apr-20	Positive	
5-Apr-20	Positive	
6-Apr-20	Positive	33.95
11-Apr-20	Positive	
6-Apr-20	Positive	25.09
6-Apr-20	Positive	
11-Apr-20	Positive	37.948
9-Apr-20	Positive	29.39

9-Apr-20	Positive	31.378
10-Apr-20	Positive	21.2
10-Apr-20	Positive	15.01
6-Apr-20	Positive	30.5
6-Apr-20	Positive	35.57
6-Apr-20	Positive	26.459
5-Apr-20	Positive	
9-Apr-20	Positive	33.33
15-Apr-20	Positive	31.714
6-Apr-20	Positive	29.4
15-Apr-20	Positive	
7-Apr-20	Positive	33.346
6-Apr-20	Positive	18.5
6-Apr-20	Positive	
6-Apr-20	Positive	26.81
6-Apr-20	Positive	
6-Apr-20	Positive	
6-Apr-20	Positive	
10-Apr-20	Positive	
7-Apr-20	Positive	21.962
13-Apr-20	Positive	33.943
9-Apr-20	Positive	15.9
7-Apr-20	Positive	32.662
22-Apr-20	Positive	
7-Apr-20	Positive	33.712
7-Apr-20	Positive	31.28
8-Apr-20	Positive	33.03
7-Apr-20	Positive	35.4
8-Apr-20	Positive	22.2
9-Apr-20	Positive	33.958
9-Apr-20	Positive	24
7-Apr-20	Positive	
16-Apr-20	Positive	26.076
7-Apr-20	Positive	25.89
7-Apr-20	Positive	25.086
14-Apr-20	Positive	
7-Apr-20	Positive	31.955
7-Apr-20	Positive	20.503
7-Apr-20	Positive	34.285
6-Apr-20	Positive	22.81
7-Apr-20	Positive	33.9
7-Apr-20	Positive	31.491
10-Apr-20	Positive	22.185
15-Apr-20	Positive	21.455
9-Apr-20	Positive	
13-Apr-20	Positive	
9-Apr-20	Positive	25.401

8-Apr-20	Positive	33.9
8-Apr-20	Positive	
18-Apr-20	Positive	
14-Apr-20	Positive	33.98
8-Apr-20	Positive	33.5
10-Apr-20	Positive	18.21
9-Apr-20	Positive	24.4
7-Apr-20	Positive	
28-Apr-20	Positive	31.017
8-Apr-20	Positive	31.4
12-Apr-20	Positive	22.258
8-Apr-20	Positive	
17-Apr-20	Positive	36.64
12-Apr-20	Positive	31.14
8-Apr-20	Positive	
10-Apr-20	Positive	
9-Apr-20	Positive	23.036
7-Apr-20	Positive	35.762
18-Apr-20	Positive	
8-Apr-20	Positive	35.023
7-Apr-20	Positive	36.417
14-Apr-20	Positive	
16-Apr-20	Positive	32.95
9-Apr-20	Positive	18.99
9-Apr-20	Positive	22.8
10-Apr-20	Positive	
9-Apr-20	Positive	24.471
9-Apr-20	Positive	
7-Apr-20	Positive	21.388
13-Apr-20	Positive	27.678
14-Apr-20	Positive	21.218
15-Apr-20	Positive	
7-Apr-20	Positive	32.374
9-Apr-20	Positive	35.3
8-Apr-20	Positive	29.362
8-Apr-20	Positive	
8-Apr-20	Positive	
14-Apr-20	Positive	
8-Apr-20	Positive	20.65
8-Apr-20	Positive	31.8
14-Apr-20	Positive	27.816
9-Apr-20	Positive	30.4
9-Apr-20	Positive	37.6
13-Apr-20	Positive	
10-Apr-20	Positive	25.61
12-Apr-20	Positive	30.816
9-Apr-20	Positive	22.83

9-Apr-20	Positive	18.75
8-Apr-20	Positive	
8-Apr-20	Positive	
7-Apr-20	Positive	36.7
7-Apr-20	Positive	29.751
14-Apr-20	Positive	29.969
8-Apr-20	Positive	25
16-Apr-20	Positive	
9-Apr-20	Positive	25.321
9-Apr-20	Positive	31.3
8-Apr-20	Positive	
15-Apr-20	Positive	
14-Apr-20	Positive	
13-Apr-20	Positive	
9-Apr-20	Positive	24.8
9-Apr-20	Positive	20.84
9-Apr-20	Positive	36.795
7-Apr-20	Positive	36.456
9-Apr-20	Positive	32.905
12-Apr-20	Positive	25.408
13-Apr-20	Positive	29.001
13-Apr-20	Positive	33.469
10-Apr-20	Positive	26.67
13-Apr-20	Positive	27.783
10-Apr-20	Positive	35.681
10-Apr-20	Positive	31.68
13-Apr-20	Positive	34.204
10-Apr-20	Positive	28.802
9-Apr-20	Positive	34.345
10-Apr-20	Positive	
14-Apr-20	Positive	22.445
8-Apr-20	Positive	33.652
10-Apr-20	Positive	
10-Apr-20	Positive	35.77
10-Apr-20	Positive	
10-Apr-20	Positive	23.789
15-Apr-20	Positive	
12-Apr-20	Positive	28.427
10-Apr-20	Positive	28.411
10-Apr-20	Positive	
8-Apr-20	Positive	28.595
18-Apr-20	Positive	22.21
12-Apr-20	Positive	
13-Apr-20	Positive	30.46
13-Apr-20	Positive	
26-Apr-20	Positive	
13-Apr-20	Positive	

11-Apr-20	Positive	
18-Apr-20	Positive	24.49
11-Apr-20	Positive	
17-Apr-20	Positive	
11-Apr-20	Positive	
11-Apr-20	Positive	
10-Apr-20	Positive	27.74
11-Apr-20	Positive	
10-Apr-20	Positive	20.05
13-Apr-20	Positive	
13-Apr-20	Positive	28.293
11-Apr-20	Positive	38.117
11-Apr-20	Positive	31.298
13-Apr-20	Positive	34.383
14-Apr-20	Positive	
13-Apr-20	Positive	22.67
11-Apr-20	Positive	32.085
17-Apr-20	Positive	
13-Apr-20	Positive	31.2
11-Apr-20	Positive	
11-Apr-20	Positive	
9-Apr-20	Positive	21.16
12-Apr-20	Positive	23.452
13-Apr-20	Positive	23.63
13-Apr-20	Positive	29.278
11-Apr-20	Positive	36.693
16-Apr-20	Positive	
15-Apr-20	Positive	
14-Apr-20	Positive	
13-Apr-20	Positive	
26-Apr-20	Positive	
12-Apr-20	Positive	
14-Apr-20	Positive	
13-Apr-20	Positive	
15-Apr-20	Positive	
14-Apr-20	Positive	22.958
16-Apr-20	Positive	34.3
20-Apr-20	Positive	31.1
12-Apr-20	Positive	
14-Apr-20	Positive	
14-Apr-20	Positive	27.755
13-Apr-20	Positive	24.78
13-Apr-20	Positive	
13-Apr-20	Positive	
13-Apr-20	Positive	30.825
11-Apr-20	Positive	21.79
16-Apr-20	Positive	28.42

25-Apr-20	Positive	
13-Apr-20	Positive	
16-Apr-20	Positive	
13-Apr-20	Positive	
13-Apr-20	Positive	37.459
13-Apr-20	Positive	26.96
14-Apr-20	Positive	33.541
17-Apr-20	Positive	
13-Apr-20	Positive	26.27
12-Apr-20	Positive	29.418
14-Apr-20	Positive	22.22
13-Apr-20	Positive	34.027
18-Apr-20	Positive	21.729
13-Apr-20	Positive	25.19
14-Apr-20	Positive	
14-Apr-20	Positive	22.815
12-Apr-20	Positive	35.359
13-Apr-20	Positive	32.146
19-Apr-20	Positive	16.96
17-Apr-20	Positive	
13-Apr-20	Positive	
13-Apr-20	Positive	34.141
14-Apr-20	Positive	34.984
13-Apr-20	Positive	30.475
13-Apr-20	Positive	27.75
19-Apr-20	Positive	
16-Apr-20	Positive	
16-Apr-20	Positive	22.699
13-Apr-20	Positive	22.69
13-Apr-20	Positive	28.323
13-Apr-20	Positive	
14-Apr-20	Positive	
13-Apr-20	Positive	18.43
13-Apr-20	Positive	35.731
14-Apr-20	Positive	
14-Apr-20	Positive	
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15-Apr-20	Positive	
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15-Apr-20	Positive	
15-Apr-20	Positive	
18-Apr-20	Positive	
15-Apr-20	Positive	
14-Apr-20	Positive	32.121
16-Apr-20	Positive	

14-Apr-20	Positive	
15-Apr-20	Positive	
18-Apr-20	Positive	28.51
18-Apr-20	Positive	23.61
14-Apr-20	Positive	23.037
16-Apr-20	Positive	
14-Apr-20	Positive	29.849
14-Apr-20	Positive	17.81
16-Apr-20	Positive	33.619
15-Apr-20	Positive	
16-Apr-20	Positive	
22-Apr-20	Positive	
17-Apr-20	Positive	25.427
14-Apr-20	Positive	31.179
17-Apr-20	Positive	36.192
17-Apr-20	Positive	
24-Apr-20	Positive	
15-Apr-20	Positive	
20-Apr-20	Positive	29.9
22-Apr-20	Positive	
15-Apr-20	Positive	
21-Apr-20	Positive	22.551
18-Apr-20	Positive	22.436
14-Apr-20	Positive	
17-Apr-20	Positive	
16-Apr-20	Positive	31.764
15-Apr-20	Positive	
15-Apr-20	Positive	
17-Apr-20	Positive	
17-Apr-20	Positive	
21-Apr-20	Positive	24.429
15-Apr-20	Positive	25.755
14-Apr-20	Positive	
16-Apr-20	Positive	24.566
16-Apr-20	Positive	23.55
16-Apr-20	Positive	26.906
17-Apr-20	Positive	29.57
16-Apr-20	Positive	31.189
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16-Apr-20	Positive	
16-Apr-20	Positive	
16-Apr-20	Positive	
17-Apr-20	Positive	
16-Apr-20	Positive	
16-Apr-20	Positive	
17-Apr-20	Positive	21.728
22-Apr-20	Positive	

16-Apr-20	Positive	23.576
17-Apr-20	Positive	
16-Apr-20	Positive	
23-Apr-20	Positive	
18-Apr-20	Positive	
20-Apr-20	Positive	24.88
14-Apr-20	Positive	
16-Apr-20	Positive	35.716
23-Apr-20	Positive	
21-Apr-20	Positive	25.04
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22-Apr-20	Positive	
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18-Apr-20	Positive	
16-Apr-20	Positive	23.973
17-Apr-20	Positive	
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18-Apr-20	Positive	27.82
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17-Apr-20	Positive	
18-Apr-20	Positive	30.67
17-Apr-20	Positive	
17-Apr-20	Positive	25.939
16-Apr-20	Positive	15.952
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17-Apr-20	Positive	
17-Apr-20	Positive	
17-Apr-20	Positive	
20-Apr-20	Positive	23.5
17-Apr-20	Positive	
26-Apr-20	Positive	
22-Apr-20	Positive	37.475
18-Apr-20	Positive	
18-Apr-20	Positive	

18-Apr-20	Positive	26.69
18-Apr-20	Positive	
20-Apr-20	Positive	28.69
18-Apr-20	Positive	
18-Apr-20	Positive	18.009
17-Apr-20	Positive	29.007
18-Apr-20	Positive	23.831
18-Apr-20	Positive	23.434
18-Apr-20	Positive	
18-Apr-20	Positive	31.98
18-Apr-20	Positive	24.477
18-Apr-20	Positive	
17-Apr-20	Positive	
18-Apr-20	Positive	18.994
20-Apr-20	Positive	25.9
18-Apr-20	Positive	22.748
18-Apr-20	Positive	20.378
18-Apr-20	Positive	23.43
18-Apr-20	Positive	
18-Apr-20	Positive	23.54
17-Apr-20	Positive	
18-Apr-20	Positive	19.928
18-Apr-20	Positive	
21-Apr-20	Positive	23.516
18-Apr-20	Positive	21.61
18-Apr-20	Positive	26.413
18-Apr-20	Positive	35.52
18-Apr-20	Positive	
18-Apr-20	Positive	
18-Apr-20	Positive	
18-Apr-20	Positive	22.389
18-Apr-20	Positive	26.457
18-Apr-20	Positive	25.43
19-Apr-20	Positive	
18-Apr-20	Positive	17.349
18-Apr-20	Positive	33.8
18-Apr-20	Positive	24.09
18-Apr-20	Positive	
20-Apr-20	Positive	29.4
27-Apr-20	Positive	
18-Apr-20	Positive	27.62
20-Apr-20	Positive	24.7
18-Apr-20	Positive	21.603
1-May-20	Positive	36.534
18-Apr-20	Positive	30.331
21-Apr-20	Positive	20.54
20-Apr-20	Positive	23.1

18-Apr-20	Positive	
18-Apr-20	Positive	
19-Apr-20	Positive	33.45
18-Apr-20	Positive	19.19
28-Apr-20	Positive	29.53
26-Apr-20	Positive	
18-Apr-20	Positive	31.774
20-Apr-20	Positive	31.4
22-Apr-20	Positive	
20-Apr-20	Positive	32.44
19-Apr-20	Positive	29.76
20-Apr-20	Positive	23.6
22-Apr-20	Positive	
21-Apr-20	Positive	26.275
19-Apr-20	Positive	35.81
20-Apr-20	Positive	24.35
19-Apr-20	Positive	
21-Apr-20	Positive	30.672
20-Apr-20	Positive	32.2
22-Apr-20	Positive	
20-Apr-20	Positive	22.282
20-Apr-20	Positive	31.53
22-Apr-20	Positive	
20-Apr-20	Positive	21.112
23-Apr-20	Positive	23.252
20-Apr-20	Positive	25.502
29-Apr-20	Positive	20.607
20-Apr-20	Positive	24.5
20-Apr-20	Positive	37.319
20-Apr-20	Positive	21.7
20-Apr-20	Positive	32.5
22-Apr-20	Positive	
22-Apr-20	Positive	
20-Apr-20	Positive	39.203
20-Apr-20	Positive	34.7
22-Apr-20	Positive	
20-Apr-20	Positive	25.5
20-Apr-20	Positive	
20-Apr-20	Positive	
20-Apr-20	Positive	
21-Apr-20	Positive	28.321
23-Apr-20	Positive	
23-Apr-20	Positive	24.047
26-Apr-20	Positive	
21-Apr-20	Positive	19.47
20-Apr-20	Positive	31.8
28-Apr-20	Positive	24.96

22-Apr-20	Positive	
20-Apr-20	Positive	31.324
20-Apr-20	Positive	27.2
23-Apr-20	Positive	
20-Apr-20	Positive	
20-Apr-20	Positive	
23-Apr-20	Positive	18.9
26-Apr-20	Positive	26.43
20-Apr-20	Positive	24.9
21-Apr-20	Positive	41.516
20-Apr-20	Positive	21.7
22-Apr-20	Positive	
20-Apr-20	Positive	26.7
23-Apr-20	Positive	
23-Apr-20	Positive	
22-Apr-20	Positive	
21-Apr-20	Positive	24.1
22-Apr-20	Positive	
21-Apr-20	Positive	24.8
21-Apr-20	Positive	15.924
21-Apr-20	Positive	16.267
24-Apr-20	Positive	
21-Apr-20	Positive	26.8
21-Apr-20	Positive	36.753
24-Apr-20	Positive	
22-Apr-20	Positive	
21-Apr-20	Positive	17.44
22-Apr-20	Positive	28.666
21-Apr-20	Positive	36.368
23-Apr-20	Positive	
21-Apr-20	Positive	23.11
21-Apr-20	Positive	22.02
21-Apr-20	Positive	22.98
21-Apr-20	Positive	30.9
21-Apr-20	Positive	27.671
21-Apr-20	Positive	20.064
23-Apr-20	Positive	
21-Apr-20	Positive	35.51
22-Apr-20	Positive	
22-Apr-20	Positive	
20-Apr-20	Positive	31.961
21-Apr-20	Positive	30.9
24-Apr-20	Positive	
22-Apr-20	Positive	
22-Apr-20	Positive	
22-Apr-20	Positive	
22-Apr-20	Positive	

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22-Apr-20	Positive	
21-Apr-20	Positive	35.261
22-Apr-20	Positive	
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22-Apr-20	Positive	
23-Apr-20	Positive	
1-May-20	Positive	
22-Apr-20	Positive	28.55
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23-Apr-20	Positive	
24-Apr-20	Positive	
22-Apr-20	Positive	
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25-Apr-20	Positive	
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22-Apr-20	Positive	
23-Apr-20	Positive	37.7
27-Apr-20	Positive	33.94
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28-Apr-20	Positive	24.32
4-May-20	Positive	32.188
22-Apr-20	Positive	
22-Apr-20	Positive	
23-Apr-20	Positive	
28-Apr-20	Positive	20.05
23-Apr-20	Positive	28.84
25-Apr-20	Positive	
25-Apr-20	Positive	26.539
23-Apr-20	Positive	
23-Apr-20	Positive	
27-Apr-20	Positive	34.651
23-Apr-20	Positive	
24-Apr-20	Positive	
24-Apr-20	Positive	
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24-Apr-20	Positive	
24-Apr-20	Positive	
24-Apr-20	Positive	
27-Apr-20	Positive	

25-Apr-20	Positive	33.61
25-Apr-20	Positive	
25-Apr-20	Positive	28.399
26-Apr-20	Positive	
25-Apr-20	Positive	18.479
27-Apr-20	Positive	25
26-Apr-20	Positive	
27-Apr-20	Positive	22.594
28-Apr-20	Positive	
22-Apr-20	Positive	
25-Apr-20	Positive	
26-Apr-20	Positive	
29-Apr-20	Positive	27.374
29-Apr-20	Positive	22.971
27-Apr-20	Positive	
1-May-20	Positive	
28-Apr-20	Positive	28.962
25-Apr-20	Positive	20.72
25-Apr-20	Positive	23.669
27-Apr-20	Positive	15.1
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26-Apr-20	Positive	20.778
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26-Apr-20	Positive	
28-Apr-20	Positive	24.574
28-Apr-20	Positive	37.967
26-Apr-20	Positive	28.85
26-Apr-20	Positive	
26-Apr-20	Positive	
27-Apr-20	Positive	
27-Apr-20	Positive	
27-Apr-20	Positive	25.56
27-Apr-20	Positive	
27-Apr-20	Positive	
29-Apr-20	Positive	23.777

2-May-20	Positive	32.307
28-Apr-20	Positive	31.52
3-May-20	Positive	26.534
29-Apr-20	Positive	20.825
28-Apr-20	Positive	31.394
28-Apr-20	Positive	36.252
28-Apr-20	Positive	31.54
29-Apr-20	Positive	23.975
28-Apr-20	Positive	26.914
3-May-20	Positive	
1-May-20	Positive	24.1
28-Apr-20	Positive	20.466
30-Apr-20	Positive	20.606
29-Apr-20	Positive	30.938
28-Apr-20	Positive	22.22
28-Apr-20	Positive	
3-May-20	Positive	21.825
28-Apr-20	Positive	27.09
28-Apr-20	Positive	
30-Apr-20	Positive	
30-Apr-20	Positive	19.79
30-Apr-20	Positive	25.97
8-May-20	Positive	
4-Sep-20	Positive	36.94
30-Apr-20	Positive	
29-Apr-20	Positive	23.347
29-Apr-20	Positive	35.832
5-May-20	Positive	
30-Apr-20	Positive	31.238
30-Apr-20	Positive	29.63
30-Apr-20	Positive	28.58
30-Apr-20	Positive	36.59
30-Apr-20	Positive	31.19
30-Apr-20	Positive	
4-May-20	Positive	
1-May-20	Positive	
30-Apr-20	Positive	34.645
2-May-20	Positive	35.167
1-May-20	Positive	
4-May-20	Positive	24.869
3-May-20	Positive	39.233
6-May-20	Positive	21.6
1-May-20	Positive	
2-May-20	Positive	19.132
6-May-20	Positive	33.161
2-May-20	Positive	
4-May-20	Positive	27.159

2-May-20	Positive	
8-May-20	Positive	
5-May-20	Positive	
3-May-20	Positive	30.278
6-May-20	Positive	28.371
3-May-20	Positive	23.992
4-May-20	Positive	17.603
3-May-20	Positive	24.413
4-May-20	Positive	22.2
5-May-20	Positive	27.651
3-May-20	Positive	24.745
3-May-20	Positive	
5-May-20	Positive	
3-May-20	Positive	35.573
3-May-20	Positive	31.143
5-May-20	Positive	
5-May-20	Positive	25.968
7-May-20	Positive	
6-May-20	Positive	24.82
5-May-20	Positive	
5-May-20	Positive	
5-May-20	Positive	
6-May-20	Positive	35.8
6-May-20	Positive	21.829
16-May-20	Positive	
8-May-20	Positive	
7-May-20	Positive	28.288
12-May-20	Positive	
8-May-20	Positive	
8-May-20	Positive	
12-May-20	Positive	
9-May-20	Positive	18.037
9-May-20	Positive	
9-May-20	Positive	21.083
9-May-20	Positive	
10-May-20	Positive	36.605
9-May-20	Positive	
13-May-20	Positive	
16-May-20	Positive	
15-May-20	Positive	
11-May-20	Positive	35.125
14-May-20	Positive	
12-May-20	Positive	
14-May-20	Positive	
14-May-20	Positive	
13-May-20	Positive	
14-May-20	Positive	

14-May-20	Positive	
14-May-20	Positive	
14-May-20	Positive	
14-May-20	Positive	
14-May-20	Positive	
16-May-20	Positive	
14-May-20	Positive	
16-May-20	Positive	
16-May-20	Positive	
17-May-20	Positive	
18-May-20	Positive	36.589
23-May-20	Positive	
19-May-20	Positive	
24-May-20	Positive	
23-May-20	Positive	
20-May-20	Positive	
21-May-20	Positive	23.4
22-May-20	Positive	34.853
27-May-20	Positive	
24-May-20	Positive	
28-May-20	Positive	23.943
25-May-20	Positive	
27-May-20	Positive	
30-May-20	Positive	32.6
1-Jun-20	Positive	24.05
3-Jun-20	Positive	
6-Jun-20	Positive	
7-Jun-20	Positive	36.273
6-Jul-20	Positive	34.02
29-Jun-20	Positive	16.88
29-Jun-20	Positive	25.2
28-Jun-20	Positive	30.05
4-Jul-20	Positive	
13-Jul-20	Positive	
29-Jul-20	Positive	25.01
31-Jul-20	Positive	35.18
29-Jul-20	Positive	32.7
31-Jul-20	Positive	26.34
13-Aug-20	Positive	17.3
12-Aug-20	Positive	27.11
12-Aug-20	Positive	34.585
17-Aug-20	Positive	24.79
15-Aug-20	Positive	26.924
18-Aug-20	Positive	16.895
22-Aug-20	Positive	27.4
21-Aug-20	Positive	13.1
20-Aug-20	Positive	23.26

24-Aug-20	Positive	20.62
26-Aug-20	Positive	
26-Aug-20	Positive	
28-Aug-20	Positive	
4-Sep-20	Positive	36.94
30-Aug-20	Positive	
21-Sep-20	Positive	
28-Sep-20	Positive	
30-Sep-20	Positive	20.715
9-Oct-20	Positive	
8-Oct-20	Positive	17.16
9-Oct-20	Positive	
16-Oct-20	Positive	
16-Oct-20	Positive	
15-Oct-20	Positive	
14-Oct-20	Positive	35.2
13-Oct-20	Positive	
22-Oct-20	Positive	18.83
17-Oct-20	Positive	
22-Oct-20	Positive	
24-Oct-20	Positive	17.661
1-Nov-20	Positive	
28-Oct-20	Positive	
29-Oct-20	Positive	30.373
25-Oct-20	Positive	20.38
1-Nov-20	Positive	
31-Oct-20	Positive	
28-Oct-20	Positive	26.657
30-Oct-20	Positive	
29-Oct-20	Positive	23.79
28-Oct-20	Positive	
28-Oct-20	Positive	
30-Oct-20	Positive	
16-Nov-20	Positive	
5-Nov-20	Positive	
31-Oct-20	Positive	
1-Nov-20	Positive	
5-Nov-20	Positive	
2-Nov-20	Positive	
2-Nov-20	Positive	
5-Nov-20	Positive	
5-Nov-20	Positive	19.8
7-Nov-20	Positive	
8-Nov-20	Positive	17.9
8-Nov-20	Positive	23.64
6-Nov-20	Positive	

6-Nov-20	Positive	
4-Nov-20	Positive	
9-Nov-20	Positive	28.7
		25.7
9-Nov-20	Positive	19.2
8-Nov-20	Positive	17.57
13-Nov-20	Positive	
12-Nov-20	Positive	
11-Nov-20	Positive	
7-Nov-20	Positive	31.217
14-Nov-20	Positive	23.663
12-Nov-20	Positive	
12-Nov-20	Positive	
12-Nov-20	Positive	
11-Nov-20	Positive	
13-Nov-20	Positive	
12-Nov-20	Positive	
15-Nov-20	Positive	
13-Nov-20	Positive	
14-Nov-20	Positive	
15-Nov-20	Positive	26.57
15-Nov-20	Positive	19.83
15-Nov-20	Positive	27.68
15-Nov-20	Positive	21.7

Ct Value E gene for LDT	Ct Value Orf1a for Cobas 6800
32.5	
07.60?	
33	
27.79	
25.454	
32.29	
19	
UNK	
24.13	
29.58	
28.4	
26.98	
32.9	
20.672	
33.5	
25.47	
28.159	
25.18	
18.84	
27.23	
34	
20.578	
24.33	
21.3	
24.9	
34.2	32.86
	33.39
25.2	
19.18	
27.288	
33.96	
31.535	
27.839	
20.77	
24.58	
23.11	
29.719	
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32.22	
16.5	
35.478	
20.4	
31.811	
32.22	
21.656	

32.231	
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18.8	
27.351	
19.556	
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25.76	
23.94	
29.74	
24.876	
34.25	
22.821	
16.35	
33.74	
26.687	
23.27	
19.869	
28.043	
30.4	
17.516	
23.738	
33.3	
	32.94
36.496	
22.974	
24.706	
25.738	
25.6	
29.7	
21.38	
15.03	
20.8	

28.7	
17.2	
31.94	
19.82	
23.71	
21.195	
31.17	
21.44	
35.169	
26.344	
30.34	
30.34	
26.611	
24.4	
	34.28
30.13	
26.6	
26.1	
26.2	
30.282	
37.726	
34.598	33.91
29.926	
27.304	
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26.736	
36.683	
35.1	
16.798	
26.928	
17.38	
	28.19
31.556	

18.639	
15.38	
36.598	34.11
	17.29
20.788	
23.757	
22.6	
	32.39
24.9	
22.32	
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22.507	
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20.39	
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22.694	
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18.12	
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20.1	
	32.04
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	32.13
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	26.43
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23.8	
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26.51	
	31.19
35.981	
	26.05
	31.73
25.502	
30.2	
28.6	
27.407	
26.5	
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25.462	
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21.9	
18.2	
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27.524	
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26	
27.75	
	22.75
19.2	
34.7	
	21.2
21.1	
17.53	
33.867	32.28
32.9	
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20.511	
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	34
26.814	
26.455	
35	
NEG	
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32.197	
32.202	
	33.67
22.58	
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22.693	
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22.8	
23.6	
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	34.25
31.07	
	30.68
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23.719	
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NEG	
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26.56	
22.3	
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	22.08
24.4	
28.94	
34.587	30.96
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	28.02
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20.28	
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18.672	
	29.11
	27.56
	34.08

	31.84
29.8	
23.52	
21.511	
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31.89	
19.34	18.55
25.722	
23.55	
	25.56
	20.13
	31.4
	25.98
40.432	32.86
23.562	
31.489	
29.47	
27.313	
16.78	
	22.45
22.729	
	28.86
	18.96
33.614	
27.976	
	30.2
28.11	
24.2	
	24.04
23.332	27.52
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	30.34
35.059	33.13
	27.79
	30.55
	32.47
	23.13
33.711	
29.313	27.66
	25.5
	29.87
33.36	
	31.46
24.62	
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36.364	35.28
30.25	

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13.66	
29.7	
34.242	32.06
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	34.29
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15	
31.863	29.15
	25.06
33.118	31.64
31.32	
32.72	
32.5	33.53
20.6	
33.286	
22.4	
	23.31
25.767	
25.371	
24.574	22.94
	24.5
31.278	31.25
19.537	19.18
33.03	31.38
21.8	
33.9	32.85
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20.996	
20.361	
	34.12
	31.59
24.185	

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	24.18
	26.78
33.24	
33.5	
17.35	
23.1	
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27.82	
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	33.89
NEG	34.71
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21.858	
36.144	32.82
	32.35
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NEG	32.32
	30.74
32.05	
18.21	
22.7	
	28.68
22.407	
	33.78
20.713	22.07
26.216	
19.71	
	27.83
32.386	31.91
33.8	
30.097	27.33
	27.26
	27.49
	24.99
19.741	21.46
31.5	
26.606	
27.8	
36.9	34.62
	23.46
24.71	
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21.4	

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	35.8
32.5	33.62
29.339	30.16
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	33.71
23.986	
29.4	
	33.78
	30.1
	24.5
	33.31
23.1	
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33.841	33.75
36.103	33.94
31.38	
24.691	
28.858	
32.435	
27.11	
26.184	
35.624	34.34
30.76	
33.031	
27.775	
34.26	
	32.34
21.504	
34.334	
	28.25
33.73	33.43
	30.32
22.512	
	27.95
27.433	
27.123	
	30.48
28.935	27.46
21.59	
	20.24
30.118	
	32.32
	NEG
	24.25

	21.35
23.05	
	26.48
	25.44
	20.52
	25.61
28.02	
	26.24
20.58	
	34.39
27.194	
35.945	34.54
30.085	
34.69	
	31.27
20.97	
30.615	
	18.56
29.79	
	19.16
	30.74
21.29	
22.215	
21.19	
28.269	
35.486	34.26
	29.61
	26.25
	21.02
	24.73
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	34.41
	24.92
	29.12
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21.866	
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29.8	
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28.335	

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	28.53
	26.01
34.459	34.09
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24.88	
27.921	
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25.01	
	35.37
21.111	
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27.966	
	28.36
	26.26
17.58	
38.15	33.92
	28.96
	24.68
	20.33
	31.26
	30.06
	24.61
	22.91
	20
	26.6
	23.55
	33.33
31.294	
	19.3

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22.061	
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24.599	
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33.968	
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	26.78
	26.32
28.3	
	35.75
	33
20.237	
20.163	
	30.48
	34.19
31.44	
	23.57
	21.58
	21.65
	19.33
22.443	
24.745	
	32.48
22.645	
23.071	
26.631	
27.84	
30.775	
	31.22
	21.87
	21.56
	32.45
	28.79
	23.26
	25.09
20.432	
	29.81

22.329	
	31.98
	33.34
	32.5
	33.48
23.43	
	31.52
38.315	33.96
	30.28
22.962	
	31.62
	23.8
	35.25
	20.43
21.526	
	27.15
	25.89
	28.96
25.86	
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	24.22
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	25.57
28.476	
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	25.58
	33.9
	33.37
	35.45
	31.07
	28.74
	29.45
	32.17
	26.97
	22.44
	25.67
	22.2
	35.22
20.4	
	24.17
	22.36
NEG	34.55
	29.13
	20.91

26.96	
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27.44	
	21.61
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21.699	
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17.515	
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	28.52
27.11	
23.5	
21.256	
36.11	35.65
30.132	
19.61	
21.4	

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	24.67
32.5	
16.973	
27.88	
	33.38
29.254	
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	34.21
31.16	
28.61	
21.9	
	29.72
25.42	
33.8	
22.76	
	30.71
28.725	
31.1	
	35.14
21.349	
30.97	
	30.47
19.996	
21.284	
25.298	
20.414	
25.7	
NEG	34.53
19.5	
31.9	
	36.14
	26.01
38.327	33.76
UNK	
	31.18
27.2	
	33.14
	35.44
	32.11
26.642	
	27.03
22.412	
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18.34	
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23.58	

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30.611	
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	33.11
	31.1
18.8	
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24.1	
37.906	NEG
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	24.8
25.9	
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	28.06
	21.99
22.76	
	34.47
23.9	
13.901	
13.641	
	26.45
24.2	
35.948	31.86
	26.21
	34.35
16.61	
27.511	
36.143	33.91
	22.71
21.8	
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18.299	
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32.51	
	36.24
	31.63
31.407	
30.1	
	32.01
	30.59
	28.35
	27.32
	34.06

	29.35
	30.84
33.169	32.8
	30.72
	28.31
	34.67
	25.88
	30.81
27.28	
	22.07
	26.1
	31.33
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	21.37
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	30.26
	22.86
	34.3
	32.13
	32.37
	19.35
	31.73
	32.97
36.13	NEG
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UNK	
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	23.95

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22.544	
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	30.38
	33.17
	25.13
25.509	
22.076	
	31.16
	27.02
26.004	
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22.618	
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	28.15
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29.31	
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	31.83
	33.11
	34
	25.47
	34.95
	33.88
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	35.17
	32.23
	33.24
21.52	
36.632	33.18
27.13	
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	30.5
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	22.02
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21.665	

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34.349	32.7
	24.4
27.499	
28.37	
27.67	
34.05	33.22
29.81	
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	24.17
	28.54
31.894	
34.275	32.43
	31
24.062	
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27.753	

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	34.86
	18.21
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28.489	
22.888	
19.519	
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22.879	
	25.12
	28.65
32.13	32.02
27.513	
	27.61
24.814	
	21.11
21.57	
	33.94
	24.79
	28.49
34.1	32.44
21.848	
	26.54
	22.1
26.13	
	29.96
	22.36
	34.23
	25.29
12.743	
	27.52
16.386	
	27.56
NEG	NEG
	25.85
	23.36
	29.55
	26.67
34.223	32.82
	30.77
	25.76
	23.09
	30.78
	17.8
	30.25

	29.59
	25
	22.12
	30.53
	28.84
	21.63
	33.65
	23.32
	21.8
	26.5
38.02	34.29
	16.72
	26.13
	25.07
	15.79
	23.89
22.1	
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	15.25
23.64	
	NEG
	30.78
29.9	
21.86	
	33.19
36.42	NEG
32.19	
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23.9	
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	31.95
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26.852	
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25.39	
27.447	
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13.9	
23.8	

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	20.99
34.45	
	32.83
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	19.52
	26.17
34.1	
19.2	
	25.17
	26.27
17.989	
	18.53
29.609	
20.08	
	25.09
26.087	
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23.826	
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	33.27
	17.03
	22.13
	31.07
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18.8	
24.96	

29.1	
24.1	
19.6	
18.53	
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	27.9
	17.7
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	22.24
	23.57
	20.38
25.89	
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Primer on CT values for the QEII laboratory, Central Zone NSH

Table outlining CT value for currently used COVID 19 tests and their interpretation

	Lab Developed Test	GeneXpert SARS-CoV-2	Roche 6800 SARS-CoV-2	Panther
Total cycles	45	45	Not described	Not described
Genetic Targets	RdRp gene	E gene N2 gene	E gene ORF1 gene	ORF 1a/b gene
Definition of positive	RdRp CT <35	Dual gene positive: E POS and CT ≤ 37* N2 POS and CT ≤ 37*	Dual gene positive: E POS and CT ≤ 38* ORF1 POS and CT ≤ 38*	As per instrument
Definition of negative	RdRp CT ≥38	E Neg N2 Neg	ORF1 Neg E Neg	As per instrument
Definition of indeterminate**	RdRp CT 35 - 38	Single gene positive: E POS and CT ≤ 37* N2 Neg E Neg N2 POS and CT ≤ 37*	Single gene positive: E POS and CT ≤ 38* ORF1 Neg E Neg ORF1 POS and CT ≤ 38*	As per instrument

* Positive results with CT above this value needs to be discussed with director who examines the amplification curve to help determine if this is a true or non-specific amplification

****Indeterminate report phrase:** SARS-CoV-2 (COVID 19) result indeterminate. This may represent early disease, late disease, or a false positive result. Please recollect once after 24 hrs if clinically warranted. If indeterminate result persist, please discuss with public health

Important factors to consider in interpreting Ct values:

1) *Ct values will depend on the stage of infection* - During pre-symptomatic and early infection, the baseline viral load can be initially low which is associated with high Ct values i.e. >30 and above. This period may last hours to days. Ct value interpretation is further complicated by asymptomatic infections where the time of infection onset may be unknown. **Therefore, if clinically indicated, patients should undergo repeat testing within 24 to 48 hrs to determine if the Ct value is stable, rising or declining**.

2) *Individuals can shed detectable SARS-CoV-2 RNA for a prolonged period* – RT-PCR can be positive for over 100 days or more after infection, but are unlikely to transmit to others beyond 10 days post symptom onset.

3) *Ct values are affected by the type AND quality of the specimen* - Nasopharyngeal swabs (NPs) are the most sensitive specimen type in the outpatient setting; throat/nares swabs, and gargles may be less sensitive. Also in patient with lower tract infection (e.g. pneumonias), lower tract specimens are preferred as upper tract specimens may be negative. The quality of the sample collection directly impacts the amount of respiratory material collected and this directly affects the generated Ct value i.e., poorly collected samples can yield an artificially high Ct value (low RNA levels).

4) *Ct values are not comparable between different testing platforms* - The Ct ranges and distributions differ by the PCR technology used. There is no international standard to allow for comparison.

TITLE: Procedure - Amplification - ABI COVID-19	**Doc #:** 86825
Section: Management System\PLM\Microbiology\5-VIM Molecular Manual\Procedures\	**Version:** 1.5 Current
Document Owner: MB1 Immunology Virology Technical Specialist	**Effective Date:** 11/25/2020
Final Approval: Dr. Jason Leblanc	**Review Date:** 11/1/2021

Purpose

The purpose of this assay is to use RT-Real Time PCR technology to qualitatively detect the SARS-CoV-2 virus that will aid in patient treatment and isolation.

Abbreviations

RT-PCR - Reverse-Transcription Polymerase Chain Reaction
RNA - Ribonucleic acid
ABI - Applied Biosystems, now known as Life Technologies
UTM - Universal transport medium
QC - Quality control
QA - Quality assurance
Ct - Threshold Cycle
BSC - Biological Safety Cabinet, class IIA
LoD - Limit of detection

Materials

Reagents	Stability and Storage	Preparation (Y/N)
Taqman Fast Virus 1-step master mix (4x)	-20°C, until expiry	N
20x Primer/probe mix COVID	4°C, 1 week -20°C, 1 year	Y

Notes:

- Avoid repeated freeze/thaw cycles for all reagents.
- Do not pool reagents from different lots or use reagents past the expiration date.
- All primers and probes should have a lyophilized “back-up”.
- The performance of each new lot of primers and kit must be evaluated prior to use (see Quality Control – Lot release).

Primer/Probe mix COVID-19 (20x):

- For each oligonucleotides, a quality control document is provided by the manufacturer. Ensure the primer/probe sequences match those described below.

Name	Sequence (5'-3')
RdRP_Lee_F	TGCCGATAAGTATGTCCGCA
RdRP_Lee_R	CAGCATCGTCAGAGAGTATCATCATT
E_Sarbeco_F1	ACAGGTACGTTAATAGTTAATAGCGT
E_Sarbeco_R2	ATATTGCAGCAGTACGCACACA
RdRP_Lee_probe	FAM-MGB TTGACACAGACTTTGTGAATG
E_Sarbeco_probe	CY5-TAO ACACTAGCCATCCTTACTGCGCTTCG

Preparation:

- Complete the **Form - Quality Control – Primers – ABI COVID-19**
- Reconstitute the lyophilized primer or probes to 100 µM by adding in TE buffer. Let sit for 10 minutes, mix by inversion, and pulse spin.
  Note:
  - The volume (µl) required is 10 times the amount of nmol provided.
    - For example, if 26 nmol are provided, add 260 µl TE buffer.
  - Extended exposure to light can result in probe degradation. Protect all probes by covering them with the lid of the cold block or with aluminum foil.

- Determine which probe (or primer) is the limiting reagent (i.e. reagent with the smallest volume of 100 µM stock). This is usually a probe.
  - The probes have a volume defined as "**4(x)**". Solve for "x"
    - Ex: We have 200 µl of FluB probe as the limiting reagent which corresponds to 4(x). Therefore, x = 50 µl.

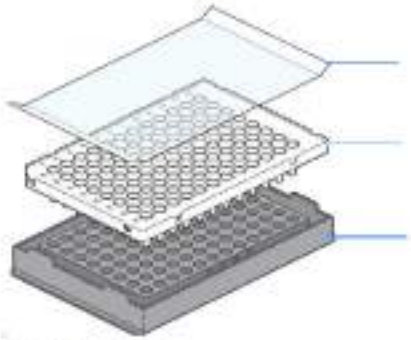
- The other probes and primers will have a volume that is a multiple of (x).
  - Ex: For a limiting reagent of 200 µl of FluB probe, the amount of water required is 58(x) = 58(50) = 2250 µl.

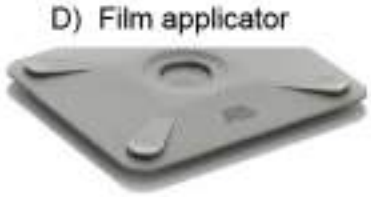
- Calculate the required volumes of reagents and verifying that sufficient quantities of all reagents are present.

Name	Stock (µM)	Final Conc (nM)	Stock for 100 reactions (µL)
RdRP_Lee_F	100	400	8
RdRP_Lee_R	100	400	8
E_Sarbeco_F1	100	400	8
E_Sarbeco_R2	100	400	8
RdRP_Lee_probe	100	200	4
E_Sarbeco_probe	100	200	4
TE Buffer			60
Total	**-**		**-**

- Discuss your approach with a Director.
- Combined the reagents as described above, mix by inversion, and dispense into 110 µl aliquots. Label 0.5 ml microtubes with CoV. Store at -20ºC in a labeled box. The box should contain a label with primer names, lot numbers (oligo number), the date (dd/mm/yy), and reference to the **Form – Quality Control – Primers – ABI COVID19**

Supplies
1.5 and 2.0 ml microtubes (nuclease free) and racks
Micropipettors and aerosol preventative nuclease-free tips
Gloves, powder-free (**Note**: Powder is known to increase background signal)
Lightcycler cold block (reagent room).
2.0 ml cryotubes
96-well base (plate holder)
96-well Fast Plates (0.1 ml)
Optical adhesive film
Film applicator





Equipment
Vortex mixer
Centrifuge with plate adapters
Microfuge with rotor compatible with 1.5 ml microtubes
ABI 7500 Fast instrument with 7500 software (v 2.0.5)

Sample

Sample type	Amount required	Transport and Storage
Nasopharyngeal swab	200 µL	2-30°C 48 hours -70°C, indefinitely
Nares/throat Roche swab in UTM	200 µL	
Throat gargle	200 µL	
Pleural Fluid	200 µl	4°C, 72h -70°C, indefinitely
BALs	1.5 ml, centrifuge and use pellet, digest only if unable to pipet	
NP aspirate	200 µL if able to pipet 1.5 mL if viscous, centrifuge and digest	
Endotracheal aspirate	1.5 mL, centrifuge and digest	
Tissue	25 mg	
Sputum	Digest if unable to pipet	

Notes:

Specimens should be aliquoted according to **Respiratory PCR Archive Procedure.**

Limitations: Repeated freeze-thaw cycles should be avoided.

Sample retention: Positives indefinitely. Negatives are stored at 2-8°C for 4 days then discarded.

Special Safety Precautions	• Handle all specimens as if they are capable of transmitting infectious agents. • Appropriate protective equipment should be worn, which includes but is not limited to: protective eyewear, clothing/lab coat or gowns, and gloves. • All work should be conducted in the designated areas. • When performing the assay or maintenance on the instrument, be cautious of warning signs on the instrument. Possible hazards include high-temperature surfaces, electrical shock hazard, moving parts, and chemical hazards. Do not try to move equipment. • Before handling any chemical, refer to the Material Safety Data Sheet (MSDS) provided by the manufacturer, and observed all relevant precautions. • Discard waste in accordance with federal and local regulations. • Follow standard decontamination procedures. • Wash hands thoroughly after handling samples and reagents.
Maintenance	• Routine calibration must be performed for the ABI 7500 Fast (**Procedure - Maintenance and Calibration - ABI 7500 Fast**). While the software may alert users when a calibration is necessary, scheduled maintenance should be planned.
Quality Control	**Negative Extraction Control**: PCR-grade water. **Positive Control**: RDRP positive control (diluted with 320 µL TE) • Verify the **Form – Quality Control - Positive Control logsheet** for current control. **Other QC:** • With any new lot of reagent or kit, verify that the kit insert provided is the same as cited in this SOP. If not, notify a technical specialist or Director. • For each experiment, the lot numbers for all reagents and equipment used should be recorded on the indicated areas on the Sample List, Extraction, and Amplification worksheets. • After each RT-PCR assay, the performance of the controls should be recorded on the **Form – Quality Control - Molecular QC logsheet**. • **Lot release**: The performance of kits should be verified prior to use, using positive and negative controls. If the expected results are obtained, the QC passes and the kits are released for general use. Record the results on the **Form – Quality Control - Molecular QC logsheet**. • QC records shall be kept for a period of 3 years.

Procedure

Workflow in the laboratory must proceed in a unidirectional manner, beginning in the extraction area proceeding to the amplification area. As with any test procedure, good laboratory technique is crucial to prevent amplicon contamination. Extreme care should be taken to preserve the purity of the kit reagents and amplification mixtures. Reagents or equipment should not be moved from their dedicated areas.

1. Sample preparation

Step	Action
1.1	Create a worklist using VGMB COVID Holding. See Job Aid - Genlab LIS COVID document # 90523 for details
1.2	Record the specimens and controls on the Sample List section of the **Form - Sample List – Real-time PCR and RT-PCR (ABI7500Fast) for Magnapure 32 and Form - Sample List – Real-time PCR and RT-PCR (ABI7500Fast) Mag96 for Magnapure 96.** Number the tubes accordingly. **Notes:** • The sample order will be: Positive control (tube #1), Negative extraction control (tube #2), and patient specimens (#3 to end). • To avoid cross-contamination during processing, the positive controls should be manipulated following the specimens (see below).

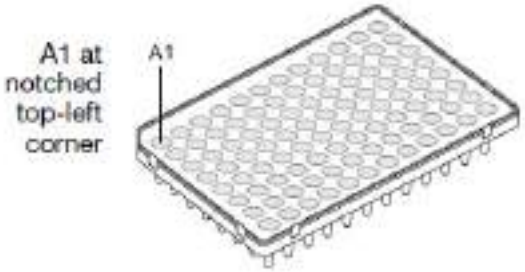
1.3	In a BSC, process specimens according to the **Job Aid – Specimen Preparation**. o **Swabs in UTM/fluids easily pipetted**: Vortex for a minimum of 10 seconds and aliquot into labeled 5.0 ml 12x75 tubes. This process is done in MPA. o **Viscous fluids/Bronch wash/Sputum**: Vortex and transfer 1.5 ml of fluid to a 1.5 ml microtube. Centrifuge ~14,000 x g, 3 min. Remove the majority of the supernatant (keep ~210 µl and the pellet). If viscous, perform a proteinase K digestion prior to extraction (**Form – Sample List - Proteinase K Digestion**). Store remaining specimen. o **Tissues:** Place specimen in a sterile Petri dish. Mince with a sterile scalpel and transfer to cryotube. Perform a proteinase K digestion prior to extraction (**Form – Sample List - Proteinase K Digestion**). Store the remaining specimen.
1.4	Change your gloves and proceed to extraction.

2. Extraction

Step	Action
2.1	Refer to the **Procedure - Extraction - TNA – Automated** or **Procedure – Extraction – Magnapure 96** **Notes**: • Prior to amplification, purified RNA or TNA can be stored at 4°C (maximum 24h). Freeze at -70°C following the RT-PCR.
2.2	Add 200 ul of the sample/control to the appropriate well of the MagnaPure Sample Cartridge or labeled microtube. **Note**: The sample order should be as follows: water, negative extraction control, and finally the specimens (**Form - Sample List – Real-time PCR and RT-PCR (ABI7500Fast) or Form - Sample List – Real-time PCR and RT-PCR (ABI7500Fast) Mag96**.

3. Amplification

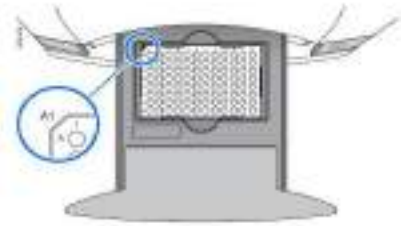
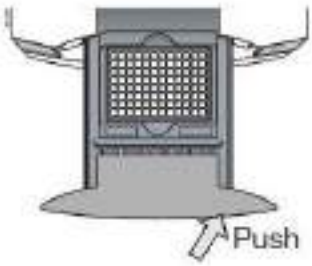
Step	Action
3.1	In the reagent room, you will need the following: • Cold block containing the 4x TaqMan Fast Virus 1-step master mix (found in the -20°C). • Cold block to hold reagents (found at 4°C)

	• Primer/probe mix COVID-19 (found in the -20°C) • **Form – Amplification – ABI COVID-19 Real-time RT PCR**
3.2	Calculate the volume required by accounting for all specimens and controls, and add one additional reaction for pipetting error for every 16 specimens. Record the amounts on worksheet and record the required information. **Master mix** **Reagents** / **Volume per reaction (µl)** / **Volume* for ___ specimens (µl)** PCR grade H2O — 9 TaqMan Fast Virus 1-step mix (4x) — 5 20x Primer/probe mix CoVID-19 — 1 **Total** — 15
3.3	Thaw aliquot of 20x primer probe mix. Place it in the 4°C cold block. **Notes:** • Ensure that all of the RT-PCR reagents are completely homogenous prior to use. Mix reagents by gentle pipetting and pulse spin. DO NOT vortex the enzyme mix or RNase inhibitor. • Protect the probes from extended exposure to light. • Record all lot numbers on the RT-PCR worksheet.
3.4	Complete the **Form – Amplification – ABI COVID-19 Real-Time RT PCR** and prepare the master mix. Mix by gentle pipetting and pulse spin.
3.5	Add **15 µl** of the RT-PCR master mix to each well of the 96-well fast plate. Seal the plate. **Notes:** • Standard plates are not compatible with the 7500 Fast system and may be crushed by the 96-Well Fast Block. Fast plates have a notched top-left corner (above A1). 
3.6	Once finished, return the reagents to their proper storage

	conditions, clean the dead air box with 10% bleach followed by ethanol, and retrieve the master mix tube and worksheet.
3.7	Proceed to the extraction area.
3.8	Add **5 µl of extracted RNA (or total nucleic acids)** to the respective tubes or wells starting at well A1, B1, C1, etc. Magnapure 96 does a volume transfer process to add the template to the plate. Magnapure 32 requires manual transfer. For a Magna 96 extraction and Magna 32s, add 5 µL positive control to A1 after the volume transfer and manual transfer respectively. Seal the plate with an ABI optical adhesive film using the film applicator. DNA (or TNAs) and specimens should be placed at -80ºC within 24 hours after template addition.
3.9	Remove any bubbles formed during master mix / template addition by gentle aspiration/expulsion with a micropipette.
3.10	Transport the sealed plate to the amplification area.
3.10	Centrifuge the plates or tubes (along with the base) at 1500 rpm for 2 min. **Note**: Ensure the rotor is balanced with a blank plate.
3.11	Verify that the liquid in each well plate is at the bottom of the well and there are no bubbles.

4. Instrument set-up

Step	Action
4.1	Place the 96-well plate into the Fast plate holder found in the front drawer of the ABI 7500 Fast instrument.    **Notes:** • There are two different plate holders; one for plates and one

	for 8-well strips. Choose the appropriate holder. • The plate holder for the Fast 8-tube strips cannot be used with Fast 96-well plates or other microtubes. • The plate holder for 96-well Fast plates cannot be used for microtubes or alternative plates. Note the notched edge. 
4.2	Slowly close the drawer of the 7500 Fast System to avoid shaking the tubes/plate strips. Apply pressure to the right side of the tray door at an angle.  
4.3	Turn on the ABI 7500 Fast instrument and log-on to the computer. Room 406 Username: Administrator Password: FLU Room 409 Username: INSTR-ADMIN Password: INSTR-ADMIN (instrument on right) Room 409 Username: Administrator Password: Administrator (instrument on left)
4.4	On the desktop, click on the icon for the 7500 software.
4.5	A log-in screen will appear. Hit **OK**. The software should open. **Note**: If a pop-up window will appears stating that "One or More Calibrations is Expired or Not Valid", hit ignore and proceed with the run; however, notify a Director and refer to **Procedure - Maintenance and Calibration - ABI 7500 Fast.**
4.6	Choose the Template icon. On the desktop, you will find a folder named “Run Templates (clinical). Select the file entitled

		"COVID_triplex March 12 2020.edt"
	4.7	Once the program opens, save the file immediately under a different name. DO NOT overwrite the template file. • **File – Save As.** On the desktop, choose the Shortcut to LAB. Under folder COVID "current year", save as under a DIFFERENT name (acc. No., COVID, and Date).
	4.8	Verify that all conditions are as follows: **Experiment properties** (ensure the following are highlighted): • 7500 FAST (96 wells) • Quantitation – Standard curve • Taqman reagents • Fast (~40 min to complete a run) **Plate Setup – Define targets and Samples:** • Under the **Define targets** tab, ensure the target name, reporter, and quencher are as follows: 
	4.9	In the **Define Samples** tab, scroll down and verify that all 96 specimens are selected. Well #1 should correspond to the positive control, well #2 the negative control, and specimen start at #3, etc.

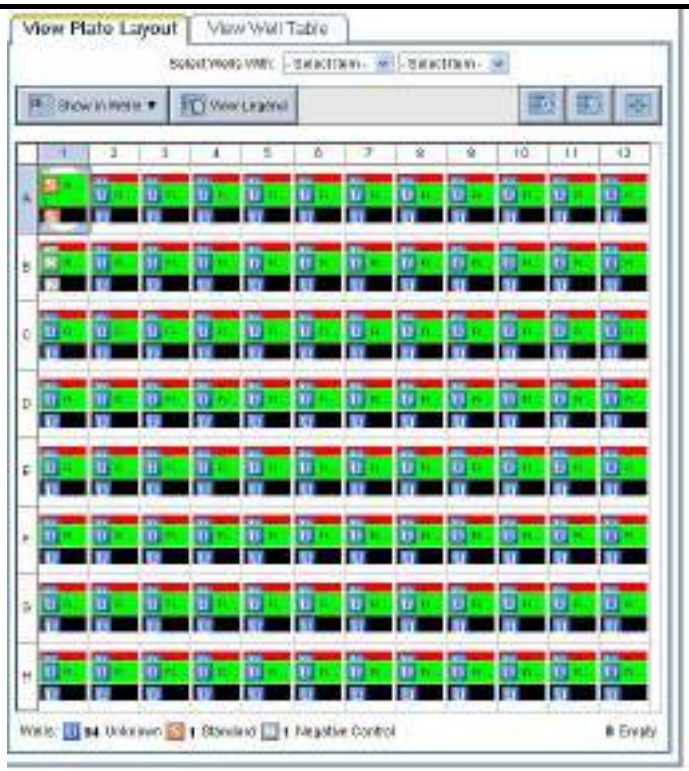
Note: This is where specimen accession numbers can be entered using a barcode reader.

Under "**Assign Targets and Samples**", a plate setup should automatically be loaded.

- Each well should be assigned all targets (RdRP, E and RNaseP) and the highlighted tasks include: unknown (U), standard (S), and negative (N).

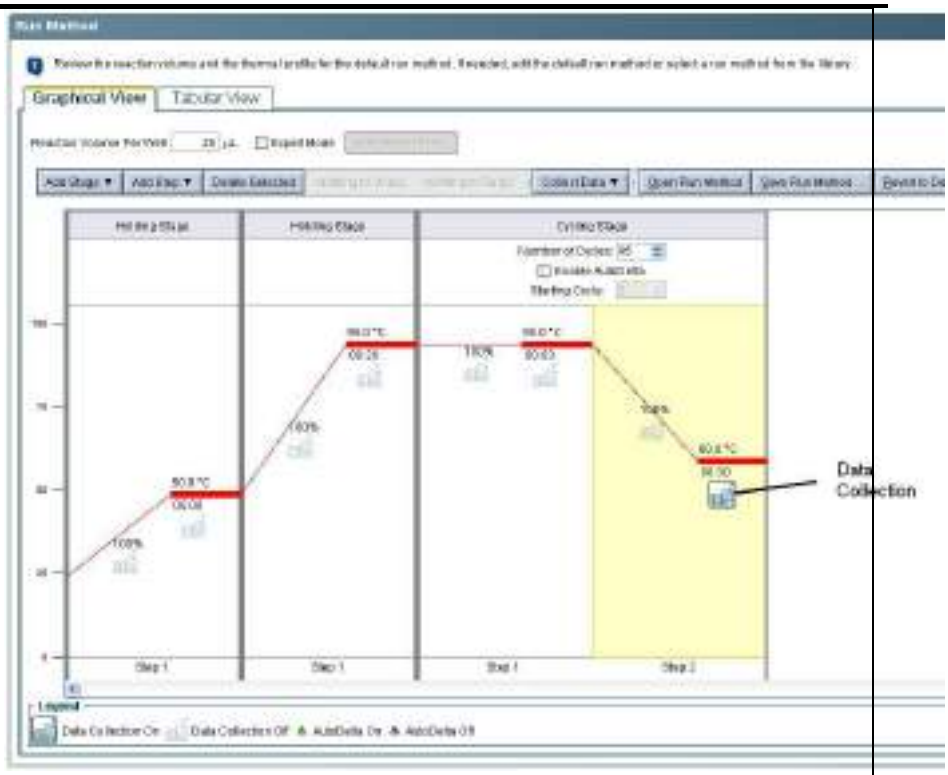
Notes:

- Well A1 (positive control) should display "S"
- Well B1 (negative control) should display "N"
- All others wells should display "U"



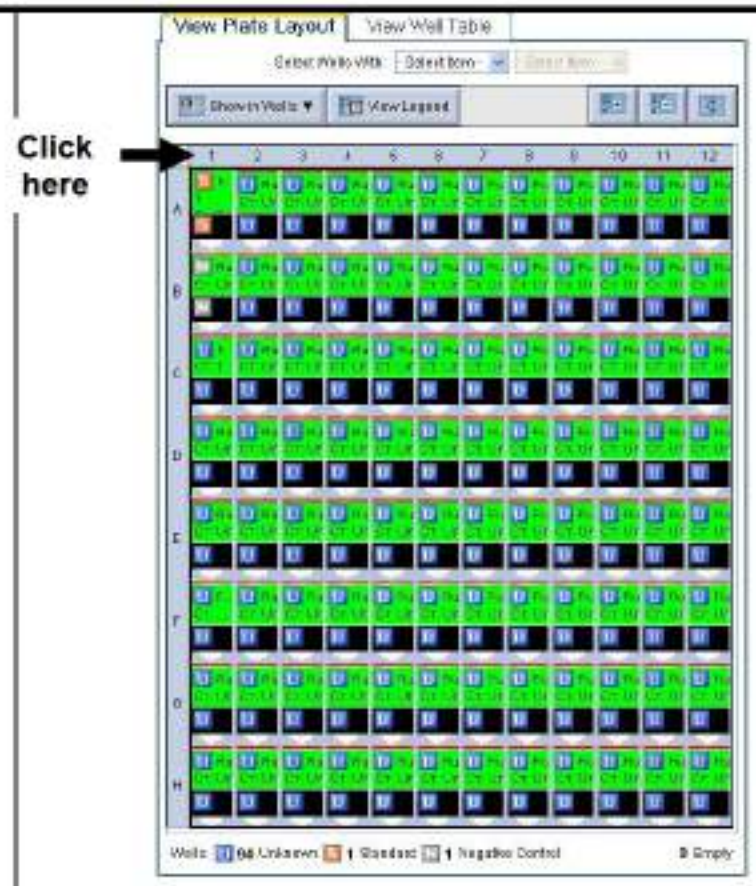
Run Method (verify the thermocycling parameters)

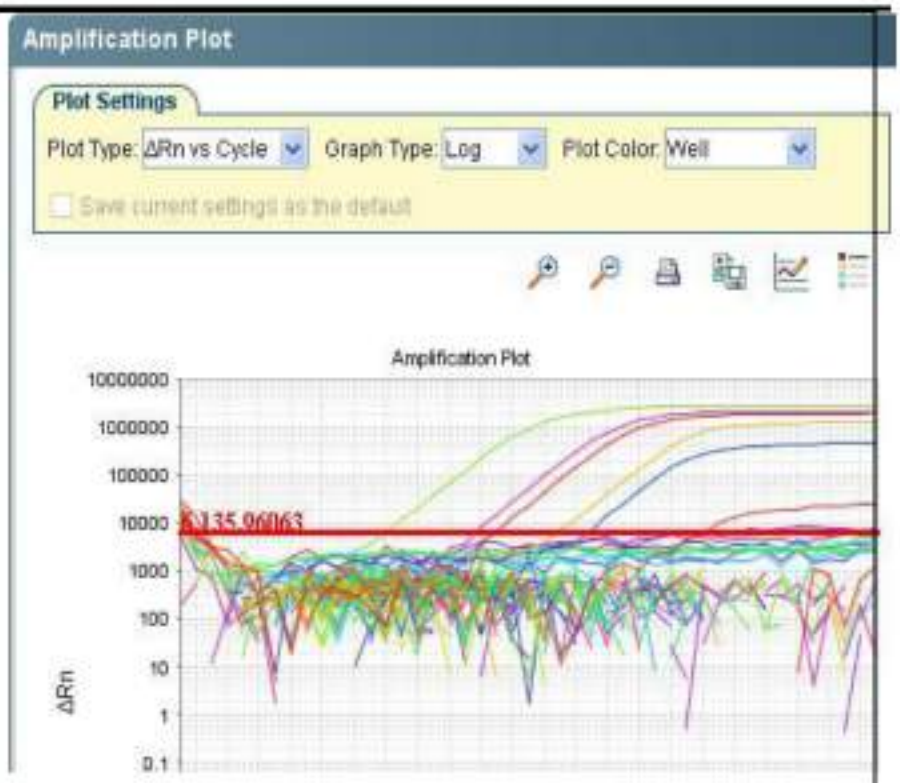
Step	Stage	Cycles	Temp. (°C)	Time (min:sec)
Reverse Transcription	1	1	50	5:00
Initial denaturation	2	1	95	0:20
Amplification	3	45	95	0:03
			60	0:30

	 **Note:** Verify that the data collection "on" icon is visible and "ON" at the elongation stage.
4.10	If all parameters are correct, select **Run** and **Start Run**.
4.11	During cycling, return to **Experiment Menu/Plate Setup/Define Samples** to assign the specimens and controls names. **Notes:** • The positive control should be in well A1, the negative control in well B1, followed by the specimens. • If using the barcode reader to enter the accession numbers, scan the patient label and hit enter in between each one.
4.12	Complete the **Form – Amplification – ABI COVID 19**
4.13	When the amplification is complete, proceed to data analysis.

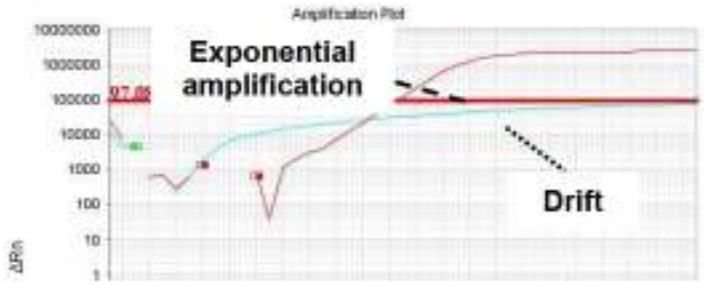
5. Data analysis

Step	Action
5.1	Open the **Analysis tab**, then **Amplification plot**. Verify the following parameters: Under the **Plot Settings** tab: • The Plot Type should read **"ΔRN vs. Cycle**" • The **Graph Type** should read "**Log**" • The **Plot Color** should be "target"  Under the **Options** tab: • Select **Target**: RdRP • **Threshold: Auto** should be unchecked • **Auto Baseline, Show: Threshold and Baseline Start** should ALL be checked. 
5.2	On the right side panel, in the first tab ("**view Plate Layout"**), click on the square on the top left corner to highlight all wells. **Note**: The wells for the controls/specimens can be highlighted instead of the whole plate by using shift or controls and clicking on the desired wells.

		
	5.3	On the graph in **"log"** scale, adjust the threshold so that it is above background fluorescence. Hit the green **Analyze** button after the final adjustment. • **Note:** The threshold should be set as close to the background as possible to ensure assay sensitivity.

	
5.4	Repeat steps 5.3 and 5.4 for the other target **E** by changing the target in the **Options** tab. • **Note:** Hit the **Analyze** button after each target adjustment.
5.5	To facilitate visualization in the results table, go into the right side panel, in the second tab (**"view Well Table"**). Click on the button **"Group By"** and **Select Well Position (column)**. 

	5.6	Then, click on the button "**Show in Table**".  • Deselect the following options: o **Omit** o **Flag** o **Ct mean** o **Ct SD** o **Quantity** o **Quantity Mean** o **Quantity SD** • Ensure the following are selected: o **Well** o **Sample Name** o **Target Name** o **Task** o **Dyes** o **Ct** o **Comments** 
	5.7	Proceed to the analysis of each specimen/control.

	5.8	For each specimen/control, check for Ct values and exponential amplification in each of the target channels. • Start by clicking on well **A1** (positive control) and select the **RdRP** channel under Options/Target (left panel). Record the results in **Target 1** column of the **Form - Sample List – Real-time PCR and RT-PCR (ABI7500Fast) or Form - Sample List – Real-time PCR and RT-PCR (ABI7500Fast) Mag96**. • Proceed to the next well B1 (negative control), then to the specimens in wells **C1, D1, etc.** • Once the RdRP analysis is complete, repeat the process for the other target by changing the channel to **E.** Record the results in **Target 2** column of the **Form - Sample List – Real-time PCR and RT-PCR (ABI7500Fast)**. **Notes:** • Record all results on the **Form - Sample List – Real-time PCR and RT-PCR (ABI7500Fast)**. • For positive targets, record the Ct values. • Ensure that the amplification curve is exponential. If unsure, consult a Director. • Some reactions may contain non-specific increases in background signal ("drift") and may not represent true amplification despite having a Ct value (see below). 
	5.9	Verify the controls to ensure quality control • **Negative Extraction:** all viral targets should be negative. • The **Positive Control** should have a signal in each of the viral targets with exponential amplification AND the Ct values should be ~35.
	5.10	Indicate on the worksheet whether the QC passed or failed, sign and date. Turn off the instrument and shut down the computer.
	5.11	Prior to reporting, copy the results of the controls on the **Form – Quality Control - Molecular QC logsheet.**

Result Interpretation

1. A specimen is considered **POSITIVE** if there is exponential amplification in the RdRP viral target channel.

- If Ct <35 for RdRp, report as positive.

  Report result in ARE using the drop down list beside the result. Hit Verify.

  Note: Record Ct value for positives and which instrument the specimen was run on in an Order Note.

  Email all positive results to PHProvincialCOVID@nshealth.ca, Todd Hatchette, Jason Leblanc, Janice Pettipas and the DHW Epi team surveillancedhw@novascotia.ca)

2. A specimen is considered **NEGATIVE** if the RdRP viral target channel is negative, non-exponential amplification (drift), or RdRP Ct ≥38.0

.

Report negatives in Batch Result Entry using the saved worklist. See Job Aid - Genlab LIS COVID document # 90523 for details

3. A result may be deemed **INDETERMINATE** if:

- RdRP has a Ct of ≥ 35.0 to <38.0 with exponential amplification.
- **Report as Indeterminate.** Put results in an Order Note.

Report result in ARE using the drop down list beside the result.
Add NCOVIND in an Order Comment.

Email all indeterminate results to PHProvincialCOVID@nshealth.ca, Todd Hatchette, Jason Leblanc, Janice Pettipas and the DHW Epi team surveillancedhw@novascotia.ca)

Reporting, Cancellation, and Workload:

- Positive for inpatients, the inpatient floor should be contacted to confirm they have received the report. Document all tasks (obtain the first/last name of the person to which the information was relayed).

- Enter the total workload under the **QC patient**, using **ENCOVQC.** This accounts for the RT-PCR and extraction (any number of samples).
- When appropriate, enter the patient workload under the **patient accession number,** using:
  - **GRIND** – processing for tissue or a viscous fluid
  - **REXA or RPCR** – repeat extraction or PCR, respectively

Limitations

- Reagent controls are not routinely performed; however, if contamination is suspected, may be added after consultation with a Director.
- Internal controls are not incorporated in this assay and therefore, PCR inhibition cannot be ruled out in negative specimens.

Procedural Notes

- If needed, the 96-well plates could accommodate processing of nucleic acids from three MagNAPure LC extractions; however, a more practical workflow would be the processing from two extractions (2 x 32 samples).
- Pooling of specimens requires Director approval. If specimens are pooled (ex: BALs), only one test should be reported and the other cancelled with **CN15**, (Laboratory Order Error). Enter "specimens have been pooled" under the chartable comment tab.
- Specimens with insufficient volume require Director approval. If processed and the final result is negative, enter a **PNSQ** chartable comment.
- If multiple pathogens are detected, notify a Director.

Related Procedures

Document Name	Document #	Location
Critical Results Reporting Microbiology Procedure	4010	General Documents Manual
Respiratory PCR Archive Procedure	13470	Molecular Manual
Procedure – Influenza Subtyping	33342	Molecular Manual
Procedure – Amplification - Respiratory Viruses – Conventional RT-PCR	26439	Molecular Manual
Procedure - Extraction - RNA - Manual	26443	Molecular Manual
Procedure - Extraction - TNA - Automated	26444	Molecular Manual

Job Aid and Forms

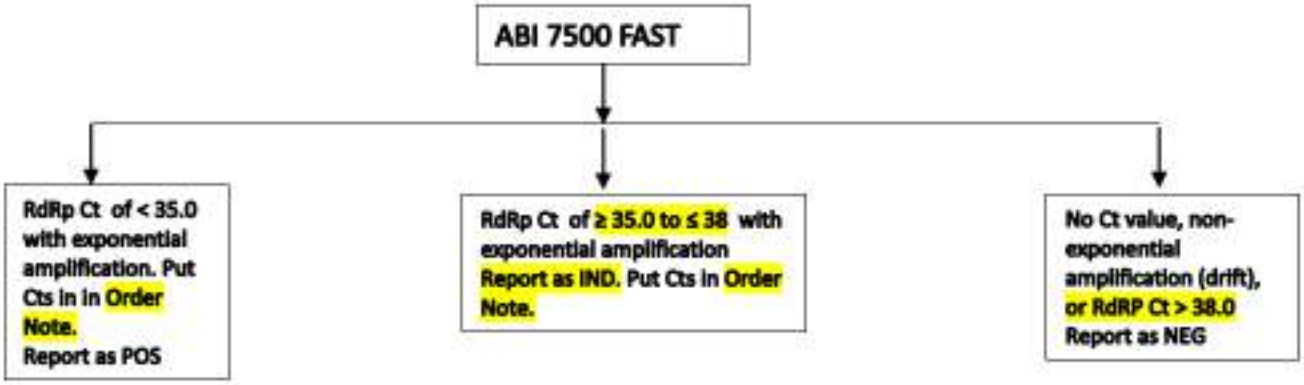
Document Name	Document #	Location
Form - Amplification - Influenza A, B, and RSV Real-time RT-PCR	26423	Molecular Manual
Form - Quality Control - Molecular QC logsheet	26431	Molecular Manual
Form - Quality Control - Positive Control logsheet	26432	Molecular Manual
Form - Quality Control - Primers - Influenza A, B, and RSV	30587	Molecular Manual
Form – Sample List – Real-time PCR or RT-PCR (ABI7500Fast)	29838	Molecular Manual
Form – Sample List - Proteinase K Digestion	28030	Molecular Manual
Job Aid - Respiratory Virus Reporting	29822	Molecular Manual
Job Aid - Specimen Preparation	26452	Molecular Manual
Job Aid - Genlab LIS COVID	90523	Paradigm

References

Detection of COVID-19 virus (2019-nCoV) using a triplex quantitative reverse transcriptase PCR (qRT-PCR) on the ABI Real-time PCR System.
BCCDC Public Health Laboratory
Version 1.0 Feb 20, 2020

Process - ABI COVID Reporting

Final Approval: Dr. Jason Leblanc



TITLE: MB Panther Sars CoV-2 COVID 19 Procedure	**Doc #:** 89768
Section: Management System\PLM\Microbiology\5-VIM Panther\	**Version:** 1.1 Current
Document Owner: MB Administrator VIM Bact	**Effective Date:** 11/10/2020
Final Approval: Dr. Jason Leblanc	**Review Date:** 5/1/2022

Purpose The Aptima SARS CoV-2 assay is a nucleic acid amplification test for the qualitative detection of RNA from SARS CoV-2 isolated and purified from respiratory specimens.

Abbreviations and Definitions

MTU: Multi-Tube Unit
TCR: Target Capture Reagent
wTCR: Working Target Capture Reagent
TMA: Transcription Mediated Amplification
HPA: Hybridization Protection Assay
IC: Internal control
RLU: Relative Light Units
RT: Room Temperature

Safety Precautions

- Avoid contact with Auto Detect 1 and Auto Detect 2 with skin, eyes and mucous membranes. In case of eye or skin contact, flush immediately with water and seek medical attention.
- The NaOCl Bottle and the Liquid Waste Bottle contain sodium hypochlorite. Avoid contact with skin, eyes, and mucous membranes. Wash affected area with water if contact with this fluid occurs. If the fluid spills, dilute with water before wiping dry.
- Follow Universal Precautions when handling all samples, when performing all maintenance activities and when handling liquid or solid waste.
- A 1:1 dilution of 5% and 7% sodium hypochlorite solution should be used to treat gross spills of specimens, positive controls or amplified reaction mixtures.

Materials

Reagents	Stability and Storage	Preparation (Y/N)
Amplification Reagent	2-8 ˚C	Y
Enzyme Reagent	2-8 ˚C	Y
Probe Reagent	2-8 ˚C	Y
Internal Control Reagent	2-8 ˚C	Y

Amplification Reconstitution Solution	15-30 ˚C	Y
Enzyme Reconstitution Solution	15-30 ˚C	Y
Probe Reconstitution Solution	15-30 ˚C	Y
Target Capture Reagent	15-30 ˚C	Y
Selection Reagent	2-30 ˚C	N
Negative Control	2-8 ˚C	N
Positive Control	2-8 ˚C	N
Wash solution	15-30˚C	N
Oil reagent	15-30˚C	N
Buffer for deactivation fluid	15-30˚C	N
Auto detect reagent 1	15-30˚C	N
Auto detect reagent 2	15-30˚C	N

Reagent preparation: If selection reagent is stored in the fridge, allow it to come to RT before use.

Reagents are stable until expiry date on the bottle before reconstitution, 30 days at 2-8 ˚C after reconstitution or 72 hours on board once prepared.
Unopened controls are stable until the date indicated on the vials.

Supplies
Multi-Test Units (MTUs)
Waste bags
Waste cover
Tecan 1000 µL tips
Bleach
Bleach Enhancer
Panther Fusion Specimen Lysis Tubes
Replacement reagent caps
Penetrable caps
Disposable gowns
Disposable gloves
Disposable pads

Equipment
Panther instrument
Water bath

Sample

Sample type	Amount required	Transport and Storage	Stability
Nasopharyngeal Swab collected in UTM	500 µL	2˚C to 8˚C Once specimen is added to the Panther tube: 2˚C to 30˚C	96 hours 6 days
Roche swab in UTM	500 µL	2˚C to 8˚C Once specimen is added to the Panther tube: 2˚C to 30˚C	96 hours 6 days
Throat gargle	500 µL	2˚C to 25˚C	48 hours

Sample retention: Processed Panther Fusion tubes can be discarded once the results are reported. Cryovial aliquots are archived indefinitely in the molecular lab.

Maintenance See MB Panther Maintenance Procedure Doc # 64744

Quality Control

Control	Stability	Frequency	Preparation (Y/N)
Positive control	2-8˚C until expiry on box	Once every 24 hours	N
Negative control	2-8˚C until expiry on box	Once every 24 hours	N

An internal control (IC) is added to each sample with the wTCR. If the IC is invalid the specimen must be repeated.

Procedure

1.

Step	Action
1.1	Create a Worklist list for NCOV using Worklist Request in LIS. Use the VGMB COVID Holding worklist. Refer to PLM General Applications-Worklist Request Procedure Document #6674. Using Pending Inquiry, transfer the specimens on this worklist from VGMB COVID-19 Holding Bench to VGMB Panther. Log these specimens into MBCP under VGMB Panther. Refer to 10-0 MB Pending Inquiry Procedure Document # 51368 (section 3).
1.2	Record temperature/humidity.
1.3	Clean any bench surface that will be used with bleach enhancer (refer to MB Panther Maintenance Procedure document #64744 and MB Panther Daily Operation and CTGC Procedure document #64740).
1.4	Remove a set of controls from the fridge to warm to room temperature if required (run every 24 hours, if new reagent lot or reagents removed and reloaded).
1.5	Check the Panther Fusion instrument for messages. Messages will appear related to required maintenance, consumables that need to be refilled and any errors on the system. Once Messages are noted click Clear All.
1.6	Load any required consumables on Panther (tips, MTU's, fluids). To load tips, MTU's and Panther universal fluids refer to Panther Daily Operation and CTGC Procedure document #64740.
1.7	Perform any required Panther maintenance (Prime, change sample shield, PC Reboot, replace mag wash, empty waste) refer to Panther Daily Operation and CTGC Procedure document #64740.
1.8	Take previously prepared reagents out of the fridge to come to room temperature. Once at RT the probe reagent can be heated for 1-2 minutes in a waterbath ≤62˚C. After this heat step the probe can be used even if precipitate remains. Mix Amplification, Enzyme and Probe reagents by inversion.
1.9	Reconstitute more reagents if required: Make sure the RT and refrigerated boxes of reagent are the same lot number. Pair each reconstitution reagent with its lyophilized reagent. Open the lyophilized vial and firmly insert the reconstitution collar into the vial opening. Open the matching reconstitution solution bottle and while holding it on the bench insert the other end of the collar. Slowly invert the assembled bottles. Allow the solution to drain from the bottle into the glass vial.

	Gently swirl the solution in the bottle to mix. Wait 30 minutes for the lyophilized reagent to go into solution. Mix the solution in the glass bottle until it is completely dissolved then invert the assembled bottles again. Allow all of the liquid to drain back into the plastic bottle. Remove the reconstitution collar and glass vial. Record the date and initials on the bottle. Remove foam or bubbles with individually packaged swabs. Place each bottle in the reagent rack. Selection Reagent is ready to use. Record the date and initials on the bottle. Gently swirl then remove foam or bubbles with individually packaged swabs. Pair the TCR and IC bottles. Open the bottle of TCR. Open the bottle of IC and pour the entire contents into the bottle of TCR. Cap the TCR bottle and gently swirl then remove foam or bubbles with individually packaged swabs. Record the date and initials on the bottle.
1.10	If controls are required (see Quality Control section above), load control tubes in a specimen rack.
1.11	Allow all patient specimens to come to room temperature. Add 500 µL of UTM to Panther Fusion Specimen Lysis Tube. Load prepared lysis tubes into a sample rack and load into Panther.
1.12	Specimen pipetting will begin when there is a pair of controls processing or valid results for controls are registered on the system. Once the controls and specimens have been sampled they can be removed from the system. If a specimen has a sampling error due to bubbles or volume error it can be centrifuged for 5 minutes at 420 RCF and rerun. Controls can only be used once and should be discarded.
1.13	Once results are complete a report can be printed. Negative results will auto release from the Panther and autoverify in LIS. Any specimens which are invalid should be repeated. If the specimens repeats as invalid report as Indeterminate. For indeterminate results add NCOVIND in an Order Comment. Positive results will hold in LIS. Manually verify positive results. Public health needs to be notified about all positives and indeterminates. This can be done by sending an email to PHProvincialCOVID@nshealth.ca (also copy Dr. Hatchette, Dr. Leblanc, Janice Pettipas and the DHW Epi team surveillancedhw@novascotia.ca) and including the following information for each patient : **Name:** **HCN:** **Accession #:** **Result:** For **inpatients**, the floors must also be phoned and the **CR template** must be completed in the order comment.

1.14	Take QC biochemical Panther QC under the QC patient.

Result Interpretations Verify QC is valid. RLU's should be around 250 for the Negative control and 1250 for the positive control.
The Panther Fusion system automatically determines the test results for samples and controls. A test result may be negative, positive, or invalid. The IC result must be valid for negative COVID-19 results to be valid.

Procedural Notes Avoid cross-contamination during the specimen handling steps. Ensure specimen containers do not contact one another. Discard used material without passing over **any open container.**

Recap all reconstituted reagents with new reagent caps each time prior to storage.

Probe reagent is photosensitive. Protect this reagent from light during storage.

Do not top off reagent bottles. The Panther system will recognize the volume discrepancy and reject the reagent.

Principle The Aptima Sars CoV-2 assay is a NAAT that utilizes target capture, transcription-mediated amplification, and hybridization protection assay technologies to detect two conserved regions of the Orf1ab gene.

Related Procedures and Documents

Document Name	Document #	Location
MB Panther Maintenance Procedure	64744	Paradigm
MB Panther Daily Operation and CTGC Procedure	64740	Paradigm
10-0 MB Pending Inquiry Procedure	51368	Paradigm
PLM General Applications-Worklist Request Procedure Document	6674	Paradigm

Reference Hologic® Aptima Sars CoV-2 Assay AW-21677-001 Rev. 001

Privacy Office
Legal Services
Centennial 1-031
1276 South Park Street
Halifax NS B3H 2Y9
Telephone: (902)4732869
Fax: (902)473-7850

January 4, 2021

Sent via e-mail

Re: Disclosure – OUR FILE# NSHA-2020-74

On December 15 2020, Nova Scotia Health received your request by a way of transfer from the Department of Health under the Freedom of Information and Protection of Privacy (FOIPOP) Act for a copy of the following:

documents and records which detail the process and evaluation criteria which are applied to ascertain and report a PCR test result as positive, negative and inconclusive. The designations of "positive", "negative" and "inconclusive" are used in communication with the public, however, internally, there may be both different names and additional categories of results. For greater clarity on the specific information being sought, the documents would contain the "CT" (cycle threshold) values which test results are evaluated against. These values are not industry standards, rather, each lab would establish its own evaluation criteria and thresholds which categorize a result as positive, negative or inconclusive. For example, if a test returns an inconclusive result, what specific steps are taken by the lab? Are the samples reprocessed/retested? What is the process to minimize the number of "false positives"?

Documents must exist that spell out the evaluation criteria. The records may exist in the form of original documents, revised documents, addendums to these documents and or communication records such as email messages to and from lab leaders and technicians discussing or specifying the criteria for categorizing assay results. The requester is also seeking reports or data which detail, in the aggregate, the test results, categorized according to the value which the marker required for the fluorescent signal to cross the threshold.

Please find attached copies of the records located in response to your request. These records are being provided to you in their entirety. Please kindly note that for the latter part of the request, 'reports or data which detail, in the aggregate, the test results, categorized according to the value which the marker required for the fluorescent signal to cross the threshold,' we do not collect this data in the way specified. While we would like to assist you in creating this data, it is a task that will involve a tremendous amount of time and the responsible parties for this data are currently leading Nova Scotia's COVID-19 response. Noting that the provisions of FOIPOP does not require us to create records that do not exist, we have nevertheless developed a datatset with a line list of positive results with the CT values as requested in your FOIPOP. We believe that these documents answer the questions generated in your request. The other documents provided to you are the standard operating procedures for our testing, the kit inserts for commercial assays, the FAQ we have generated for end-users to

understand the testing and a summary table of CT values with a nice reference from Ontario that goes into more detail on how CT values should be interpreted.

We are now closing your application with our Office.

Should you have any questions or comments, please do not hesitate to contact me at the address or telephone number provided above.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review

Sincerely,

Fola Adeleke

For: The Privacy Office
Nova Scotia Health Authority

c/c: to file

TITLE: 04-0 MB GeneXpert SARS-COV-2 Procedure	**Doc #:** 86326
Section: Management System\PLM\Microbiology\2-BACT GeneXpert\COVID\	**Version:** 1.7 Current
Document Owner: MB MPA Technical Specialist	**Effective Date:** 12/7/2020
Final Approval: Dr. David Haldane	**Review Date:**

Purpose

The Xpert® Xpress SARS-CoV-2 assay on the Cepheid GeneXpert system is a qualitative, real-time PCR *in-vitro* diagnostic test for the detection of SARS-CoV-2 nucleic acid from a UTM Viral Transport Media Swab, Aptima® swab or saline gargle specimen.

NOTE: Processing on specimen for COVID-19 testing requires containment level 2+ conditions.

Abbreviations and Definitions

BSC- Biological Safety Cabinet
LIS- Laboratory Information System
MPA- Microbiology Processing Area
MRE- Result Entry
NPS- Nasopharyngeal Swab
ORV- Order Result Viewer
UTM- Universal Transport Medium

Materials

Equipment
• GeneXpert Dx system equipped with GX 4.7b software or higher: GeneXpert instrument, computer, barcode reader and operator manual • Printer • Disposable gloves, mask, eye protection, disposable gown • Biosafety cabinet • Micropipet with 1000 uL tips • Labels/permanent marker • Xpert® Xpress SARS-CoV-2 cartridge (stored at 2-28ºC until expiry date) • Plastic cartridge holder (if supplied by manufacturer)

Sample

Sample type	**Amount required**
Nasopharyngeal swab sample in a UTM swab	300 µL
Throat/nose swab sample in Aptima® swab	300 µL
Saline gargle specimens	300 µL

Sample retention: Store and transport specimens at 2-8ºC prior to processing. Sample is stable for 72 hours at 2-8ºC.

Limitations

This assay is validated for nasopharyngeal swabs collected in UTM Viral Transport Media, throat/nose swabs collected in Aptima® media and saline gargle specimens.

Calibration

It is recommended that the instrument be recalibrated once per year or at 2000 tests per instrument module, whichever comes first. To schedule a calibration contact Cepheid Service Support.

Quality Control

Sample-processing control (SPC) – Ensures a sample was correctly processed. The SPC is included in the cartridge, and with each cartridge, it verifies that sample processing is adequate.

Probe Check Control (PCC) – Before the start of the PCR reaction, the GeneXpert System measures the fluorescence signal from the probes to monitor bead rehydration, reaction tube filling, probe integrity, and dye stability.

External QC – Upon new shipment

Each shipment of cartridges are to be evaluated upon arrival with a SeraCare AccuPlex™ Reference Material Kit (purchased separately).

External QC Instructions for use on the GeneXpert System:

Step	Action
1.	Allow one positive and negative control tube to come to room temperature.
2.	Thoroughly mix controls by vigorously inverting several times immediately before use.
3.	Pre-label two cartridges as positive and negative control.
4.	Add 300 µL of each positive and negative control to the two labelled SARS-CoV-2 cartridges.
5.	Enter the sample ID, scan the cartridge, load the cartridge and start the run as outlined below in Procedure 2 for each the positive and negative controls.
6.	The two controls should generate a positive and negative result before the shipment should be released for use.

Procedure

DO NOT turn the cartridge on its side to scan the barcodes. The cartridge must stay upright at all times. Cartridges that have not been kept upright after opening can cause invalid results. It is best practice to leave the cartridge in the plastic tray supplied by the manufacturer.

Always pick up the cartridge by its body. Do not pick up the cartridge by the protruding reaction tube located at the back of the cartridge.

All samples are to be ordered with the test code: **E NCOVST** (Rapid COVID-19).

The time for the completed test on the GeneXpert is approximately 50 mins.

1. Preparation of GeneXpert cartridge

Step	Action
1.1	Perform all work in a BSC.
1.2	Specimen Receiving Area will vortex the UTM NPS or Aptima® throat/nares swab for approximately 10 seconds.

1.3	Prepare two aliquots from the vortexed swab into two, 2 mL screw capped tubes. Both aliquots are to be frozen at -70°C for archiving once testing is complete. Note: The MLT receiving an aliquot for testing from MPA is to ensure: • The ordered test code is correct: **E NCOVST**. • Clinical MLT has to check **ORV** to ensure that there is not a pending **E NCOV** ordered. If there is, Clinical MLT is to cancel the **E NCOV**. The 4th floor does not need to be told the test was cancelled.
1.4	If the aliquot sample contains particles from the nasal cavities, these particles must not be pipetted into the GeneXpert cartridge. The aliquot can be centrifuged in a micro-centrifuge at 13,000 g for 5 mins. The centrifugation either has to be performed inside the BSC or the sealed rotor head must be placed in the BSC before opening after centrifugation. Note: If the micro-centrifuge does not have a sealed rotor head or if the centrifuge is not performed inside the BSC, an aliquot tube with snap lids is not advisable- use screw on lids.
1.5	Obtain one Xpert® Xpress SARS-CoV-2 cartridge for each sample. Take care not to tip the cartridge so the liquid is not spilled. It is preferred that the cartridge be placed in the provided plastic cartridge carrier supplied by the manufacturer so that it is not tipped. Do not touch the circle pattern on the top of the cartridge and do not touch the protruding plastic on the back of the cartridge as not to contaminate the cartridge.
1.6	Label the cartridge with a small LIS label on the right hand side of the cartridge, being careful not to cover the bar code located on the front of the cartridge.
1.7	Flip open the lid of the cartridge (by only handling the edges of the blue lid) and pipette 300 µL of liquid from the aliquot sample. **Note:** return both aliquots to MPA fridge to go up to 4th floor for archiving once testing is complete. If the sample is **Positive**, write POS on the outside of the plastic bag with the 2 aliquots. If pipetting from an Aptima® tube: • Pipette very gently so as not to create bubbles or dislodge any particles that have settled to the bottom of the aliquot tube. • When dispensing the 300 µL from the aliquot sample into the GeneXpert cartridge, gently touch the pipette tip to the inside wall of the cartridge just inside the cartridge opening and

	slowly dispense the liquid by letting it run down the inner wall of the cartridge. This is to avoid the production of bubbles will can cause reduced sensitivity or invalid test results. If pipetting from a UTM tube or saline gargle: • Pipette 300 µL of liquid from the aliquot sample and take care not to dislodge any particles that have settled to the bottom of the aliquot tube. Snap the lid of the cartridge closed (by only touching the edges of the blue lid) ensuring not to tip the cartridge at any time.
1.8	The cartridge can be loaded for testing immediately (no rest time is required after sample addition) but the cartridge must be tested within 30 minutes of the sample being added.
1.9	Continue with section 2 below, create test.

2. Create Test

This section lists the basic steps of running the test. For detailed instructions, see the *GeneXpert® Dx System Operator Manual.*

Step	Action
2.1	Click **Create Test** on the menu bar**.**
2.2	Scan the **LIS Patient ID barcode** using the barcode scanner (leave the cartridge in the plastic tray so it is not tipped). The **LIS Patient ID barcode** can also be entered manually by clicking the **Manual Entry** button and then click **OK.** **DO NOT** turn the cartridge on its side to scan the barcodes. The cartridge must stay upright at all times. Cartridges that have not been kept upright after opening can cause invalid results. **Always** pick up the cartridge by its body. Do not pick up the cartridge by the protruding reaction tube located at the back of the cartridge**.**
2.3	Scan the cartridge barcode on the front of the cartridge or the barcode on the box. The cartridge lot number can also be entered manually by clicking **Manual Entry** and then click **OK**. The Create Test dialog box appears.
2.4	Click **Start Test** to begin test (note: the cartridge is still not loaded yet).
2.5	The green light above the instrument module door will begin blinking when it is ready to load the cartridge. Open the instrument module door below the module with the blinking green light.
2.6	Place the cartridge on the module bay floor with the cartridge label facing out. Make sure the cartridge sits level on the bay floor and is

	positioned flush with the front of the bay.
2.7	Close the instrument module door until the green light stops blinking. Note: Be very gentle while closing the door until it clicks. The doors are delicate and if a door breaks then the whole module has to be replaced and not just the broken door.
2.8	During the first few minutes after you start the test, the system moves the cartridge contents and rehydrates the reagent beads. If applicable to the specific assay, the system also performs a probe check to see if the master mix is reconstituted properly and that the probes are present in the master mix.
2.9	If the probe check fails, the test will abort. You can check the error message to review the cause of the probe check failure. If the probe check passes, the test continues.
2.10	To check the status of a cartridge, click **Check Status**. In the **Modules** section of the screen there is a column labelled **Remaining Test Time**. For each **Module Names** (i.e. A1- A4 containing the cartridges), the amount of time remaining in the test is displayed.
2.11	When the test finishes, the instrument module door unlatches and the green light turns off.
2.12	Unload the completed cartridge from a section (the light will be out and the door will be slightly ajar) by grasping the cartridge and gently lifting it up without tilting the cartridge so as not to spill any of its contents. Discard the used cartridge in a discard bucket.

3. Viewing and Printing Results

For more detailed instructions on how to view and print the results, see the *GeneXpert Dx System Operator Manual.*

Step	Action
3.1	The test results should print automatically when the test is completed. If needed, a copy can be printed following the step listed below.
3.2	Click on the **View Results icon**.
3.2	Click on **View Results** in the Menu Bar at the top of the screen (not the View Results Icon).
3.3	Click on **View Test**.
3.4	Double Click on the accession number of the test to be viewed. The list of tests can be sorted by clicking on the column heading that you want to sort.
3.5	Click on **Report** at the bottom of the screen.
3.6	Click on **Preview PDF**. Click **Print** icon.
3.7	If any detailed information is needed when viewing an accession number, the following tabs can be clicked to see each individual piece of information (it is available on the printed report).The tabs are: **Test Result**, **Analyte Result**, **Detail**, **Errors**, **History** and **Support**.

Result Interpretation and Reporting

RESULTS

The printed report includes a Test Result that is SARS-CoV-2 NEGATIVE, PRESUMPTIVE POSITIVE, POSITIVE and INVALID. The "**presumptive positive**" test result interpretation **is not to be used**. The interpretations listed below in the table are to be used to report.

Analyte Result			Instrument SARS-CoV-2 Test Result (Do not use these interpretations)	Lab Interpretation for Reporting	LIS Test Code Phrasing
E	N2	SPC			
POS and Ct ≤37**	POS and Ct ≤37**	N/A	Positive	**Positive**	**FP**
POS and Ct ≤37***	NEG	N/A	Presumptive Positive	**Indeterminate**	**FI**
NEG	POS and Ct ≤37***	N/A	Positive	**Indeterminate**	**FI**
NEG	NEG	PASS	Negative	**Negative**	**FN**
NEG	NEG	FAIL	Invalid	**Invalid**	*

*Test is invalid and must be run again with a new cartridge. If the patient sample is **Invalid** with the 2nd cartridge, notify the 4th floor so that the sample can be tested there.

** Any **FP** results with a Ct result >37 must be discussed with a Director prior to reporting.

*** Any **FI** results with a Ct result >37 must be discussed with a Director prior to reporting.

REPORTING:

FP- Positive. (See **MB GeneXpert SARS-COV-2 Reporting Job Aid Doc 86410** before reporting).

"**Positive for COVID-19**"

FN- Negative. "**Negative for COVID-19 virus**"

FI- Indeterminate. (See **MB GeneXpert SARS-COV-2 Reporting Job Aid Doc 86410** before reporting).

"**SARS-CoV-2 (COVID-19) result indeterminate. This may represent early disease, late disease, or a false positive result. Please recollect once after 24hr if clinically warranted. If the indeterminate result persists, please discuss with Public Health**."

--Text the following information into the MRE screen for **Positive** and **Indeterminate** results:

- The GeneXpert number on which the cartridge was tested. This can be found on the top left corner of the printed result (i.e. #1, 2 or 3).
- The Ct values for the Analyte targets E and N2.

Refer to the **GeneXpert SARS-COV-2 Reporting Job Aid Doc 86410** for all phone calls and/or emails that must be completed to report the result of the test to the appropriate people.

Amend Report (if needed):

- Changing a report from **Negative** to **Positive**:
  - AMEND
  - CORR (Refer to **Corrected Results Procedure Doc 6356** for corrected report protocols).
  - P
  - For
  - COVID19
- Changing a report from **Positive** to **Negative**:
  - AMEND
  - CORR (Refer to **Corrected Results Procedure Doc 6356** for corrected report protocols).
  - N
  - For
  - COVID19N

Procedural Notes	**Chamber chimneys remain sealed after opening cartridge lid** – Break the seal with a pipette tip or other tool **Reasons to Repeat the Assay** • An **INVALID** result indicates that the internal SPC failed. The sample was not properly processed or PCR was inhibited. An invalid result can also be

caused by air bubbles in the reaction tube

• An **ERROR** result indicates that the assay was aborted. Possible causes include: the reaction tube was filled improperly; a reagent probe integrity problem was detected; the maximum pressure limit was exceeded; a system component failed.

• A **NO RESULT** indicates that insufficient data were collected. For example, the operator stopped a test that was in progress, a load error occurred, the software was closed prematurely, or a power failure occurred.

- Note: If any of the above are observed, repeat the Xpert SARS-CoV-2 test. If the error persists, send the specimen for routine processing.

Related Procedures and Documents

	Document #	Location
MB GeneXpert Maintenance Procedure	68651	Paradigm
MB GeneXpert General Use and Operation of GeneXpert Procedure	68652	Paradigm
MB GeneXpert Maintenance Log Form	68653	Paradigm
MB GeneXpert SARS-COV-2 Reporting Job Aid	86410	Paradigm
MB Respiratory Coding Process	75097	Paradigm
MB Corrected Results Procedure	6356	Paradigm

References

- Xpert Xpress SARS-CoV-2 Cepheid package insert, 302-35621

TITLE: 04-2-1 MB GeneXpert SARS-COV-2 Reporting Job Aid	**Doc #:** 86410
Section: Management System\PLM\Microbiology\2-BACT GeneXpert\COVID\	**Version:** 1.4 Current
Document Owner: MB MPA Technical Specialist	**Effective Date:** 12/7/2020
Final Approval: Dr. David Haldane	**Review Date:** 9/1/2021

This Job Aid lists the phone calls and emails required for GeneXpert results.

NOVA SCOTIA Patients:

For a **Positive** SARS-CoV-2 result with both target Ct results ≤37* or an **Indeterminate** with a Ct result ≤37*:

- These patient reports can be sent out immediately without any consultation with a Director (use appropriate code of either **FP** or **FI**).
- Record the Ct results for both the E and N2 Analytes and the GeneXpert number on which the cartridge was tested in MRE. This can be found on the top left corner of the printed result (i.e. #1, 2 or 3).
- Email phprovincialCOVID@nshealth.ca
  - Subject Line of Email: **Rapid COVID-19 Laboratory Result**
  - Copy to Dr. Hatchette, Dr. Leblanc and Janice Pettipas.
  - Copy DHW Epi team at surveillancedhw@novascotia.ca
  - Email is to include: Patient's name
    HCN
    Lab Assession Number
    Result
    Date Reported
- Record email in the workcard in MRE.
- Record phone calls in Order Comments in MRE.
- **In-patients must be phoned to the floor**. Call the hospital and ask to speak to the nurse looking after the patient.

*For any SARS-CoV-2 result with one or both target Ct results >37:

- **DO NOT REPORT**- The result must be discussed with a Director before reporting. If it is late in the Evening or Night shift, hold the result until the morning to show the Director and then send the report.

PEI Patients:

For a **Positive** SARS-CoV-2 result with both target Ct results ≤37*:

- A **FP** patient report can be sent out immediately without any consultation with a Director.
- Record the Ct results for both the E and N2 Analytes and the GeneXpert number on which the cartridge was tested in MRE. This can be found on the top left corner of the printed result (i.e. #1, 2 or 3).
- Phone Dr. Greg German at [redacted]- anytime of the day or night.
- If no answer- call 902-894-2515 and leave a voice mail and then also email Dr. German at [redacted]Note: the address is [redacted]. It is hard to see the lower case j in-between the two g's with the underline).
- Will need to provide Patient's name, HCN and DOB.

*For any SARS-CoV-2 result with one or both target Ct results >37:

- **DO NOT REPORT**- The result must be discussed with a Director before reporting. If it is late in the Evening or Night shift, hold the result until the morning to show the Director and then send the report.

For an **Indeterminate** SARS-CoV-2 result with a Ct result ≤37:

- This result can be reported without showing a Director. Follow all instructions as a Positive result above.
- Record the Ct results for both the E and N2 Analytes and the GeneXpert number on which the cartridge was tested in MRE. This can be found on the top left corner of the printed result (i.e. #1, 2 or 3).

St. Pierre et Miquelon Patients:

For a **Positive** SARS-CoV-2 result only with both target Ct results ≤37*:

- A **FP** patient report can be sent out without any consultation with a Director.
- Record the Ct results for both the E and N2 Analytes and the GeneXpert number on which the cartridge was tested in MRE. This can be found on the top left corner of the printed result (i.e. #1, 2 or 3).
- Call to Dr. Leblanc so that he can call them to relay the result.

*For any SARS-CoV-2 result with one or both target Ct results >37:

- **DO NOT REPORT**- The result must be discussed with a Director before reporting. If it is late in the Evening or Night shift, hold the result until the morning to show the Director and then send the report.

For an **Indeterminate** SARS-CoV-2 result with a Ct result ≤37:

- This result can be reported without showing a Director.
- Record the Ct results for both the E and N2 Analytes and the GeneXpert number on which the cartridge was tested in MRE. This can be found on the top left corner of the printed result (i.e. #1, 2 or 3).
- Send the report. No calls or emails required.

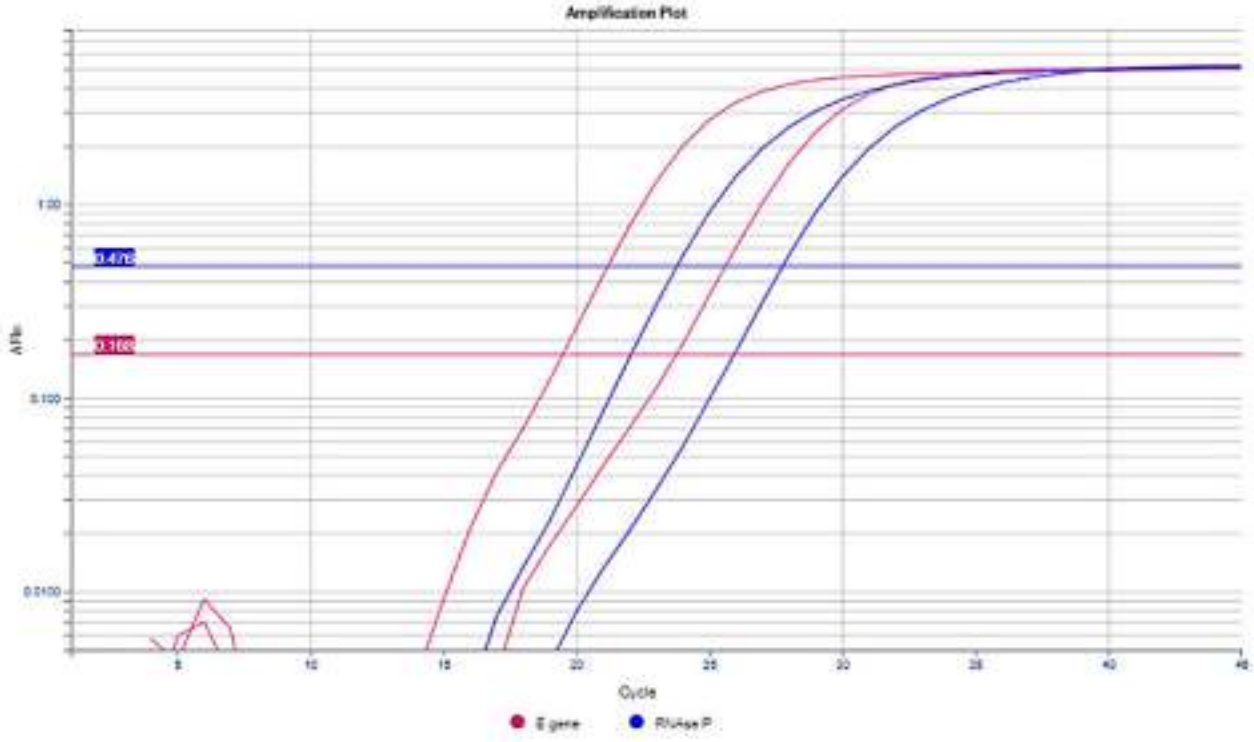
Referenced to:

Document Name	Document #	Document Location
MB GeneXpert SARS-COV-2 Procedure	86326	Paradigm

Public Health Ontario | Santé publique Ontario

FOCUS ON

An Overview of Cycle Threshold Values and their Role in SARS-CoV-2 Real-Time PCR Test Interpretation



September 17, 2020

Introduction

This document provides an overview of Ct values with a focus on how they are determined, their relationship to viral load, and how Ct values may contribute to the interpretation of positive rRT-PCR results among patients with low pretest probability. Key factors that contribute to test performance are also discussed, and guidance on investigating a possible false positive result is provided. Data generated at Public Health Ontario (PHO) Laboratory is also presented which demonstrates the impact pretest probability has on the positive predictive value (PPV) of a SARS-CoV-2 rRT-PCR laboratory test in the Ontario context.

Background

COVID-19 was first reported in Wuhan, China in December, 2019 and subsequently spread globally, with declaration of the pandemic in early March, 2020. This resulted in the rapid and widespread development and implementation of a plethora of tests and platforms for the detection of SARS-CoV-2, the virus responsible for this newly emerged disease. Testing has proven critical to the pandemic response with early detection and subsequent public health and clinical interventions based on testing as key to both patient and outbreak management. With advances in testing and technology so too have there been advances in understanding both the disease and its epidemiology. For example, through testing it has become apparent that persons may test positive (i.e., SARS-CoV-2 detected) without symptoms, including for those who are asymptomatic (i.e., never develop symptoms) or presymptomatic (i.e. later develop symptoms), or due to a false positive laboratory test.

The risk of false positive results increases as the pretest probability of COVID-19 decreases, such as in instances of low prevalence. Moreover, positive real-time reverse transcription (rRT)-PCR test results that are close to the limit of detection (LOD) of an assay have a greater likelihood of being false positives. One key explanation for this is that when specimens become contaminated with very low levels of test target during the laboratory testing process, it produces a high Ct positive result near the assay LOD. Nonspecific signals can also occur during later rounds of amplification that are misinterpreted as amplification due to presence of target in the specimen, also giving false positive results associated with high Ct values.

Accordingly, current guidance in Ontario recommends contacting the testing laboratory to discuss the test results and review the Ct when a positive result is reported for an asymptomatic patient with low pretest probability (i.e., no known high risk exposures).[1] Clarification of the results within the epidemiological context may enable the discernment of true positives from false positives thereby informing appropriate public health follow up (e.g. case management, contact tracing and/or outbreak declaration). Asymptomatic low pretest probability detections have been identified during broad testing campaigns, such as periodic test-based surveillance of asymptomatic residents, staff and visitors of long-term care homes, in the absence of cases/outbreaks.

Understanding Ct values and their interpretation in the context of laboratory testing is of particular importance to public health practitioners, where test results contribute to the classification of persons as meeting (or not meeting) the provincial case definition and subsequent decisions regarding public health management, including contact tracing and/or outbreak declaration.[1] There can also be important clinical scenarios where patients told they are positive for SARS-CoV-2 question where they may have been exposed, or may have a false sense of security for having been “previously positive”.

Methods

The Ontario COVID-9 Testing Technical Working Group includes microbiology representatives from a large number of SARS-CoV-2 testing laboratories from across Ontario. The group discusses topics of priority and shares experiences related to SARS-CoV-2 testing.

It became apparent that there was a need to provide stakeholders with additional information to help healthcare providers understand some key areas around interpretation of rRT-PCR testing, in particular the application of cycle threshold (Ct) values to test interpretation. The Working Group identified the need for a guidelines document to cover some key topics in this area, and together agreed on the topics to be included. PHO Laboratory also provided laboratory data from a study that has been conducted to help understand the impact that pre-test probability of a patient having COVID-19 has on PPV of rRT-PCR test results.

The document initial draft was prepared by PHO Laboratory and shared with the other Working Group members, as well as other PHO stakeholders, for input prior to finalization and posting.

Important Questions and Information to Consider

1. What is the cycle threshold (Ct) value?

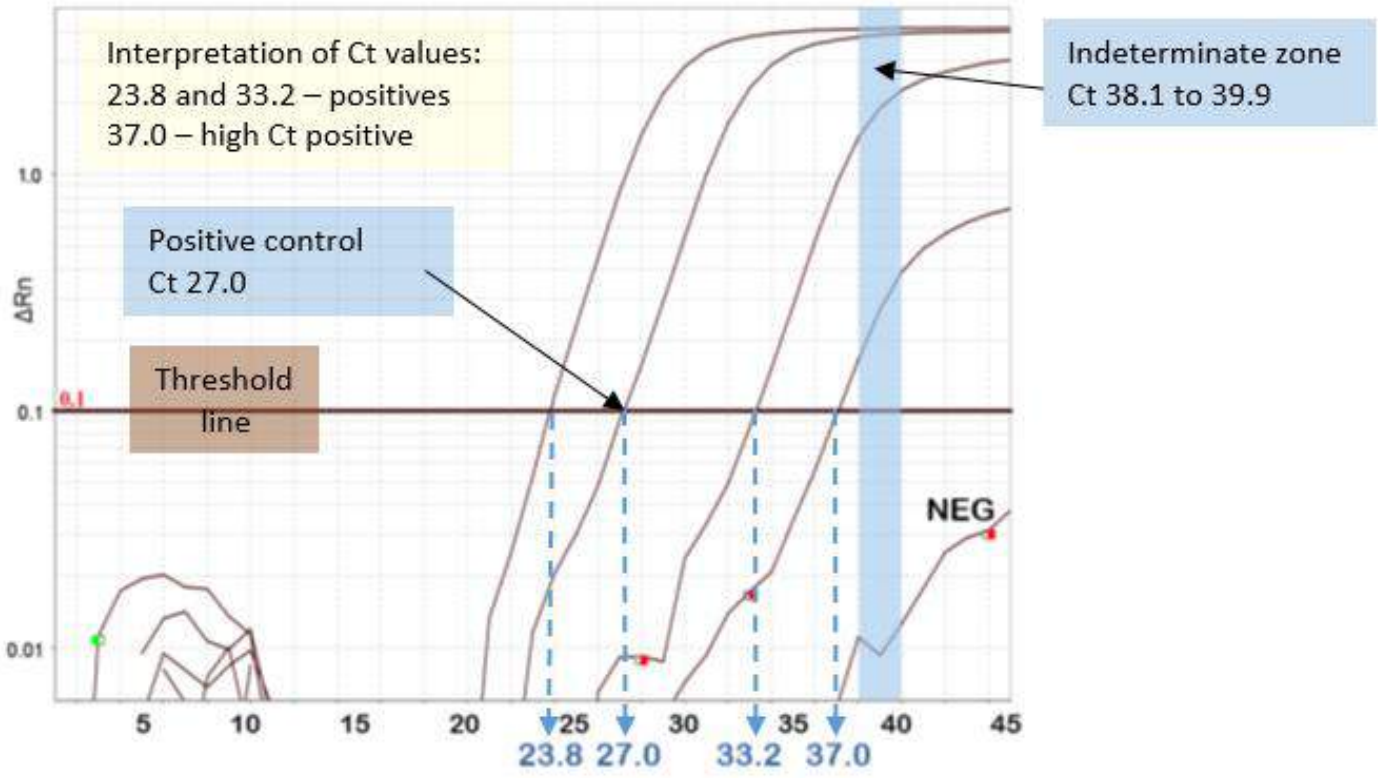
The Ct value is defined as the number of cycles of amplification (using rRT-PCR) required for the fluorescence of a PCR product (i.e. the target/amplicon) to be detected crossing a threshold, which is above the background signal (a low level signal that is present in the assay regardless of whether target is present). When rRT-PCR is performed, a predetermined number of cycles (rounds) of amplification of target (e.g. SARS-CoV-2) nucleic acid occur. If target is present in the specimen then each round of amplification results in a doubling of the amount of target present. As a result, amplification occurs exponentially, producing an exponential curve of amplification (Figure 1). This exponential amplification is visualized by the use of a fluorescent nucleic acid probe. Probes are fluorescently labelled DNA oligonucleotides, which bind to the target. As amplification proceeds, more target becomes available for binding by the fluorescent probe, increasing the fluorescent signal. In general, the amount of fluorescent signal observed increases as amplification proceeds and is proportional to the amount of target present in the specimen.

Amplification is considered significant, and equates with ‘detection’ of target, if the threshold of fluorescence is reached (see horizontal brown line in Figure 1). The threshold of fluorescence is usually set at the midpoint of the exponential phase of amplification of the positive control included in the assay run.

The positive control is typically a previously characterised positive clinical specimen, inactivated virus culture, or viral nucleic acid. If positive control material is limited, synthetic RNA sequence, identical to the target region of the virus, is used as an alternative.

A vertical line (see blue dashed lines in Figure 1) is orthogonally dropped from the point where the amplification curve crosses the threshold to where it meets the X axis of the graph, corresponding to the Ct value. The Ct value is essentially the number cycles of doubling amplification at which target detection has occurred.

Figure 1: An Example of a Real-Time PCR Amplification Curve



Note: This amplification curve is presented on a logarithmic scale. Curves can also be viewed on a linear scale, which will look different but does not change the Ct interpretation. Not all commercial real-time PCR assays provide Ct values or amplification curves for viewing by the user. In addition, some molecular assays are based on other technologies (e.g. flow cytometry), and hence, do not provide Ct values.

2. How are Ct cut-off values interpreted for detected, indeterminate and not detected results?

During assay development and validation, the limit of detection (LOD) is determined using a target of known quantity which is serially diluted, usually using 1 log (i.e., 10 fold) dilutions, and tested with the PCR assay. The cut-off (highest Ct value) for positivity is usually placed at a Ct value similar to that generated by the lowest copies of target that can be reliably detected in the assay (e.g. Ct ≤ 38). This Ct cut-off value is determined by manufacturers of commercial assays, or by laboratories during the validation of laboratory developed tests (LDTs). In some commercial assays, the cut-off is determined individually for each run based on the amplification curve and Ct value of the positive control.

A negative cut-off is assigned to the Ct value at which target is no longer expected to be detected based on the LOD determinations (e.g. Ct ≥40).

Some assays include an indeterminate zone, the Ct range of which falls between the cut-offs for detected and not detected results (e.g. Ct 38.1 to 39.9 for the PHO LDT). Indeterminate results are those Ct values which fall between the cut-offs for detected and not detected results later in the amplification process. This may be due to low quantity of viral target in the clinical specimen that is at or near the LOD

of the assay, or it may represent nonspecific reactivity (false signal) in the specimen. When clinically relevant, indeterminate results should be investigated further by retesting for a different gene target using a validated real-time PCR assay that is equally or more sensitive than the initial assay or method used. Alternatively, nucleic acid sequencing of the amplified target may be performed. Figure 1 shows a light blue bar that outlines the range of Ct values PHO Laboratory employs (Ct 38.1 to 39.9) to designate a result as indeterminate when the amplification curve crosses the threshold line within this pre-set range.

3. Do Ct values correspond to the quantity of target present in a specimen?

Most rRT-PCRs are qualitative (i.e. target is *detected* or *not detected* with no target copy number reported), not quantitative (target copy number per unit volume of specimen matrix or per reaction is reported). In isolation, Ct values provide a *relative* measure of viral quantity in the specimen, but **do not** provide the actual quantity. The Ct value can potentially provide a measure of viral copies if standards of different known quantities are included in the same run and tested in parallel to the clinical specimens. The Ct value(s) at a given quantity of the standard is then used to extrapolate the quantity of virus in the specimen from the Ct value generated when tested. The use of standards and quantification adds more complexity to a rRT-PCR assay and requires appropriate reference materials. Each round of PCR doubles the amount of target in the reaction. Based on this, it can be extrapolated that each 3.3 increase in Ct value correlates with approximately 1 log (i.e., 10 fold) less target in the primary clinical specimen undergoing the PCR reaction.

Quantitative PCR assays are predominantly used in circumstances whereby they inform clinical (e.g., treatment) or public health (e.g., contact tracing) management, such as antiviral therapy for some blood-borne viruses (e.g. HIV, cytomegalovirus and hepatitis viruses). Blood-borne viruses are more amenable to being measured quantitatively, because blood is a more standardized specimen type. When respiratory specimens are tested, there is much more variability, which can affect the result and is unrelated to the actual quantity present in the specimen. This includes the type of swab used for collection, the transport media, the method and quality of specimen collection, the PCR assay, and the way that the threshold line is set for each run (predetermined, *de novo*, by a human, or by software, etc.). In addition, viral shedding in respiratory secretions can be variable over time.

Ct values obtained from PCR testing performed on consecutive specimens collected on the same patient, run using the same assay, in the same testing laboratory, could be compared to give a *relative* indication of the quantity of virus in the different specimens. However, as outlined above, they do *not* indicate the actual quantity of virus in the sample.

Several studies have been conducted in an attempt to correlate Ct values with infectivity of SARS-CoV-2 virus. For example, viability of virus can be determined by inoculating cell lines in culture and assessing for evidence of viral replication. This is a laborious process, which can only be performed in a Containment Level 3 (CL3) laboratory. It is not currently standardized and cannot be used to guide clinical decisions. Critically, it has not been established that persons with PCR-positive specimens that cannot be cultured are not infectious. This is particularly important as in some laboratories it has been relatively difficult to culture SARS-CoV-2 compared to other viruses.

For example, a study in which virus culture was performed at Canada's National Microbiology Laboratory (NML) documented that specimens with Ct values > 24 were viral culture negative.[2]

However, the US CDC has reported that they were able to culture virus from specimens with Ct values up to the low 30s (unpublished data).[3] It is important to note that each of these laboratories (NML and CDC) used different real-time PCR assays in their evaluations. A SARS-CoV-2 proficiency testing panel was distributed to 26 different SARS-CoV-2 testing laboratories in Ontario in April 2020 by The Institute of Quality Management in Healthcare (IQMH), the organization that administers the Quality Management Program for laboratory services in Ontario. Variability of Ct values of up to 8 cycles were observed for the same specimen material tested across the participating laboratories. These different findings reinforce that it is inappropriate to compare Ct values from different assays, and to extrapolate Ct cut-offs for virus viability from one laboratory to any other laboratory and that Ct cut-offs cannot be reliably used for the determination of virus viability. The US CDC applies these principles to advise that the correlation presented between Ct values and the ability to recover replication-competent virus is only applicable to upper respiratory specimens tested at their laboratory. Further, the relationship between the ability to grow a virus in culture (viral replication) in a laboratory and infectivity to humans is not currently known.

Some experts have argued that Ct values should be provided routinely on laboratory reports to assist with clinical and public health decision making.[4] This may be applicable in a limited setting where healthcare providers only receive reports from a single laboratory, and can be educated about the test performance and Ct value characteristics of a particular assay. However, in complex laboratory network environments, such as in Ontario, where specimens may be tested at one of several laboratories (> 40 laboratories conducting SARS-CoV-2 rRT-PCR in the province on a variety of different extraction and PCR platforms), utility of such reporting is questionable. Moreover, test results are received and reviewed by a myriad of healthcare providers, as well as patients, with varying understanding of Ct values. As such, the inclusion of Ct values on laboratory reports issued in Ontario (and Canada) is not recommended - they are of limited utility if used in isolation when interpreting the rRT-PCR result. In the rare, specific scenarios where it is thought that the Ct value might inform clinical or public health management, clinical and public health providers should contact the testing laboratory to discuss Ct interpretation, in the context of the epidemiology and clinical scenario, with the microbiology team.

4. How common are false positive COVID-19 tests? What is the cause of false positive results and how might this be minimized?

Based on PHO Laboratory data, the rate of false positive tests that are later determined to be negative requiring results to be corrected is extremely low. How commonly this occurs in the province is not known, as individual reports that are corrected are not centrally documented. In Ontario, incidents of a significant number of specimens (as determined by the testing laboratory) with false positive results are notified to the Laboratories and Genetics Branch of the Ministry of Health, and to IQMH.

As of August 15, 2020, PHO Laboratory detected possible false positive SARS-CoV-2 results on approximately 30 occasions among over 850,000 specimens tested for COVID-19, with ~17,500 (approximately 2%) specimens testing positive. This represents a false positivity rate of less than 0.01% (specificity of >99.99%), which is well beyond performance targets for a laboratory test, even acknowledging there are likely to be some false positive tests that go undetected.

In general, the positive predictive value (PPV) of COVID-19 PCR assays is excellent among patients with high pretest probability, and approaches 100%. This was determined at PHO Laboratory, using viral sequencing of PCR-positive specimens, excluding those for which viral copy number was near the LOD of the assay.

However, in the context of low prevalence when the virus is not circulating at a high level in the community, PPV drops significantly. For example, if the community prevalence of SARS-CoV-2 is 1%, with a test sensitivity of 80%, and specificity of 99%, the PPV of a positive test is only 44.7%. If prevalence increases to 5% or 10%, then the PPV increases significantly to 80.8% and 89.9%, respectively. A recent serosurvey by PHO using residual convenience specimens found a low adjusted seroprevalence of 1.1% (95% CI 0.8, 1.3) in June.[5] This supports that Ontario is currently a low prevalence setting for SARS-CoV-2 infection.

False positive results can occur at various stages of laboratory testing, and can be grouped into the following categories:

1. Pre-analytical errors. These are errors that occur prior to the actual testing and include issues such as mislabelling of specimens, resulting in incorrect results being reported. These errors may also result from specimen contamination at time of collection, in transport, or during aliquoting in the laboratory.

2. Analytical errors. These occur during the laboratory testing process. These include, for example, errors related to reagent contamination. Reagents can arrive contaminated from the supplier. To mitigate this, each new lot of reagents undergoes a quality assurance check before being put into use. False positive results can also arise from contamination due to pipetting errors, which can be due to human error or defects in automated equipment. Such analytic errors are controlled through the use of negative and positive controls on each run of the assay, which are reviewed prior to releasing results.

3. Post-analytical errors. These errors occur at the stage of test result interpretation and reporting of results. Incorrect interpretation of amplification curves could lead to a false positive result. Transcription errors may also result in false positive results being generated. Such errors are mitigated by ensuring all results and interpretations are reviewed prior to reporting.

5. What steps can be taken to investigate a positive result for an asymptomatic patient with low pretest probability and re-positive results?

It is notable that true false positive SARS-CoV-2 PCR test results in Ontario are rare. In most cases, a positive result represents COVID-19 infection irrespective of the presence of symptoms or known risk factors. This veracity of the result is distinct from the assessment of the public health measures recommended for the asymptomatic person with the positive result and their contacts. During investigation, any individuals with positive results should be treated as infectious and be isolated until cleared by the local public health unit.[1] Contacts should be identified, but do not necessarily have to quarantine while further investigating the positive result. For further information, health care providers should contact their local public health unit.[6]

To investigate a possible false positive result in an asymptomatic patient with low pretest probability (i.e., no contact with a confirmed case of COVID-19, other high risk exposure, or known higher levels of circulation of virus in the community), several steps can be taken. These include:

1. Review the clinical history, in particular symptoms or clinical findings compatible with COVID-19, or contact with a confirmed case of COVID-19, or other exposure.[7] If symptoms or

epidemiological risk factors are elucidated, then pretest probability is not low, and the likelihood of a false positive result declines significantly. See Case Study below. In the context of higher levels of community transmission, the pretest probability may not be low, even with no symptoms or specific epidemiological risk exposures.

2. If the assay used consists of more than one target, and more than one target is detected, this suggests a higher viral load in the sample. Specimens with higher relative viral load, with multiple targets detected, are less likely to be false positive results.

3. Contact the testing laboratory to determine if systemic technical issues have occurred, or are occurring, which may impact testing, potentially resulting in a false positive test.

4. In general, specimens with Ct values well below the assay cut-off for positivity (e.g. Ct < 35 with the laboratory positivity cut-off for that assay set at Ct = 38) are less likely to be false positive. If in doubt, contact the testing laboratory to have the Ct value and report reviewed (provided the assay in use generates a Ct value). The amplification curve may also be reassessed to ensure no interpretive errors were made at the time of reporting. See Figure 1 for an example of a good amplification curve in a high Ct positive specimen.

5. Current public health guidance recommends asymptomatic patients with low pretest probability have a repeat test right away.[1] If the repeat test is positive, this would contribute to the evidence supporting a true positive. However, if the initial positive result was of high Ct value, near the assay cut-off, a repeat collection will typically be negative due either to lower viral shedding over time and/or inconsistent assay performance for specimens at or near the cut off. A negative retest does not necessarily indicate the first test was a false positive. However, the follow-up negative test may provide additional context to the public health management of the individual and whether contact management is warranted.

6. Consider requesting that the specimen be retested on the same assay and/or a different assay if this is available to the testing laboratory. If the result can be reproduced this would increase the likelihood that the result is true positive. However, a negative result on retesting does not necessarily mean the initial testing was incorrect, as assay performance near the LOD is not consistent, with varying results on repeat testing. In addition, different assays will perform differently on the same specimen with virus quantity near the LOD.

While the above steps are being taken, it is important to treat the patient as positive for COVID-19 and ensure that appropriate infection prevention and control and public health measures are in place.

RE-POSITIVE RESULTS

Ongoing detection of positive results after clearance from isolation, either by time-based or test-based clearance, is now a well-established phenomenon, and such cases are referred to as re-positive.[8] In general, repeat testing in someone who has been previously positive is not recommended unless clinically indicated.[9] However, given the limited evidence on immunity and the emerging evidence on risk of true re-infection, re-positive results in a patient who is symptomatic and/or had a recent high risk of exposure to a case may cause concern for whether a repeat positive result may represent re-infection. To investigate whether a re-positive result is more likely to be ongoing detection from an original infection episode or a true new re-infection, the Ct value and number of targets detected may be helpful additions to the clinical context, and whether additional public health follow-up is necessary for a true re-infection. A re-positive value with lower Ct value (e.g., <32) would be required to conduct

further analysis, such as viral genetic sequencing, to determine similarity to the original specimen or other cases that the re-positive individual was exposed to before the re-positive result.

6. Case Study: Impact of pretest probability on positive predictive value (PPV).

When considering the possibility that a positive result may be false positive, the pretest probability is an important factor to consider. PHO Laboratory conducted a limited evaluation among patients with high Ct positive specimens (Ct ≥35) using a laboratory developed or commercial assay targeting the E gene. PCR and sequencing of a second, independent target (RNA dependent RNA polymerase; RdRp) demonstrated differing proportions of detection depending on the pretest probability.

In brief, among convenience-selected specimens from 103 patients tested at PHO Laboratory with Ct values ≥ 35 included in the study, virus was confirmed by RdRp PCR and sequencing as follows

- 18 (78%) of 23 patients previously confirmed to be SARS-CoV-2 positive on an earlier specimen collected.
- 17 (85%) of 20 patients who were symptomatic at the time of testing.
- 10 (67%) of 15 asymptomatic patients who were close contacts of confirmed COVID-19 cases.
- 16 (50%) of 32 of asymptomatic patients who were tested as part of an outbreak within an institution with ≥10 confirmed cases.
- 5 (16%) of 32 asymptomatic patients who were tested as part of an outbreak or for surveillance purposes, within an institution where only 1 to 3 patients were SARS-CoV-2-positive (all asymptomatic).

See Tables 1A and 1B, located in the Appendix for more information on the above analysis.

Notably, specimens from patients that were asymptomatic and had no epidemiological links to COVID-19 cases had the lowest proportion of specimens confirmed by RdRp sequencing (5/32, 16% confirmed), which was significantly lower than that for asymptomatic patients tested with epidemiological links to multiple confirmed cases (16/32, 50% confirmed; Fisher's Exact p= 0.007). This suggests that a high Ct positive result is more likely to be false positive when observed in an asymptomatic patient with no epidemiological links to cases during low community prevalence of disease. However, it is difficult to know exactly which patients among this subgroup are true positive versus false positive, as we know that not all true positive high Ct positive specimens are repeat positive when retested on the same or a different platform. Ct values in the absence of detailed clinical and epidemiological data cannot identify false positive results and their utility is limited to be supportive of investigating suspected false positive results in the right clinical context.

Ontario's Ministry of Health has provided guidance on Management of Cases and Contacts of COVID-19 which allow for reduced public health action when a positive result in an asymptomatic low pretest probability patient is immediately followed by a negative test on a new specimen.[1] This approach reduces the need to fully clarify if all such tests are true positive versus false positive, which is often very

difficult to determine at the individual test level unless there are systemic technical laboratory issues occurring that are identified, or the specimen can be confirmed as positive with an independent assay. Additionally, in the context of emerging evidence on immunity and re-infection, determination of whether an individual truly was or was not infected does not impact their recommendations for maintaining public health measures to prevent a potential future infection.

Conclusions

The COVID-19 pandemic has led to large scale testing of asymptomatic persons with low pretest probability, a practice not previously employed for any respiratory viral pathogen. SARS-CoV-2 Ct values may be of use when interpreting positive laboratory results derived from patients with low pretest probability, in particular, asymptomatic persons with no epidemiological link to a confirmed COVID-19 case. The province of Ontario has produced guidance documents that facilitate risk-based patient management and follow up that do not rely on definitively concluding that a test is a true or false positive. Ongoing education regarding the increased possibility for false positive test results when testing high numbers of asymptomatic persons during periods of low community prevalence of SARS-CoV-2, even when utilizing assays with excellent performance is required. This would benefit the healthcare community and potentially avoid unnecessary patient isolation, contact tracing and outbreak declaration.

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Appendix: High cycle threshold case study category descriptions, definitions and data tables

Table 1A: High cycle threshold case study patient categories and definitions

CATEGORY	DEFINITION
Control group: second sample (high Ct) from previously positive specimen (low Ct)	Control group – persons who initially tested positive with a low Ct value (Ct <30) and had a subsequent test with a high Ct value (Ct ≥35)
Symptomatic with high Ct	Having a positive test with high Ct value (Ct ≥35) and at least one symptom as noted in the PHO LIS
Asymptomatic: Exposure to probable or confirmed case*	Indicated as asymptomatic in the PHO LIS. Tested due to exposure to probable or confirmed case OR residing at same address as another positive case
Asymptomatic: Facility with ≥10 positive cases	Indicated as asymptomatic in the PHO LIS and tested as part of an outbreak with at least 10 positive cases
Asymptomatic: Facility with institution-wide screening, with ≤3 positive cases, all asymptomatic.	Tested as part of an outbreak or surveillance testing investigation having 3 or fewer asymptomatic positive tests and no symptomatic positive cases in PHO LIS

PHO LIS = Public Health Ontario Laboratory Information System
*Note - this category contains specimens from institutional outbreaks (as well as non-outbreaks), and thus some specimens could also be classified in the "facility 10+ positive category"

Table 1B: Summary of high Cycle Threshold case study results: Initial E gene real-time PCR and RdRp PCR results, stratified by patient category

	PATIENTS			DETECTED BY RdRp PCR		NOT DETECTED BY RdRp PCR	
Category	N	Median Age (Range)	Median Ct (Range) on initial E gene PCR	N (%)	Median Ct (Range) on initial E gene PCR	N (%)	Median Ct (Range) on initial E gene PCR
Control group – persons who initially tested positive with a low Ct value (Ct <30) and had a subsequent test with a high Ct value (Ct ≥35)*	23	52 (14-99)	36.9 (35.0-38.4)	18 (78.3)	36.7 (35.0-38.3)	5 (21.7)	38.1 (35.9-38.4)
Symptomatic with high Ct (≥35)	20	68.5 (26-94)	36.6 (35.0-38.3)	17 (85.0)	36.9 (35.03-38.3)	3 (15.0)	36.3 (35.6-37.4)
Asymptomatic: Exposure to probable or confirmed case	15	38 (10-93)	36.1 (35.4-38.0)	10 (66.7)	36.0 (35.4-37.2)	5 (33.3)	37.5 (36.0-38.0)
Asymptomatic: Facility with ≥10 positive cases	32	57.5 (15-97)	37.5 (35.4-40.6)	16 (50.0)	36.6 (35.4-40.6)	16 (50.0)	37.7 (35.5-38.3)
Asymptomatic: Facility with institution-wide screening, with ≤3 positive cases, all asymptomatic.	32	46 (17-95)	36.9 (35.2-39.8)	5 (15.6)	36.2 (35.6-37.5)	27 (84.3)	37.0 (35.2-39.8)
Total	122	53.5 (10-99)	36.9 (35.0-40.6)	66 (54.1)	36.2 (35.0-40.6)	56 (45.9)	37.5 (35.2-39.8)

Ct = cycle threshold; E = envelope gene real-time Reverse-Transcription PCR; RdRp = RNA dependent RNA polymerase gene endpoint PCR with Sanger sequencing confirmation) * 20 patients were symptomatic, 2 were asymptomatic at time of first test, and 1 did not have symptom information available at time of first test

Authors

Public Health Ontario
The Ontario COVID-19 Testing Technical Working Group

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Disclaimer

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Public Health Ontario

Public Health Ontario is an agency of the Government of Ontario dedicated to protecting and promoting the health of all Ontarians and reducing inequities in health. Public Health Ontario links public health practitioners, front-line health workers and researchers to the best scientific intelligence and knowledge from around the world.

Public Health Ontario provides expert scientific and technical support to government, local public health units and health care providers relating to the following:

- communicable and infectious diseases
- infection prevention and control
- environmental and occupational health
- emergency preparedness
- health promotion, chronic disease and injury prevention
- public health laboratory services

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Ontario

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LAB Testing for COVID- 19 – Frequently Asked Questions

KEY Points:

- PCR remains the gold standard test as it is the most sensitive and specific
- Rapid point of care assays, such as antigen testing, are less sensitive. Because of that they are currently being used for outbreak settings **in parallel** with RT-PCR and as a standalone test in asymptomatic population based testing in the popup community setting
- Negative upper respiratory tract (URT) specimens (e.g. nasopharyngeal (NP) or oropharyngeal (throat)/nares (OP/N) swabs) can occur when:
  - the person is not infected;
  - the sample is poorly collected;
  - the test is done too early or too late in the course of illness
  - the person has a lower respiratory tract (LRT) infection
- The sensitivity of URT samples (NP, OP/N, gargle) in patients with LRTI is lower than those with an URT infection
- For inpatients with persistent respiratory symptoms or pneumonia on imaging, follow IPAC guidance, retest URT, and obtain LRT specimens at 48 hrs if possible
- The sensitivity of the NP swab and OP/N swabs in persons with mild infection are 94% and 92% respectively
- The sensitivity of gargles in children and adolescents aged 4-18 years with mild infection in the outpatient setting is 98% compared to NP swab
- The sensitivity of gargles in symptomatic adults is 94-97% compared to OP/N swabs
- For pre-surgical, inpatient, and emergency assessment where admission is likely, the preferred URT specimen is NP swab
- Limited supplies from collection kit manufacturers will mean that you will see swabs and tubes of different appearances throughout Nova Scotia Health – these kits have been validated and perform with equal accuracy
- Priority tests are available but extremely limited
- This FAQ will be updated as more data become available

NOTE: Always ensure safe collection of samples, including use of appropriate personal protective equipment. Avoid spillage or leakage of transport media and potentially

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infectious specimens. Transport media should not be ingested. Samples should be transported to the laboratory as soon as possible at 4˚C.

TEST TYPE

1. **What are some laboratory testing platforms that can be used to detect SARS-CoV-2 in Nova Scotia?**

Nucleic Acid Amplification Tests (NAAT) - Nova Scotia Health laboratories use molecular tests (that detect viral RNA) on a variety of sample types. Most specimens are processed on one of several polymerase chain reaction (PCR) assays that are used worldwide. PCR is by far the most sensitive test for detecting respiratory pathogens, including SARS-CoV-2. We compared our lab with others across Canada, and showed that our commercial and in-house assays are equally sensitive.

Rapid Antigen Detection Tests (RADTs) – Recently, Nova Scotia has been using rapid point of care tests that detect the antigen of the virus rather than its nucleic acid. These rapid tests are single-use and use technology similar to pregnancy tests. Although the results of these tests are available in 15 minutes, the sensitivity compared to PCR is 70-80% in symptomatic individuals. Based on data from the Department of Health and Wellness (DHW) pop up clinics, where 465 specimens from asymptomatic people who had both the rapid antigen test and the gold standard PCR test, the antigen test detected 2/3 (66.7%) of PCR positives.

TEST PERFORMANCE

2. **There are reports of people with COVID-19 whose first test was negative, only to be positive when they were tested again a few days later. How can this happen?**

There is no perfect test. How well any lab test does in real life circumstances depends on the quality of the specimen obtained, the timing of the specimen in relation to the person's illness, and the "performance characteristics" of the test, or how well it does under ideal circumstances. So, there are several things that could result in this situation:

a. The person was not infected at the time of the initial swab, but became infected from an exposure at a later date.

b. The person is infected but is not yet shedding much virus in the upper respiratory tract. Every infection has a "window period" during which time the virus may be there in quantities that are too low to be detected by any test.

c. The person is shedding virus but the sample collection was poor. Proper collection technique is essential to ensure that an adequate amount of specimen is collected from the correct site. For **NP Swab**, this means sampling with adequate depth into the nasopharynx, completing several turns of the swab, and leaving it in place for 5-10 seconds to allow for absorption of cells and virus onto the swab material. Alternatively, using **OP/N** swabs, this means swabbing the posterior oropharynx, followed by the anterior of each of the nares (1-2cm depth) with the same swab (https://vimeo.com/397169241/b793919cd5). For saline **gargles**, this means avoiding food/drink/smoking/vaping/brushing teeth for one hour prior to testing, and gargling for an adequate amount of time (https://vimeo.com/480826990)

d. The person has a lower respiratory tract infection (LRTI), where the virus has moved from the upper respiratory tract (URT) to the lower respiratory tract (LRT). In symptomatic people with mild infection, we know that the virus is shed in high numbers in the URT, lasting for at least 5-7 days (Zou et al 2020). However, in people who have a LRTI, like pneumonia, the most sensitive specimen is from the lungs, usually from a bronchoalveolar lavage (BAL). This can also happen with other severe viral LRTIs, such as influenza.

3. **How sensitive is the RT-PCR test used by the QEII?**

PCR is by far the most sensitive test for detecting respiratory pathogens, including SARS-CoV-2. To date, there are limited published data defining the COVID-19 PCR performance characteristics.

We compared our lab with others across Canada, and showed that both commercial and in-house assays are equally and highly sensitive. The literature suggests the virus is at high levels in the upper tract early in infection, and can be detected by NP and OP/N swabs, and by saline gargles.

In late disease with lower tract involvement, URT samples (NP swabs, OP/N swabs, and saline gargles) are less sensitive. A paper on patients with clinical and radiologic features of COVID-19 infection showed that of those who had BALs, 14/15 (93%) were positive, compared to 5/8 (63%) of nasal swabs[2].

4. **Can false positives happen?**

Although specificity for PCR testing is high, false positives can still occur. Even with an assay that has a specificity of 99.99% we can expect a potential false positive rate of 1/10,000. While it is very unusual to get a false positive result due to cross reactivity with RNA from a different virus, PCR testing can sometimes give non-specific results that can be hard to distinguish from a person with a low viral load (i.e. at the end of their shedding period or very early in their infection). In these cases, the laboratory may report the result as “indeterminate”.

Similarly, when using RADTs, weak bands can be sometimes seen on these tests. Based on the manufacturer’s performance data, the rate of false positives is about 4/1000 tests. Based on the 9500 test performed to date by our lab, our false positive rate is approximately 2/1000 tests. As such, all positive RADTs are confirmed using PCR.

5. **What do I do with a person with an indeterminate result?** This depends on the clinical context. In situations where the person could be incubating the infection or where it is unlikely that the person has COVID-19 (i.e. a suspect false positive), repeating the swab is helpful. Repeat sampling of the URT should be by NP swab. Given these are uncommon situations, you can contact the QEII microbiologist on call to discuss options.

6. **If I still think an inpatient has COVID after a negative test, what should I do?**

   The virus is detected at high levels in the URT early in infection, and decreases with time, usually over a 7-10 day period. If the patient is later in the infection, or has developed a LRTI, the viral load can fall below the limit of detection of assay in NP swab or OP/N specimens.

   If there is a high suspicion of COVID-19 even after a negative NP or OP/N swab, the patient should be re-tested and have imaging of their lungs. If possible, obtain a LRT specimen as well. If they are not producing sputum or are not intubated (allowing for collection of an endotracheal aspirate), a BAL can be considered. While BAL may facilitate a specific diagnosis, the risks of an invasive and aerosol generating medical procedure need to be balanced against the potential diagnostic value.

   NOTE: For any inpatient with persistent respiratory symptoms or pneumonia on imaging, in the absence of a confirmed alternative diagnosis, strong consideration should be given to maintaining contact and droplet precautions in coordination with Infection Prevention and Control guidance.

7. **How long does it take to get my results?**

   Depending on testing volumes, if the swab arrives to the lab within 10-12 hours of collection, your results should be available in 24 - 30 hours. Transportation runs have been increased to minimize transport time.

8. **How do I see the results?**

   All inpatient collections and those in most Primary Assessment Centres are registered in the STAR registration system. That means these results can be viewed on the SHARE portal as soon as they are reported.

   Other specimens (e.g. from asymptomatic testing, LTC worker testing, etc.) are entered into Millennium only. While these results are emailed or called to the person, these results will not be available on the SHARE or Clinical Portal, but can be viewed on Millennium or obtained by calling lab reporting (902-473-2266).

SAMPLE TYPES

9. What sample types are acceptable for SARS-CoV-2 detection in Nova Scotia?

The type of sample collected is dependent on the setting and the person being tested. The reference ("gold standard") URT collection method for SARS-CoV-2 detection in acute infection is the NP swab. NP swabs can always be used as the main sample type for PCR (except in the setting of LRTI, for which an NP swab should be paired with a LRT sample if possible). Use the table below to determine the best specimen collection type for a given situation:

•Preferred sample °Alternative sample if preferred unavailable	Symptomatic ambulatory testing	Pre-surgical *	Pre-admission to hospital or institution	Inpatients (for clinical and IPAC management)	Asymptomatic testing (community/contact tracing/public exposures or as directed by Public Health)^	LRTI	Serial testing as directed by Public Health or Nova Scotia Health	Past infection	Population Pop up clinics and outbreaks (in parallel with PCR testing when directed by Public Health)
NP swab for PCR	•	•	•	•	•	(paired with LRT sample if possible)	•		
OP/N swab for PCR	•	°	°		•	(paired with LRT sample if possible)	•		
LRT fluid for PCR						• (paired with NP swab)			
Saline gargle (age 4 years-18)	•				•		•		
Saline gargle (>18 years)					•		•		
Self-collected OP/N swab for PCR							•		
NP swab for rapid antigen test									•

Blood for serology (not available)								•	

*for urgent pre-surgical testing (i.e. not elective, unable to await result from usual testing streams), call the laboratory in advance for STAT testing with GeneXpert platform (NP preferred).

^collection/testing has been validated for symptomatic patients, therefore negative result does not completely eliminate the possibility of asymptomatic or pre-symptomatic infection.

10. How does one type of sample collection perform as compared to another?

Sample collections were validated only for symptomatic patients, therefore, performance in asymptomatic or pre-symptomatic patients is not known. However, we have no reason to believe that the information about sample types cannot be applied to asymptomatic patients.

OP/N is slightly less sensitive than the NP swab - The NP swab is the recognized preferred specimen for URTI. In a local validation project, we collected 190 paired NP and OP/N swabs from ambulatory adults, of which 36 were positive. Both tests performed equally well, with a sensitivity of 94% for the NP swabs, and 92% for the OP/N swabs[1]. Reduced sensitivity was found in asymptomatic (or presymptomatic) people, and those recovering from infection after a previously-positive test, likely due to low URT viral loads at that point in the infection.

Self-collected OP/N equal to health care collected OP/N - In another evaluation we did, self-collected OP/N swabs completed by 35 people (30 positives, 5 negatives) were as good as HCW-collected OP/N swabs.

Saline gargles can be used in <u>children</u> but should be reserved for outpatient settings - Saline gargles were validated in children in British Columbia in a head-to-head comparison with NP swabs and saliva samples[3,4]. Saliva samples did not perform adequately, but saline gargles had a sensitivity of approximately 98% when compared to NP swabs, among ambulatory known positives and symptomatic close contacts of cases. Testing the BCCDC gargle panel locally, and extensive in-house testing of virus-inoculated saline gargles on multiple assays confirmed the ability to detect SARS-CoV-2 in saline gargles.

Saline gargles can be used in <u>adults</u> but should be reserved for asymptomatic outpatient settings and situations that require repeated sampling for testing. When we compared gargles in previously positive adults we found that the sensitivity of gargles was 94-97% compared to OP/N specimens. However the overall amount of virus detected in each gargle compared to OP/N specimens was lower suggesting a slightly reduced sensitivity which could lead to lower detection in patients with a very low viral load. For this reason the NP swab remains the ideal specimen. Gargles can be considered in asymptomatic testing (except in pre-surgical testing) or in people who require more frequent testing (e.g. LTC workers) as these less invasive specimens may be preferable because they are better tolerated in these situations

Lower tract specimens should be collected in those with lower tract disease – As already mentioned, in later disease with lower tract involvement, URT samples (NP, OP/N, saline gargle) are less sensitive than LRT specimens.

Only the NP swab can currently be used in RADTs.

11. Are there special circumstances where one sample type is preferred over another?

The preferred specimen for those undergoing pre-surgical testing and those who are admitted to hospital (or being admitted) is the gold standard – the NP swab, given the lack of data for gargles in these scenarios, and the potential consequences of a false-negative test result.

12. What about asymptomatic testing?

As the pandemic has evolved it is clear that people can shed and transmit virus even if they do not have symptoms. Given this, Public Health has started testing asymptomatic people to help understand viral activity at the community level. Choosing the type of specimen to collect requires consideration of the acceptability of a false positive or false negative result, and the performance characteristics of the specific type of test used. There are little data published on the performance of these tests in asymptomatic individuals, and we rely on extrapolating the data from studies on symptomatic people.

Recommendations: At primary assessment centres, walk-in testing centres, for contact tracing, and case-finding investigations in the community, NP swabs, OP/N swabs, and are acceptable specimen types. Saline gargle are acceptable for both symptomatic and asymptomatic children in these settings, For once only testing (such as in symptomatic adults, an NP swab may provide the most sensitive result but in those adults who require more frequent testing (e.g. LTC workers) less invasive specimens such as the OP/N or gargle may be preferable because they are better tolerated. Regardless of the type of test (RT-PCR vs RADT), it is important to recognize that a negative test in an asymptomatic person does not mean they won't subsequently become positive if they were pre-symptomatic or had a low viral load at the time of the collection.

13. **What if I also want influenza testing?**

Although influenza activity has been low across the country, it should be considered in addition to COVID testing in patients being admitted to hospital, particularly if they present with severe infection. An **NP** swab **must be collected** for influenza testing. Other types of specimens have not been validated for influenza testing. If an NP swab was collected for COVID-19 testing, that same swab can be used for influenza testing, without the need for an additional NP swab.

14. **What is pooling?**

Pooling is a strategy to increase the numbers of tests that can be done by combining multiple specimens (usually specimens from 4-6 different people) into a single "pool" that is tested. If the pool is positive, each of the individual specimens in that pool would be re-tested to see which one was positive. If the pool is negative, all specimens in that pool would be reported as negative. The overall impact to the sensitivity of testing using this strategy is minimal.

PRIORITY TESTING

15. **Why can't the lab offer STAT testing?**

Our testing volumes often exceed 2000 specimens a day. The process moves like an assembly line. Requests for prioritization of individual specimens once they enter the pool requires laboratory staff to stop the assembly line to look for single specimens. This slows down the entire process and, in the end, take longer for you to get the results you need.

16. **What priority testing is available?**

Priority COVID-19 testing continues to be available on the GeneXpert platform in Aberdeen, CBRH, IWK, QEII, Colchester, Valley Regional, and Yarmouth laboratories.

17. **How long will I have to wait for results?**

You can expect a result in 4-6 hours. Although the GeneXpert can produce results within 1 hour once the specimen is placed on the machine, the turn-around time (TAT) will depend on the transport time to the lab and whether the laboratory can stop everything to process this specimen. In addition, the supply of test kits has reached critical limits due to the increasing demand for expedited testing during the second wave. Provincial supply is allocated on a national level and the Nova Scotia allotment is currently capped at 340 tests/week. In order to continue to provide priority testing, laboratories across the province with this instrument will be moving to a pooled sample model utilizing batch testing. Local laboratories will determine batch frequencies based on volume, with a goal of providing an overall **TAT of 4 – 6 hours.**

18. **When can I order a priority test?**

Priority tests are very limited at this time (currently 340 tests/week for the entire province). Feedback has indicated too many scenarios and site-specific logistics to be amenable to a workable provincial algorithm. The provincial laboratory program recommends that the Zones and sites exercise local decision-making around priority COVID-19 testing. Provincially, consistent principles should guide test usage (e.g. PPE conservation and patient flow). Stewardship of this will rest with the clinicians. If priority tests are depleted, testing will be routed to the normal process.

19. **If I require priority testing (such as for a critical care patient) using the GeneXpert, which type of collection kit do I use?**

Any specimen can be used for GeneXpert testing except sputum and BAL. However, an NP swab should be considered the ideal specimen. Sputum and BAL often require extra processing steps that are ideally done on other test platforms

20. **How do I order the GeneXpert test?**

On the **requisition and on the outside of the plastic sample bag** indicate **"Urgent COVID-19 GeneXpert Test".** Calling after the swab has arrived in the lab introduces delays – requiring the process to stop and identify the specimen – and is not possible.

21. **What happens if we run out of GeneXpert tests?**

    Until the supply chain of these kits can be increased, the estimated supply is 50-70 tests per zone each week. Tests will be performed based on requests and once the GeneXpert test are no longer available, the QEII laboratory will make every effort to put the specimen to the front of the routine testing queue as described above. There is capacity to run 2500 "routine" tests/day.

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GeneXpert
Powered By CEPHEID INNOVATION

Xpert® Xpress SARS-CoV-2

Instructions for Use
For Use Under an Emergency Use Authorization (EUA) Only

Rx only

REF **XPRSARS-COV2-10**

For Use with GeneXpert Dx or GeneXpert Infinity Systems

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Cepheid
904 Caribbean Drive
Sunnyvale, CA 94089 USA
Phone: +1 408 541 4191
Fax: +1 408 541 4192

Xpert® Xpress SARS-CoV-2

For use under the Emergency Use Authorization (EUA) only.

1 Proprietary Name

Xpert® Xpress SARS-CoV-2

2 Common or Usual Name

Xpert Xpress SARS-CoV-2

3 Intended Use

The Xpert Xpress SARS-CoV-2 test is a rapid, real-time RT-PCR test intended for the qualitative detection of nucleic acid from the SARS-CoV-2 in upper respiratory specimens (such as nasopharyngeal, oropharyngeal, nasal, or mid-turbinate swab and/or nasal wash/ aspirate) collected from individuals suspected of COVID-19 by their healthcare provider.

Testing of nasopharyngeal, oropharyngeal, nasal, or mid-turbinate swab and nasal wash/aspirate specimens using the Xpert Xpress SARS-CoV-2 test run on the GeneXpert Dx and GeneXpert Infinity systems is limited to laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. § 263a, to perform high and moderate complexity tests.

Testing of nasopharyngeal, nasal, or mid-turbinate swab specimens using the Xpert Xpress SARS-CoV-2 test run on the GeneXpert Xpress System (Tablet and Hub Configurations) is authorized to be distributed and used in patient care settings outside of the clinical laboratory environment.

Results are for the detection of SARS-CoV-2 RNA. The SARS-CoV-2 RNA is generally detectable in upper respiratory specimens during the acute phase of infection. Positive results are indicative of active infection with SARS-CoV-2; clinical correlation with patient history and other diagnostic information is necessary to determine patient infection status. Positive results do not rule out bacterial infection or co-infection with other viruses. The agent detected may not be the definite cause of disease. Laboratories within the United States and its territories are required to report all positive results to the appropriate public health authorities.

Negative results do not preclude SARS-CoV-2 infection and should not be used as the sole basis for treatment or other patient management decisions. Negative results must be combined with clinical observations, patient history, and epidemiological information.

Testing with the Xpert Xpress SARS-CoV-2 test is intended for use by trained operators who are proficient in performing tests using either GeneXpert Dx, GeneXpert Infinity and/or GeneXpert Xpress systems. The Xpert Xpress SARS-CoV-2 test is only for use under the Food and Drug Administration's Emergency Use Authorization.

4 Summary and Explanation

An outbreak of respiratory illness of unknown etiology in Wuhan City, Hubei Province, China was initially reported to the World Health Organization (WHO) on December 31, 2019.[1] Chinese authorities identified a novel coronavirus (2019-nCoV), which has resulted in thousands of confirmed human infections in multiple provinces throughout China and exported cases in several Southeast Asian countries and more recently the United States. Cases of severe illness and some deaths have been reported. The International Committee for Taxonomy of Viruses (ICTV) renamed the virus SARS-CoV-2.[2]

The Xpert Xpress SARS-CoV-2 test is a molecular *in vitro* diagnostic test that aids in the detection and diagnosis SARS-CoV-2 and is based on widely used nucleic acid amplification technology. The Xpert Xpress SARS-CoV-2 test contains primers and probes and internal controls used in RT-PCR for the *in vitro* qualitative detection of SARS-CoV-2 RNA in upper respiratory specimens.

The term "qualified laboratories" refers to laboratories in which all users, analysts, and any person reporting results from use of this device are proficient in performing real-time RT-PCR assays.

5 Principle of the Procedure

The Xpert Xpress SARS-CoV-2 test is an automated *in vitro* diagnostic test for qualitative detection of nucleic acid from SARS-CoV-2. The Xpert Xpress SARS-CoV-2 test is performed on GeneXpert Instrument Systems.

The GeneXpert Instrument Systems automate and integrate sample preparation, nucleic acid extraction and amplification, and detection of the target sequences in simple or complex samples using real-time PCR assays. The systems consist of an instrument, computer, and preloaded software for running tests and viewing the results. The systems require the use of single-use disposable cartridges that hold the RT-PCR reagents and host the RT-PCR process. Because the cartridges are self-contained, cross-contamination between samples is minimized. For a full description of the systems, see the *GeneXpert Dx System Operator Manual* or the *GeneXpert Infinity System Operator Manual*.

The Xpert Xpress SARS-CoV-2 test includes reagents for the detection of RNA from SARS-CoV-2 in nasopharyngeal, oropharyngeal, nasal, or mid-turbinate swab and/or nasal wash/aspirate specimens. A Sample Processing Control (SPC) and a Probe Check Control (PCC) are also included in the cartridge utilized by the GeneXpert instrument. The SPC is present to control for adequate processing of the sample and to monitor for the presence of potential inhibitor(s) in the RT-PCR reaction. The SPC also ensures that the RT-PCR reaction conditions (temperature and time) are appropriate for the amplification reaction and that the RT-PCR reagents are functional. The PCC verifies reagent rehydration, PCR tube filling, and confirms that all reaction components are present in the cartridge including monitoring for probe integrity and dye stability.

The nasopharyngeal, oropharyngeal, nasal, or mid-turbinate swab specimen and/or nasal wash/aspirate specimen is collected and placed into a viral transport tube containing 3 mL transport medium or 3 mL of saline. The specimen is briefly mixed by rapidly inverting the collection tube 5 times. Using the supplied transfer pipette, the sample is transferred to the sample chamber of the Xpert Xpress SARS-CoV-2 cartridge. The GeneXpert cartridge is loaded onto the GeneXpert Instrument System platform, which performs hands-off, automated sample processing, and real-time RT-PCR for detection of viral RNA.

6 Reagents and Instruments

6.1 Materials Provided

The Xpert Xpress SARS-CoV-2 kit contains sufficient reagents to process 10 specimens or quality control samples. The kit contains the following:

Xpert Xpress SARS-CoV-2 Cartridges with Integrated Reaction Tubes	**10**
• Bead 1, Bead 2, and Bead 3 (freeze-dried)	1 of each per cartridge
• Lysis Reagent	1.5 mL per cartridge
• Binding Reagent	1.5 mL per cartridge
• Elution Reagent	3.0 mL per cartridge
Disposable Transfer Pipettes	**12 per kit**
CD	**1 per kit**
• Assay Definition File (ADF)	
• Instructions to import ADF into GeneXpert software	
Flyer	**1 per kit**
• Directions to locate the Product Insert on www.cepheid.com	

Note Safety Data Sheets (SDS) are available at www.cepheidinternational.com under the **SUPPORT** tab.

Note The bovine serum a bumin (BSA) in the beads within this product was produced and manufactured exclusively from bovine plasma sourced in the United States. No ruminant protein or other animal protein was fed to the animals; the animals passed ante- and postmortem testing. During processing, there was no mixing of the material with other animal materials.

7 Storage and Handling

- Store the Xpert Xpress SARS-CoV-2 cartridges at 2-28°C.
- Do not open a cartridge lid until you are ready to perform testing.
- Do not use a cartridge that is wet or has leaked.

8 Materials Required but Not Provided

- GeneXpert Dx or GeneXpert Infinity systems (catalog number varies by configuration): GeneXpert instrument, computer, barcode scanner, operator manual.

  For GeneXpert Dx System: GeneXpert Dx software version 4.7b or higher

  For GeneXpert Infinity-80 and Infinity-48s systems: Xpertise software version 6.4b or higher

9 Materials Available but Not Provided

SeraCare AccuPlex™ Reference Material Kit, catalog number 0505-0126 (Order Code CEPHEID)

10 Warnings and Precautions

10.1 General

- For *in vitro* diagnostic use.
- For emergency use only.
- Positive results are indicative of presence of SARS-CoV-2-RNA.
- Laboratories within the United States and its territories are required to report all positive results to the appropriate public health authorities.
- Performance characteristics of this test have been established with the specimen types listed in the Intended Use Section only. The performance of this assay with other specimen types or samples has not been evaluated.
- Treat all biological specimens, including used cartridges, as if capable of transmitting infectious agents. Because it is often impossible to know which might be infectious, all biological specimens should be handled using standard precautions. Guidelines for specimen handling are available from the U.S. Centers for Disease Control and Prevention[3] and the Clinical and Laboratory Standards Institute.[4]
- Follow safety procedures set by your institution for working with chemicals and handling biological specimens.
- Consult your institution's environmental waste personnel on proper disposal of used cartridges, which may contain amplified material. This material may exhibit characteristics of federal EPA Resource Conservation and Recovery Act (RCRA) hazardous waste requiring specific disposal requirements. Check state and local regulations as they may differ from federal disposal regulations. Institutions should check the hazardous waste disposal requirements within their respective countries.

10.2 Specimens

- Maintain proper storage conditions during specimen transport to ensure the integrity of the specimen (see Section 12, Specimen Collection, Transport, and Storage). Specimen stability under shipping conditions other than those recommended has not been evaluated.

10.3 Assay/Reagent

- Do not open the Xpert Xpress SARS-CoV-2 cartridge lid except when adding specimen.
- Do not use a cartridge that has been dropped after removing it from the packaging.
- Do not shake the cartridge. Shaking or dropping the cartridge after opening the cartridge lid may yield non-determinate results.
- Do not place the sample ID label on the cartridge lid or on the barcode label on the cartridge.
- Do not use a cartridge with a damaged barcode label.
- Do not use a cartridge that has a damaged reaction tube.
- Each single-use Xpert Xpress SARS-CoV-2 cartridge is used to process one test. Do not reuse processed cartridges.
- Each single-use disposable pipette is used to transfer one specimen. Do not reuse disposable pipettes.
- Do not use a cartridge if it appears wet or if the lid seal appears to have been broken.
- Wear clean lab coats and gloves. Change gloves between the handling of each specimen.
- In the event of a spill of specimens or controls, wear gloves and absorb the spill with paper towels. Then, thoroughly clean the contaminated area with a 10% freshly prepared household chlorine bleach. Allow a minimum of two minutes of contact time. Ensure the work area is dry before using 70% denatured ethanol to remove bleach residue. Allow surface to dry completely before proceeding. Or, follow your institution's standard procedures for a contamination or spill event. For equipment, follow the manufacturer's recommendations for decontamination of equipment.

- Biological specimens, transfer devices, and used cartridges should be considered capable of transmitting infectious agents requiring standard precautions. Follow your institution's environmental waste procedures for proper disposal of used cartridges and unused reagents. These materials may exhibit characteristics of chemical hazardous waste requiring specific disposal. If country or regional regulations do not provide clear direction on proper disposal, biological specimens and used cartridges should be disposed per WHO [World Health Organization] medical waste handling and disposal guidelines.

11 Chemical Hazards[5,6]

- Signal Word: WARNING
- **UN GHS Hazard Statements**
  - Harmful if swallowed.
  - May be harmful in contact with skin.
  - Causes eye irritation.
- **UN GHS Precautionary Statements**
  - **Prevention**
    - Wash hands thoroughly after handling.
  - **Response**
    - Call a POISON CENTER or doctor/physician if you feel unwell.
    - If skin irritation occurs: Get medical advice/attention.
    - IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
    - If eye irritation persists: Get medical advice/attention.

12 Specimen Collection, Transport, and Storage

Proper specimen collection, storage, and transport are critical to the performance of this test. Inadequate specimen collection, improper specimen handling and/or transport may yield a false result. See Section 12.1 for nasopharyngeal swab collection procedure, Section 12.2 for oropharyngeal swab collection procedure, Section 12.3 for nasal swab collection procedure, Section 12.4 for mid-turbinate swab collection procedure, and Section 12.5 for nasal wash/aspirate procedure.

Nasopharyngeal, nasal, and mid-turbinate swabs and nasal wash/aspirate specimens can be stored at room temperature (15-30 °C) for up to 8 hours and refrigerated (2-8 °C) up to seven days until testing is performed on the GeneXpert Instrument Systems. For oropharyngeal swab specimen transport and storage requirements and additional information, refer to the CDC Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens from Persons Under Investigation (PUIs) for Coronavirus Disease 2019 (COVID-19) using the link provided below.

https://www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html

12.1 Nasopharyngeal Swab Collection Procedure

Insert the swab into either nostril, passing it into the posterior nasopharynx (see Figure 1). Rotate swab by firmly brushing against the nasopharynx several times. Remove and place the swab into the tube containing 3 mL of viral transport medium or 3 mL of saline. Break swab at the indicated break line and cap the specimen collection tube tightly.

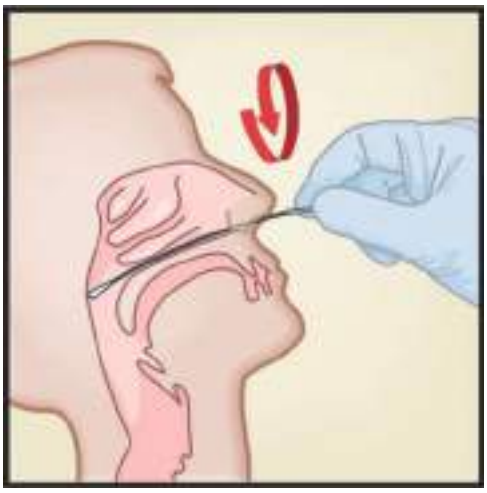

Figure 1. Nasopharyngeal Swab Collection

12.2 Oropharyngeal Swab Collection Procedure

1. Swab the posterior pharynx, tonsils, and other inflamed areas. Avoid touching the tongue, cheeks, and teeth with the swab when collecting specimens.
2. Remove and place the swab into the tube containing 3 mL of viral transport medium or 3 mL of saline. Break swab at the indicated break line and cap the specimen collection tube tightly.

12.3 Nasal Swab Collection Procedure

1. Insert a nasal swab 1 to 1.5 cm into a nostril. Rotate the swab against the inside of the nostril for 3 seconds while applying pressure with a finger to the outside of the nostril (see Figure 2).

Figure 2. Nasal Swab Collection for First Nostril

2. Repeat on the other nostril with the same swab, using external pressure on the outside of the other nostril (see Figure 3). To avoid specimen contamination, do not touch the swab tip to anything other than the inside of the nostril.

Figure 3. Nasal Swab Collection for Second Nostril

3. Remove and place the swab into the tube containing 3 mL of viral transport medium or 3 mL of saline. Break swab at the indicated break line and cap the specimen collection tube tightly.

12.4 Mid-Turbinate Swab Collection Procedure

1. Insert the mid-turbinate swab into either nostril, passing it into the mid-turbinate area (see Figure 4). Rotate swab by firmly brushing against the mid-turbinate area several times.
2. Remove and place the swab into the tube containing 3 mL of viral transport medium or 3 mL of saline. Break swab at the indicated break line and cap the specimen collection tube tightly.

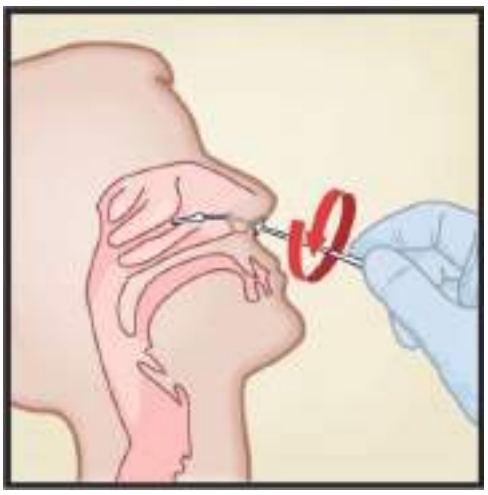

Figure 4. Mid-turbinate Swab Specimen Collection

12.5 Nasal Wash/Aspirate Procedure

Using a clean transfer pipette, transfer 600 µL of the sample into the tube containing 3 mL of viral transport medium or 3 mL of saline and then cap the tube.

13 Procedure

13.1 Preparing the Cartridge

Important **Start the test within 30 minutes of adding the sample to the cartridge.**

1. Remove a cartridge from the package.
2. Check the specimen transport tube is closed.
3. Mix specimen by rapidly inverting the specimen transport tube 5 times. Open cap on the specimen transport tube.

4. Open the cartridge lid.
5. Remove the transfer pipette from the wrapper.
6. Squeeze the top bulb of the transfer pipette completely and then place the pipette tip in the specimen transport tube (see Figure 5).

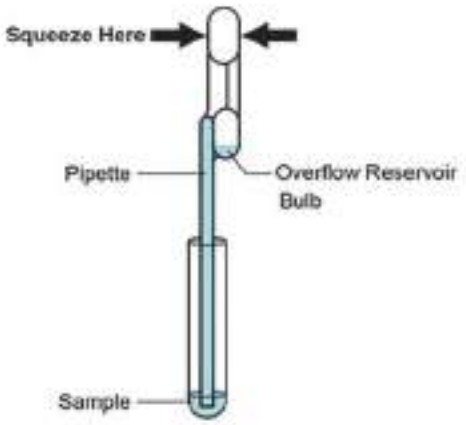

Figure 5. Transfer Pipette

7. Release the top bulb of the pipette to fill the pipette before removing from the tube. After filling pipette, excess sample will be seen in the overflow reservoir bulb of the pipette (see Figure 5). Check that the pipette does not contain bubbles.
8. To transfer the sample to the cartridge, squeeze the top bulb of the transfer pipette completely again to empty the contents of the pipette (300 µL) into the large opening (Sample Chamber) in the cartridge shown in Figure 6. Dispose of the used pipette.

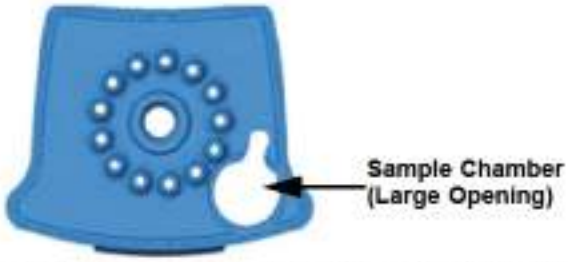

Figure 6. Xpert Xpress SARS-CoV-2 Cartridge (Top View)

Note Take care to dispense the entire volume of liquid into the Sample Chamber. False negative results may occur if insufficient sample is added to the cartridge.

9. Close the cartridge lid.

13.2 External Controls

External controls described in Section 9 are available but not provided and may be used in accordance with local, state, and federal accrediting organizations, as applicable.

To run a control using the Xpert Xpress SARS-CoV-2 test, perform the following steps:

1. Mix control by rapidly inverting the external control tube 5 times. Open cap on external control tube.
2. Open the cartridge lid.
3. Using a clean transfer pipette, transfer one draw of the external control sample (300 µL) into the large opening (Sample Chamber) in the cartridge shown in Figure 6.
4. Close cartridge lid.

13.3 Starting the Test

Note Before you start the test, make sure that the system contains modules with GeneXpert Dx software version 4.7b or higher or Infinity Xpertise software 6.4b or higher, and that the Xpert Xpress SARS-CoV-2 Assay Definition File is imported into the software.

This section lists the default steps to operate the GeneXpert Instrument System. For detailed instructions, see the *GeneXpert Dx System Operator Manual* or the *GeneXpert Infinity System Operator Manual*, depending on the model that is being used.

Note The steps you follow may be different if the system administrator has changed the default workflow of the system.

1. Turn on the GeneXpert Instrument System:
   - **GeneXpert Dx:**
     If using the GeneXpert Dx instrument, first turn on the instrument and then turn on the computer. Log into the Windows operating system. The GeneXpert software may launch automatically or may require double-clicking on the GeneXpert Dx shortcut icon on the Windows® desktop.

     or
   - **GeneXpert Infinity System:**
     If using the GeneXpert Infinity instrument, power up the instrument by turning the power switch clockwise to the **ON** position. On the Windows desktop, double-click the Xpertise Software shortcut icon to launch the software.
2. Log on to the System software. The login screen appears. Type your user name and password.
3. In the GeneXpert System window, click **Create Test** (GeneXpert Dx) or **Orders** followed by **Order Test** (Infinity).
4. Scan or type in the Patient ID (optional). If typing the Patient ID, make sure the Patient ID is typed correctly. The Patient ID is shown on the left side of the View Results window and is associated with the test result.
5. Scan or type in the Sample ID. If typing the Sample ID, make sure the Sample ID is typed correctly. The Sample ID is shown on the left side of the View Results window and is associated with the test result.
6. Scan the barcode on the Xpert Xpress SARS-CoV-2 cartridge. Using the barcode information, the software automatically fills the boxes for the following fields: Reagent Lot ID, Cartridge SN, Expiration Date and Selected Assay.

Note If the barcode on the Xpert Xpress SARS-CoV-2 cartridge does not scan, then repeat the test with a new cartridge.

7. Click **Start Test** (GeneXpert Dx) or **Submit** (Infinity) if Auto-Submit is not enabled. In the dialog box that appears, type your password, if required.

   For the GeneXpert Dx Instrument

   A. Locate the module with the blinking green light, open the instrument module door and load the cartridge.

   B. Close the door. The test starts and the green light stops blinking. When the test is finished, the light turns off and the door will unlock. Remove the cartridge.

   C. Dispose of used cartridges in the appropriate sample waste containers according to your institution's standard practices.

   or

   For the GeneXpert Infinity System

   A. After clicking **Submit**, you will be asked to place the cartridge on the conveyor belt. After placing the cartridge, click **OK** to continue. The cartridge will be automatically loaded, the test will run and the used cartridge will be placed onto the waste shelf for disposal.

   B. When all samples are loaded, click on the **End Order Test** icon.

Note Do not turn off or unplug the instruments while a test is in progress. Turning off or unplugging the GeneXpert instrument or computer will stop the test.

14 Viewing and Printing Results

For detailed instructions on how to view and print the results, see the *GeneXpert Dx System Operator Manual* or the *GeneXpert Infinity System Operator Manual*.

15 Quality Control

15.1 Internal Controls

CONTROL

Each cartridge includes a Sample Processing Control (SPC) and Probe Check Control (PCC).

Sample Processing Control (SPC) - Ensures that the sample was processed correctly. The SPC verifies that sample processing is adequate. Additionally, this control detects sample-associated inhibition of the real-time PCR assay, ensures that the PCR reaction conditions (temperature and time) are appropriate for the amplification reaction, and that the PCR reagents are functional. The SPC should be positive in a negative sample and can be negative or positive in a positive sample. The SPC passes if it meets the validated acceptance criteria.

Probe Check Control (PCC) - Before the start of the PCR reaction, the GeneXpert System measures the fluorescence signal from the probes to monitor bead rehydration, reaction tube filling, probe integrity, and dye stability. The PCC passes if it meets the validated acceptance criteria.

15.2 External Controls

External controls should be used in accordance with local, state, and federal accrediting organizations as applicable.

16 Interpretation of Results

The results are interpreted automatically by the GeneXpert System and are clearly shown in the **View Results** window. The Xpert Xpress SARS-CoV-2 test provides test results based on the detection of two gene targets according to the algorithms shown in Table 1.

Table 1. Xpert Xpress SARS-CoV-2 Possible Results

Result Text	N2	E	SPC
SARS-CoV-2 POSITIVE	+	+/-	+/-
SARS-CoV-2 PRESUMPTIVE POS	-	+	+/-
SARS-CoV-2 NEGATIVE	-	-	+
INVALID	-	-	-

See Table 2 to interpret test result statements for the Xpert Xpress SARS-CoV-2 test.

Table 2. Xpert Xpress SARS-CoV-2 Results and Interpretation

Result	Interpretation
SARS-CoV-2 POSITIVE	The 2019 novel coronavirus (SARS-CoV-2) target nucleic acids are detected. • The SARS-CoV-2 signal for the N2 nucleic acid target or signals for both nucleic acid targets (N2 and E) have a Ct within the valid range and endpoint above the minimum setting • SPC: NA; SPC is ignored because coronavirus target amplification occurred • Probe Check: PASS; all probe check results pass
SARS-CoV-2 PRESUMPTIVE POS	The 2019 novel coronavirus (SARS-CoV-2) nucleic acids may be present. Sample should be retested according to the Retest Procedure in Section 17.2. For samples with a repeated presumptive positive result, additional confirmatory testing may be conducted, if it is necessary to differentiate between SARS-CoV-2 and SARS-CoV-1 or other Sarbecovirus currently unknown to infect humans, for epidemiological purposes or clinical management. • The SARS-CoV-2 signal for only the E nucleic acid target has a Ct within the valid range and endpoint above the minimum setting • SPC: NA; SPC is ignored because a target amplification has occurred. • Probe Check: PASS; all probe check results pass.

Table 2. Xpert Xpress SARS-CoV-2 Results and Interpretation (Continued)

Result	Interpretation
SARS-CoV-2 NEGATIVE	The 2019 novel coronavirus (SARS-CoV-2) target nucleic acids are not detected. • The SARS-CoV-2 signals for two nucleic acid targets (N2 and E) do not have a Ct within the valid range and endpoint above the minimum setting • SPC: PASS; SPC has a Ct within the valid range and endpoint above the minimum setting • Probe Check: PASS; all probe check results pass
INVALID	SPC does not meet acceptance criteria. Presence or absence of the 2019 novel coronavirus (SARS-CoV-2) nucleic acids cannot be determined. Repeat test according to the Retest Procedure in Section 17.2. • SPC: FAIL; SPC and SARS-CoV-2 signals do not have a Ct within valid range and endpoint below minimum setting • Probe Check: PASS; all probe check results pass
ERROR	Presence or absence of the 2019 novel coronavirus (SARS-CoV-2) nucleic acids cannot be determined. Repeat test according to the Retest Procedure in Section 17.2. • SARS-CoV-2: NO RESULT • SPC: NO RESULT • Probe Check: FAIL[1]; all or one of the probe check results fail [1] If the probe check passes, the error is caused by the maximum pressure limit exceeding the acceptable range, no sample added, or by a system component failure.
NO RESULT	Presence or absence of the 2019 novel coronavirus (SARS-CoV-2) nucleic acids cannot be determined. Repeat test according to the Retest Procedure in Section 17.2. A **NO RESULT** indicates that insufficient data were collected. For example, the operator stopped a test that was in progress. • SARS-CoV-2: NO RESULT • SPC: NO RESULT • Probe Check: NA (not applicable)

The Xpert Xpress SARS-CoV-2 test includes an Early Assay Termination (EAT) function which will provide earlier time to results in high titer specimens. When SARS-CoV-2 titers are high enough to initiate the EAT function, the SPC amplification curve may not be seen and its results may not be reported.

17 Retests

17.1 Reasons to Repeat the Assay

If any of the test results mentioned below occur, repeat the test once according to instructions in Section 17.2, Retest Procedure.

- A **PRESUMPTIVE POS** result indicates the 2019 novel coronavirus (SARS-CoV-2) nucleic acids may be present. Only one of the SARS-CoV-2 nucleic acid target was detected (E gene) while the other SARS-CoV-2 nucleic acid target (N2 gene) was not detected.
- An **INVALID** result indicates that the control SPC failed. The sample was not properly processed, PCR is inhibited, or the sample was not properly collected.
- An **ERROR** result could be due to, but not limited to, Probe Check Control failure, system component failure, no sample added, or the maximum pressure limits were exceeded.
- A **NO RESULT** indicates that insufficient data were collected. For example, cartridge failed integrity test, the operator stopped a test that was in progress, or a power failure occurred.

If an External Control fails to perform as expected, repeat external control test and/or contact Cepheid for assistance.

17.2 Retest Procedure

To retest a non-determinate result (**INVALID**, **NO RESULT**, or **ERROR)** or a **PRESUMPTIVE POS** result, use a new cartridge.

Use the leftover sample from the original specimen transport medium tube or new external control tube.

1. Put on a clean pair of gloves. Obtain a new Xpert Xpress SARS-CoV-2 cartridge and a new transfer pipette.
2. Check the specimen transport tube or external control tube is closed.
3. Mix the sample by rapidly invert the specimen transport medium tube or external control tube 5 times. Open the cap on the specimen transport tube or external control tube.
4. Open the cartridge lid.
5. Using a clean transfer pipette (supplied), transfer sample (one draw) to the sample chamber with the large opening in the cartridge.
6. Close the cartridge lid.

18 Limitations

- Performance of the Xpert Xpress SARS-CoV-2 test has only been established in nasopharyngeal swab and nasal wash/aspirate specimens. Use of the Xpert Xpress SARS-CoV-2 test with other specimen types has not been assessed and performance characteristics are unknown.
- Oropharyngeal, nasal swabs and mid-turbinate swabs are considered acceptable specimen types for use with the Xpert Xpress SARS-CoV-2 test but performance with these specimen types has not been established. Testing of nasal and mid-turbinate nasal swabs (self-collected under supervision of or collected by a healthcare provider) is limited to patients with symptoms of
  COVID-19. Please refer to FDA's FAQs on Diagnostic testing for SARS-CoV-2 for additional information.
- A false negative result may occur if a specimen is improperly collected, transported or handled. False negative results may also occur if inadequate numbers of organisms are present in the specimen.
- As with any molecular test, mutations within the target regions of Xpert Xpress SARS-CoV-2 could affect primer and/or probe binding resulting in failure to detect the presence of virus.
- This test cannot rule out diseases caused by other bacterial or viral pathogens.

19 Conditions of Authorization for Laboratory and Patient Care Settings

The Cepheid Xpert Xpress SARS-CoV-2 Letter of Authorization, along with the authorized Fact Sheet for Healthcare Providers, the authorized Fact Sheet for Patients and authorized labeling are available on the FDA website: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#covid19ivd

However, to assist clinical laboratories and/or Patient Care Settings using the Xpert Xpress SARS-CoV-2 (referred to in the Letter of Authorization as "Your Product"), the relevant Conditions of Authorization are listed below.

- Authorized laboratories[1] and patient care settings using your product will include with result reports of the Xpert Xpress SARS-CoV-2 test, all authorized Fact Sheets. Under exigent circumstances, other appropriate methods for disseminating these Fact Sheets may be used, which may include mass media.
- Authorized laboratories using your product will use your product as outlined in the Xpert Xpress SARS-CoV-2 Instructions for Use - For Use with GeneXpert Dx or GeneXpert Infinity systems. Deviations from the authorized procedures, including the authorized instruments, authorized extraction methods, authorized clinical specimen types, authorized control materials, authorized other ancillary reagents and authorized materials required to use the Xpert Xpress SARS-CoV-2 test are not permitted.
- Patient Care Settings using your product will use your product as outlined in the Xpress SARS-CoV-2 Instructions for Use - For Use with GeneXpert Xpress System and associated Quick Reference Instructions for Xpert Xpress SARS-CoV-2 and GeneXpert Xpress System (Hub configuration), and Quick Reference Instructions for Xpert Xpress SARS-CoV-2 and GeneXpert Xpress System (Tablet configuration). Deviations from the authorized procedures, including the authorized instruments, authorized extraction methods, authorized clinical specimen types, authorized control materials, authorized other ancillary reagents and authorized materials required to use your product are not permitted.
- Authorized laboratories and patient care settings will have a process in place for reporting test results to healthcare providers and relevant public health authorities, as appropriate.
- Authorized laboratories and patient care settings that receive your product will notify the relevant public health authorities of their intent to run your product prior to initiating testing.

- Authorized laboratories and patient care settings using the Xpert Xpress SARS-CoV-2 test will collect information on the performance of the test and report to DMD/OHT7-OIR/OPEQ/CDRH (via email: CDRH-EUA Reporting@fda hhs.gov) and Cepheid (+1 888.838.3222 or techsupport@cepheid.com) any suspected occurrence of false positive or false negative results and significant deviations from the established performance characteristics of the test of which they become aware.
- All operators using your product must be appropriately trained in performing and interpreting the results of your product, use appropriate personal protective equipment when handling this kit, and use your product in accordance with the authorized labeling.
- You, authorized distributors, and authorized laboratories and patient care settings using your product will ensure that any records associated with this EUA are maintained until otherwise notified by FDA. Such records will be made available to FDA for inspection upon request.

[1] The letter of authorization refers to, "Laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. § 263a, to perform moderate or high complexity tests" as "authorized laboratories."

20 Performance Characteristics

20.1 Clinical Evaluation - AccuPlex SARS-CoV-2 Reference Material

The performance of the Xpert Xpress SARS-CoV-2 test was evaluated using contrived clinical NP swab specimens in viral transport medium obtained from U.S. patients with signs and symptoms of respiratory infection. The samples were prepared by spiking each individual negative clinical NP swab sample with AccuPlex SARS-CoV-2 (a quantitated reference material - recombinant Sindbis virus particle containing target sequences from the SARS-CoV-2 genome) at 2x LoD, 3x LoD and 5x LoD levels. The NP swab samples were determined to be negative for SARS-CoV-2 prior to spiking. Individual negative NP swab samples were also tested in the study. All positive and negative samples in the study were tested in a randomized and blinded fashion.

Table 3 shows the number of concordant results out of the total number of samples tested for each target concentration of AccuPlex SARS-CoV-2, the mean Ct values for each of the E and N2 nucleic acid targets as well as the percent agreement with the 95% CI where appropriate. The results show 100% agreement with the expected results in the AccuPlex SARS-CoV-2 spiked samples and 100% agreement with the expected results in the negative samples.

Table 3. Xpert Xpress SARS-CoV-2 Test Agreement with the Expected Results by Target Concentration

Target Concentration	Number Concordant/ Number Tested	E Mean Ct	N2 Mean Ct	% Agreement [95% CI]
2x LoD	20/20	34.8	38.0	100% [83.9% - 100%]
3x LoD	5/5	33.7	37.1	100% [NA*]
5x LoD	5/5	33.7	36.8	100% [NA*]
Negative	35/35	NA	NA	100% [90.1% - 100%]

*95% CI not computed for sample concentrations with sample size of 5 or less.

20.2 Clinical Evaluation – Live SARS-CoV-2 Virus

The performance of the Xpert Xpress SARS-CoV-2 test was evaluated using contrived clinical NP swab specimens in viral transport medium obtained from U.S. patients with signs and symptoms of respiratory infection. The samples were prepared by spiking each individual negative clinical NP swab sample with live SARS-CoV-2 virus (USA_WA1/2020) at 2x LoD, 3x LoD and 5x LoD levels. The NP swab samples were determined to be negative for SARS-CoV-2 prior to spiking. Individual negative NP swab samples were also tested in the study. All positive and negative samples in the study were tested in a randomized and blinded fashion.

Table 4 shows the number of concordant results out of the total number of samples tested for each target concentration of live SARS-CoV-2 virus, the mean Ct values for each of the E and N2 nucleic acid targets as well as the percent agreement with the 95% confidence interval (95% CI), where appropriate. The results show 100% agreement with the expected results in the live SARS-CoV-2 virus spiked samples and 100% agreement with the expected results in the negative samples.

Table 4. Xpert Xpress SARS-CoV-2 Test Agreement with the Expected Results by Target Concentration

Target Concentration	Number Concordant/ Number Tested	E Mean Ct	N2 Mean Ct	% Agreement [95% CI]
2x LoD	20/20	35.4	38.4	100% [83.9% - 100%]
3x LoD	5/5	34.2	37.2	100% [NA*]
5x LoD	5/5	33.9	37.0	100% [NA*]
Negative	30/30	NA	NA	100% [88.7% - 100%]

* 95% CI not computed for sample concentrations with sample size of 5 or less.

21 Analytical Performance

21.1 Analytical Sensitivity (Limit of Detection) - AccuPlex SARS-CoV-2 Reference Material

Studies were performed to determine the analytical limit of detection (LoD) of the Xpert Xpress SARS-CoV-2. The LoD of Xpert Xpress SARS-CoV-2 was established using one lot of reagent and limiting dilutions of AccuPlex SARS-CoV-2 prepared in simulated background matrix and NP swab clinical matrix and probit analysis. Verification of the estimated LoD claim was performed on one reagent lot in replicates of 35 prepared in pooled NP swab clinical matrix. The LoD is the lowest concentration (reported as copies/mL) of AccuPlex SARS-Cov-2 recombinant viral sequence that can be reproducibly distinguished from negative samples ≥ 95% of the time with 95% confidence. The claimed LoD for the assay is 250 copies/mL (Table 5).

Table 5. Limit of Detection of the Xpert Xpress SARS-CoV-2

Material	Claimed LoD (copies/mL)	Positives/ Replicates
SARS-CoV-2 Reference Material	250	35/35

21.2 Analytical Sensitivity (Limit of Detection) – Live SARS-CoV-2 Virus

Studies were performed to determine the analytical limit of detection (LoD) of the Xpert Xpress SARS-CoV-2. The LoD of Xpert Xpress SARS-CoV-2 was established using one lot of reagent and limiting dilutions of live SARS-CoV-2 virus (USA_WA1/2020) prepared in viral transport medium and NP swab clinical matrix and probit analysis. Verification of the estimated LoD claim was performed on one reagent lot in replicates of 22 prepared in pooled NP swab clinical matrix. The LoD is the lowest concentration (reported as PFU/mL) of live SARS-CoV-2 virus samples that can be reproducibly distinguished from negative samples ≥ 95% of the time with 95% confidence. The claimed LoD for the assay is 0.0100 PFU/mL (Table 6).

Table 6. Limit of Detection of the Xpert Xpress SARS-CoV-2

Strain	Claimed LoD (PFU/mL)	E Mean Ct	N2 Mean Ct	Positives/ Replicates
SARS-CoV-2 virus (USA_WA1/2020)	0.0100	35.9	38.9	22/22

21.3 Analytical Reactivity (Inclusivity)

The inclusivity of Xpert Xpress SARS-CoV-2 was evaluated using *in silico* analysis of the assay primers and probes in relation to 324 SARS-CoV-2 sequences available in the GISAID gene database for two targets, E and N2.

For the E target, Xpert Xpress SARS-CoV-2 had 100% match to all sequences with the exception of 4 sequences that had a single mismatch. For the N2 target, Xpert Xpress SARS-CoV-2 had 100% match to all sequences with the exception of 2 sequences that had a single mismatch. None of these mismatches found for both targets are predicted to have a negative impact on the performance of the assay, given the location of the mutations in the primer and probe regions respectively for the two variants. These mutations are not predicted to adversely affect the probe and primer binding to the sequences or reduce assay efficiency.

21.4 Analytical Specificity (Exclusivity)

An *in silico* analysis for possible cross-reactions with all the organisms listed in Table 7 was conducted by mapping primers and probes in the Xpert Xpress SARS-CoV-2 test individually to the sequences downloaded from the GISAID database. E primers and probes are not specific for SARS-CoV-2 and will detect Human and Bat SARS-coronavirus. No potential unintended cross reactivity with other organisms listed in Table 7 is expected based on the *in silico* analysis.

Table 7. Xpert Xpress SARS-CoV-2 Analytical Specificity Microorganisms

Microorganisms from the Same Genetic Family	High Priority Organisms
Human coronavirus 229E	Adenovirus (e.g. C1 Ad. 71)
Human coronavirus OC43	Human Metapneumovirus (hMPV)
Human coronavirus HKU1	Parainfluenza virus 1-4
Human coronavirus NL63	Influenza A
SARS-coronavirus	Influenza B
MERS-coronavirus	Influenza C
Bat coronavirus	Enterovirus (e.g. EV68)
	Respiratory syncytial virus
	Rhinovirus
	Chlamydia pneumoniae
	Haemophilus influenzae
	Legionella pneumophila
	Mycobacterium tuberculosis
	Streptococcus pneumoniae
	Streptococcus pyogenes
	Bordetella pertussis
	Mycoplasma pneumoniae
	Pneumocystis jirovecii (PJP)
	Parechovirus
	Candida albicans
	Corynebacterium diphtheriae
	Legionella non-pneumophila
	Bacillus anthracis (Anthrax)
	Moraxella catarrhalis
	Neisseria elongate and meningitidis
	Pseudomonas aeruginosa
	Staphylococcus epidermidis
	Staphylococcus salivarius
	Leptospira
	Chlamydia psittaci
	Coxiella burnetii (Q-Fever)
	Staphylococcus aureus

22 References

1. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/index html. Accessed February 9, 2020.
2. bioRxiv. (https://www.biorxiv.org/content/10.1101/2020.02.07.937862v1). Accessed March 3, 2020.
3. Centers for Disease Control and Prevention. *Biosafety in Microbiological and Biomedical laboratories* (refer to latest edition). http://www.cdc.gov/biosafety/publications/
4. Clinical and Laboratory Standards Institute. *Protection of Laboratory Workers from Occupationally Acquired Infections; Approved Guideline.* Document M29 (refer to latest edition).
5. REGULATION (EC) No 1272/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 2008 on the classification labeling and packaging of substances and mixtures amending and repealing, List of Precautionary Statements, Directives 67/548/EEC and 1999/45/EC (amending Regulation (EC) No 1907/2007).
6. Occupational Safety and Health Standards, Hazard Communication, Toxic and Hazard Substances (March 26, 2012) (29 C.F.R., pt. 1910, subpt. Z).

23 Cepheid Headquarters Locations

Corporate Headquarters	European Headquarters
Cepheid 904 Caribbean Drive Sunnyvale, CA 94089 USA	Cepheid Europe SAS Vira Solelh 81470 Maurens-Scopont France
Telephone: +1 408 541 4191	Telephone: +33 563 825 300
Fax: +1 408 541 4192	Fax: +33 563 825 301
www.cepheid.com	www.cepheidinternational.com

24 Technical Assistance

Before contacting Cepheid Technical Support, collect the following information:

- Product name
- Lot number
- Serial number of the instrument
- Error messages (if any)
- Software version and, if applicable, Computer Service Tag number

Region	Telephone	Email
US	+1 888.838.3222	techsupport@cepheid.com
France	+33 563 825 319	support@cepheideurope.com
Australia New Zealand	+1800 130 821 +0800 001 028	techsupportANZ@cepheid.com

Contact information for all Cepheid Technical Support offices is available on our website: www.cepheid.com/en/CustomerSupport.

25 Table of Symbols

Symbol	Meaning
REF	Catalog number
IVD	*In vitro* diagnostic medical device
2	Do not re-use
LOT	Batch code
	Consult instructions for use
	Caution
	Manufacturer
	Country of manufacture
	Contains sufficient for <n> tests
CONTROL	Control
	Expiration date
	Temperature limitation
	Biological risks
Rx only	For prescription use only

Cepheid
904 Caribbean Drive
Sunnyvale, CA 94089 USA
Phone: +1 408 541 4191
Fax: +1 408 541 4192

IVD

For use under Emergency Use Authorization (EUA) Only

Privacy Office; Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

July 29, 2021

Sent via email

Re: Full Disclosure – OUR FILE# NSHA-2021-097

On July 12, 2021 Nova Scotia Health (NSH) received your request under the *Freedom of Information and Protection of Privacy Act* (*FOIPOP Act*).

We understand your application to be for a copy of the following:
Financial information related to the operating costs, in total or per clinic (thus far), of mass COVID-19 vaccinations clinics in Nova Scotia. This includes the cost of employment of healthcare and non-healthcare personnel, administrative, operative, IT, security, and any other relevant personnel; the cost of rental or the use of physical space for the clinics; the cost of equipment not directly utilized in vaccination; and any other incendiary costs vital to the operations of such mass vaccination clinics. (Date Range for Record Search: From 02/29/2020 To 07/05/2021).

Please find a copy of the records located in response to your request below:
NS Health has spent $10 786 000 on the immunization program to the end of June 30, 2021. NS Health has spent a further $892 000 on capital purchases over and above the operational costs above. These are only the costs at NS Health, the province may have other costs.

We are providing these records to you in their entirety. We are now closing your file.

Should you have any questions, please do not hesitate to contact me.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review.

Sincerely,
Katie Smith
Freedom of Information Officer
Nova Scotia Health Authority
Halifax, Nova Scotia

Privacy Office; Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

August 25, 2021

Sent via e-mail

Re: Full Disclosure – OUR FILE# NSHA-2021-101

On July 27, 2021 Nova Scotia Health (NSH) received your request under the *Freedom of Information and Protection of Privacy Act* (*FOIPOP Act*).

We understand your application to be for a copy of the following:

1. *Based on the fact that this test (PCR) cannot differentiate between living and dead cells, flu, or covid, will the NSHA continue administering these tests?*
2. *If the NSHA decides to continue testing with the PCR test, will it change the cycle threshold to a more appropriate level?*
3. *If the cycle count is changed, to what level and when?*

Please find a copy of the records located in response to your request. We are providing these records to you in their entirety. We are now closing your file.

Should you have any questions, please do not hesitate to contact me.

You have the right to seek a review with the Review Officer within 60 days of receiving this decision. Complete details of the process are outlined on the website of the Office of the Information & Privacy Commissioner: https://foipop.ns.ca/request-a-review.

Sincerely,
Katie Smith
Freedom of Information Officer
Nova Scotia Health Authority
Halifax, Nova Scotia

Privacy Office; Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca

September 1, 2021

Sent via e-mail

FOIPOP 2021-101 Data:

1. Based on the fact that this test (PCR) cannot differentiate between living and dead cells, flu, or covid, will the NSHA continue administering these tests?

The SARS-CoV-2 assay can differentiate influenza from SARS-COV-2 because there is no cross-reactivity. They do not identify cells. These assays identify SARS-CoV-2 nucleic acid in a patient's specimen, which may be from an active infection or residual RNS present after the infectious period has cleared. Like any NNAT, differentiation from active versus old infection requires clinical correlation.

2. If the NSHA decides to continue testing with the PCR test, will it change the cycle threshold to a more appropriate level?

NS Health has no plans to change the cycle threshold levels of PCR tests.

3. If the cycle count is changed, to what level and when?

NS Health has no plans to change the cycle threshold levels of PCR tests.

Privacy Office; Legal Services
1-031 Centennial Building
1276 South Park Street
Halifax, NS B3H 2Y9
foipop@nshealth.ca