

COVID-19 Scientific Advisory Group Rapid Response Report

Key Research Question: How do the testing characteristics for the Alberta Health Services lab-developed test for COVID-19 differ between samples collected from nasal, nasopharyngeal, and throat swabs?

Context

- When this review started, there were three devices in use for collecting samples for COVID-19 testing:
 1. FLOQSwab and Universal Transport Medium (for nasopharyngeal (NP) swabs)
 2. APTIMA® Unisex Swab Specimen Collection Kit (throat or deep nasal swabs)
 3. APTIMA® Multitest Swab Specimen Collection Kit (throat or deep nasal swabs)
- While this review was ongoing, recommendations for swabbing changed and AHS and APL no longer recommend nasal swabbing as a sample collection method.
- AHS uses a validated lab-developed real-time reverse transcriptase – polymerase chain reaction (RT-PCR) assay to test for the presence of SARS-CoV-2.
- There was a recent safety incident where a patient with a history and symptoms consistent with COVID-19 was taken out of isolation and off of contact precautions due to negative test result, raising questions about the negative predictive value of COVID-19 testing.
- Clinicians have raised questions about variability in testing characteristics (eg. sensitivity, specificity, negative predictive value) depending on the anatomical site from which the sample was taken.

Key Messages from the Evidence Summary

- The analytical validity of the lab-developed test used in Alberta is not in question, as confirmatory testing by the Canadian National Microbiology Lab (NML) showed that the Alberta test was 100% accurate, and analytical specificity of PCR testing has been reported to be 100% given the methodology – at least when done during active infection phase.
- However, problems with swab collection have been noted, and it is unknown how the anatomical site of sampling and the timing of the sample relative to the disease progression affects the likelihood of RNA detection in a person who is infected with SARS-CoV-2.
- There is very limited data regarding the negative predictive values and clinical sensitivity and specificity of commercially developed molecular tests for SARS-CoV-2. What data that exists publicly is a different assay from what is used in Alberta and comparisons should be made with caution.
- Studies comparing RNA detection from different sites used samples collected from any of the following sites: nasopharynx, nose, throat, sputum, or bronchoalveolar lavage (BAL) fluid. The evidence was mixed with respect to the superiority (or inferiority) of nasal swabs compared to throat swabs. A small study (n=30) that is ongoing in Alberta indicates that NP and throat swabs may be equivalent while nasal swabs may have lower sensitivity. It is suspected that this is related to a lack of familiarity with deep nasal swab collection and poor collection technique, though this is based on anecdotal evidence.

Committee Discussion

The committee discussion focused on three key issues. First, the use of sample data to illustrate the point of negative test results not ruling out disease (Table 1) was generally supported, but there was consensus that the point would be better made and the table would be more intuitive if it displayed false negative rates with sample prevalence data. This change has been made. Second, there was consensus that this report should include information about proper swabbing technique, given that technique is frequently the source of variation in testing

characteristics. Third, as these reports are meant to inform future action, it was suggested that a recommendation be made regarding data collection for false negatives and true positives so that the clinical sensitivity of the APL RT-PCR test may be ascertained.

Recommendations

1. Based on the evidence, false negative samples are infrequent but do occur and would appear to result from insufficient sample collection, emphasizing the importance of proper collection of samples.
2. A program should be devised to identify false negative test results and correlate to clinical cases of COVID-19. To calculate the clinical sensitivity of the test, a consistent case definition and a standard for confirming positive cases will be required. The current lack of a gold standard for confirming positive cases is a significant challenge.
3. Nasopharyngeal swabs are preferred for COVID-19 sample collection. When this is not possible, for instance due to potential shortages in NP swabs, throat swabs can be used but more evidence is needed to ensure that throat swabs are equivalent in quality to NP swabs for the purposes of COVID-19 testing. Instructions for collecting an NP or throat swab can be found at this link: <https://www.albertahealthservices.ca/assets/wf/plab/wf-provlab-collection-of-nasopharyngeal-and-throat-swab.pdf> and are appended to the lab bulletin here: <https://www.albertahealthservices.ca/assets/wf/lab/wf-lab-bulletin-major-changes-in-covid-19-specimen-collection-recommendations.pdf>.
4. The operational implications of throat swabs must be considered. For example, throat swabbing often elicits a cough from the patient. Staff at assessment centres must be prepared for these reflexes and be equipped with the proper PPE.
5. Information should be distributed to remind clinicians that a negative PCR can occur and a negative result does not mean that the case is a true negative, especially when there is a high probability of disease. Clinical judgement and multiple lines of evidence (such as clinical signs and symptoms, medical imaging results, and contact with lab confirmed cases) should be considered when making decisions for patient care and staff protection.

Summary of Evidence

Literature for this review was collected from a database search covering OVID MEDLINE, EMBASE, LitCovid, TRIP PRO, PubMed, WHO Global research on coronavirus (database), Google and Google Scholar. The search was limited to articles published after 2019. 27 articles were identified from the database search, 10 pieces of grey literature were identified, and 3 articles were identified by hand-searching resources identified by committee members. Following screening and critical appraisal, 15 articles were included in the evidence review. The search was limited by the searched time period and the article language – although language was not an exclusion criterion, articles published in languages other than English (such as Chinese or Italian) could not be included. The evidence consisted largely of letters, preprints, and guidelines; combined with the small amount of evidence available, the findings of this review must be interpreted with caution.

Evidence from grey literature

Instructions for the RT-PCR novel coronavirus diagnostic panel developed by the United States Centers for Disease Control (CDC) highlight the limitations of their assay, specifying that their panel was validated only for respiratory tract specimens and that due to many factors in the sample collection chain, a negative test result should not be used to rule out disease (CDC, 2020a). This document also notes that the predictive values of diagnostic tests are highly dependent on the prevalence and risk of disease (CDC, 2020a). Specifically, false negative test results are more likely when prevalence is high and false positives are more likely when the prevalence is moderate or low (CDC, 2020a), although false positives are rare for RT-PCR based testing when primers and probes are designed appropriately. In their guidelines for specimen collection, the CDC notes that NP swabs are preferred; however, oropharyngeal and nasal mid-turbinate swab (also known as anterior nares swab)

are acceptable alternatives (CDC, 2020b). The European Centres for Disease Control (ECDC) consider NP swabs, OP swabs, and NP aspirate (or nasal wash) as acceptable specimens for upper respiratory tract sampling (ECDC, 2020).

The World Health Organization (WHO) interim guidance on lab testing also suggests using upper respiratory specimens and cautions against using negative test results to rule out disease when symptoms are clinically suspicious (WHO, 2020). In the case of inconclusive results or a result that is discordant with clinical symptoms, clinicians are advised to submit additional specimens for testing, including from the lower respiratory tract (WHO, 2020).

In table 1 below, the point that a negative test result does not rule out disease is illustrated with sample prevalence data to show that when the likelihood of disease is high prior to testing, there is a higher likelihood of a false negative test result as the sensitivity of the test decreases. Test results should be used to complement clinical judgement when making patient care decisions.

Table 1. The risk of a false negative test for COVID-19 testing, assuming RT-PCR testing has a sensitivity of 90 or 80% across a range of pretest probabilities (eg how likely the clinician thinks the patient has COVID-19 based on their assessment) from low (1%) to high (90%).

Pretest likelihood of COVID-19 disease	If test is 90% sensitive, the FALSE NEGATIVE RATE is:	If the test is 80% sensitive, the FALSE NEGATIVE RATE is:
1%	0.1%	0.2%
10%	1.0%	2%
30%	3%	6%
50%	5%	10%
90%	9%	18%

Note: These values were calculated using a range of COVID-19 pretest probability since if the likelihood of disease is high, the likelihood that a test may be falsely negative is increased.

What are the testing characteristic estimates (eg. sensitivity, specificity, predictive value) of the current RT-PCR assay used in Alberta to detect SARS-CoV-2?

The clinical sensitivity and specificity values have not been determined for the current lab-developed RT-PCR used in Alberta. The test has a high analytical sensitivity with a 95% limit of detection (LOD) for the RNA-dependent RNA polymerase (RdRP) gene of 15 copies/reaction and 4 copies/reaction for the envelope (E) gene. The test has also been shown to be 100% specific for SARS-CoV-2 when tested against 31 common respiratory pathogens. Confirmatory testing by the Canadian National Microbiology Lab (NML) showed 100% concordance.

The Alberta RT-PCR has been used in a country-wide comparison of LOD of assays used by labs throughout Canada. Initial analysis shows that it has an LOD of 3.575 log₁₀ copies/mL (95% CI 3.141-4.009 log₁₀ copies/mL), which is comparable to the assays used across the country (range of 2.638- 4.712 log₁₀ copies/mL) (Jason Leblanc, personal communication). ProvLab is also participating in a proficiency testing program administered by NML.

A large Chinese analysis of SARS-CoV-2 molecular tests (*Orf1* and *N* genes) found up to 3% of tests were inconclusive due to the amplification of one gene but not the other, potentially due to error in sample collection and processing, contamination, or individual infection dynamics (Wang, Wu, Xu et al., 2020). To limit the number of false negatives, a low threshold is applied for tests to be declared positive in Alberta. In the event of an inconclusive test where only one target is amplified, the test is repeated in duplicate and marked as positive if one

of the targets is subsequently amplified. This is done out of an abundance of caution to ensure that a positive result is not missed.

What are the testing characteristic estimates (eg. sensitivity, specificity, predictive values) of other commercially available SARS-CoV-2 detection kits?

There is very limited evidence for clinical sensitivity for kits that are commercially available. No data for commercial tests under consideration in Alberta was identified, however, the analytical sensitivity and specificity of the commercial test kits are readily available from the manufacturer. Any test performance data supplied by a manufacturer must be confirmed by an in-house verification.

The cobas SARS-CoV-2 assay (Roche) was compared to a two-target RT-PCR assay (Corman et al. 2020) used by many labs worldwide and found have an overall agreement of 98.1% for a panel of well-characterized samples (n=217) and an agreement of 99.6% for 502 prospectively collected samples (Poljak et al. 2020).

The validation study for the Mammoth Biosciences molecular lateral flow assay for SARS-CoV-2 was 90% sensitive and 100% specific for SARS-CoV-2 coronavirus in respiratory swab samples, corresponding to positive and negative predictive values of 100% and 91.7%, respectively although the sample size was small (6 SARS-CoV-2 samples, 12 influenza or other human coronavirus samples,, and 5 healthy volunteers) (Broughton et al., 2020). The reference for this study was a standard RT-PCR assay (Broughton et al., 2020).

Are there differences in testing characteristics between properly collected nasal, throat and nasopharyngeal swabs?

No evidence was identified in the literature search that evaluated or compared clinical sensitivity for any swab/sampled sites for COVID-19 screening. Preliminary data from a small Alberta study conducted by Alberta Precision Labs suggests that NP swabs and throat swabs have similar clinical sensitivity, while nasal swabs had a slightly lower sensitivity. Thirty outpatients previously testing positive for COVID-19 had three swabs performed: NP, nasal and throat. Using a reference standard of a positive result at any site, NP swab had a sensitivity of 90% (95% CI 74.4-96.5), throat swab 87% (95%CI 70.3-94.7) and nasal swab 80% (95% CI 62.7-90.5). Time from diagnostic swab to repeat swab was a mean of 4.0 days (range 1-6) (Unpublished data).

A review of best practices for respiratory virus testing published in 2011 found that the detection of 12 respiratory viruses using a nucleic acid amplification test (NAAT) panel was significantly less sensitive with oropharyngeal (OP) swab specimens (54.2%) than with either NP swabs (73.3%) or NP wash specimens (84.9%) (Ginocchio & McAdam, 2011). Further, they comment that both nasal and oropharyngeal swab samples is not recommended because of concerns about sensitivity (Ginocchio & McAdam, 2011). A systematic review of specimen collection methods for influenza found that combining nasal and OP swabs resulted in a test with approximately the same sensitivity as an NP swab in both children and adults (Spencer et al., 2019). A review by the Centre for Evidence Base Medicine (CEBM) compared the accuracy of OP swabs to NP swabs for COVID-19 and found two low-quality studies that suggested NP swabs yielded a higher detection rate than OP swabs (Carver & Jones, 2020); however, the evidence is not strong enough and there are too many contextual variables in testing predictive values to make practice recommendations based on this review.

In the literature identified by the search, sample collection methods such as NP swab, OP swab, throat swab, sputum sampling, BAL fluid, stool, or blood samples were compared for viral load. In a large Chinese case series, it was found that in 1070 specimens from 205 patients, viral RNA was detected in BAL fluid (14 of 15; 93%), sputum (72 of 104; 72%), nasal swabs (5 of 8; 63%), fibrobronchoscope brush biopsy (6 of 13; 46%), pharyngeal swab (126 of 398; 32%), feces (44 of 153; 29%), and blood (3 of 307; 1%) (Wang , Xu, Gao et al., 2020). However, this study does not allow a direct comparison of sample types collected from the same patient at the same point in time; as a result, it is not possible to draw conclusions in terms of the optimal specimen type. For example, 398 pharyngeal swabs and 15 BALs were collected from 205 patients at unknown times post-symptom onset, limiting the usefulness of this data (Wang et al. 2020).

In a different small case series, 90% of cases were detected by an NP swab and 10% by sputum collection (no comparison to throat or nasal swabbing was made) (Lo et al., 2020). Sputum was considered superior to throat swab in a study of paired specimens from 54 cases, where the positive rates of COVID-19 from sputum specimens and throat swabs were 76.9% and 44.2%, respectively (Lin et al., 2020). The latter study was performed for patients with suspected COVID-19 infection and only included patients actively producing sputum (Lin et al., 2020).

The infection dynamics of COVID-19 are also unclear, as it has been shown that both OP and NP swabs can yield negative results in positive cases (confirmed by BAL), or can test positive after long periods of negative results (Winichakoon et al., 2020; YajunYuan, Wang & Ou, 2020). Viral load between sample sites has also been compared and the evidence is inconclusive with respect to whether the nose or the throat is a better sample site (Yu et al., 2020; Zou et al., 2020). Zou (2020) suggests that nasal swabs are better during days 1-6 post-symptom onset, while Yu (2020) suggests that throat swabs are superior to nasal swabs. Another report comparing viral loads in NP and throat swabs found no difference in nine confirmed COVID-19 positive patients (Wolfel et al., 2020). The observed differences may be due to sample collection method and variability between collectors, which is not often controlled in these studies.

Evolving Evidence

The evidence for this topic does not appear to be evolving quickly, however, the human factors and intermediate steps of testing necessitate a clear understanding of the quality of each sampling site to ensure that the test is reliable.

Date question received by advisory group: 8 April 2020

Date report submitted to committee: 13 April 2020

Date of first assessment: 15 April 2020

Authorship & Committee Members

This review was written by Rachael Erdmann and scientifically reviewed by Nathan Zelyas, Alexander Doroshenko, and Byron Berenger (external reviewer). The full Scientific Advisory Group was involved in discussion and revision of the document: Braden Manns (co-chair), Lynora Saxinger (co-chair), John Conly, Shelley Duggan, Nelson Lee, Elizabeth MacKay, Andrew McRae, Jeremy Slobodan, James Talbot, and Brandie Walker.

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Appendix

List of Abbreviations

AHS: Alberta Health Services

BAL: Bronchoalveolar lavage

CDC: Centers for Disease Control

CEBM: Centre for Evidence-Based Medicine

COVID-19: Coronavirus Disease 2019

E: Envelope

ECDC: European Centres for Disease Control

KRS: Knowledge Resource Services

LOD: Limit of detection

MMAT: Mixed Methods Appraisal Tool

NAAT: nucleic acid amplification test

NML: National Microbiology Laboratory

NP: nasopharyngeal

NPV: negative predictive value

OP: oropharyngeal

PCR: polymerase chain reaction

PPV: positive predictive value

RdRP: RNA-dependent RNA polymerase

RNA: ribonucleic acid

RT-PCR: reverse transcriptase polymerase chain reaction

SAG: Scientific Advisory Group

SARS-CoV-2: Severe Acute Respiratory Syndrome – Coronavirus – 2

WHO: World Health Organization

Literature Search Details

The literature search was conducted by the Knowledge Resource Services (KRS) unit of Alberta Health Services (AHS). On April 3, 2020, the KRS librarian searched OVID MEDLINE, EMBASE, LitCovid, TRIP PRO, PubMed, WHO Global research on coronavirus (database), Google and Google Scholar for literature published between

2019 and 2020. The full search strategy is appended after the reference list. In brief, the strategy included MeSH terms and keywords related to:

- SARS-CoV-2 or COVID-19 or novel coronavirus
- Diagnostic testing or diagnostic error or RT-PCR
- Nasopharynx or nose

No language limits were placed on the search. 37 articles were retrieved from searching activities. 24 articles were excluded according to the exclusion criteria, 0 articles were discarded based on quality. After including articles identified from hand-searching relevant reference lists, 15 articles were included in this review.

Table 2. Inclusion and exclusion criteria for results of the literature search

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> - Nasal or Nasopharyngeal swab sites - RT-PCR test kit - Article describes test characteristics such as sensitivity, specificity, false negative rate, negative predictive value, positive predictive value - Article describes the risks of improper swab collection - Human study - Any jurisdiction - Guidelines - Peer-reviewed articles - Non-peer-reviewed articles with described methods 	<ul style="list-style-type: none"> - Test samples from blood, anal swab or oral swab - PCR, qPCR or other molecular test methods, biochemical testing, serological testing - Article describes test procedure or best practices for safety - Validation study for COVID-19 test kit, irrespective of sample site - Commentary, editorial, opinion

Critical Appraisal

Critical appraisal was conducted using an adapted Mixed Methods Appraisal Tool (MMAT) (Hong et al., 2018). References were evaluated on three criteria: 1) Peer reviewed or from a reputable source; 2) Clear research question or issue; 3) Whether the presented data/evidence is appropriate to address the research question. This modified MMAT method allows for a quick appraisal of the evidence and provides a yes/no decision for inclusion based on quality. However, it does not provide a ranking of the studies or detailed analysis of the aspects of quality. The table below summarizes the results of the critical appraisal and includes sources flagged by SAG members as receiving public attention or determined by the writer/reviewers to be relevant to the question.

Table 3. Summary of quality assessment results for articles included in this review

	Reference	Quality Appraisal Criteria
1.	Ginocchio, 2011	1) <input type="checkbox"/> Peer-reviewed: <specify study type> <input checked="" type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Commentary, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input checked="" type="checkbox"/> Other: Supplement 2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)
2.	Wang, Wu, Xu et al., 2020	1) <input type="checkbox"/> Peer-reviewed: <specify study type> <input checked="" type="checkbox"/> Not peer-reviewed <input checked="" type="checkbox"/> Commentary, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input type="checkbox"/> Other: <specify> 2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)
3.	Wang, Xu, Gao et al. 2020	1) <input checked="" type="checkbox"/> Peer-reviewed: <specify study type> <input type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Commentary, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input type="checkbox"/> Other: <specify> 2a) Are there clear research questions or a clearly identified issue? <input type="checkbox"/> Yes <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)
4.	Winichakoon, 2020	1) <input checked="" type="checkbox"/> Peer-reviewed: Letter <input type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Commentary, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input type="checkbox"/> Other: <specify> 2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)

5.	YajunYuan, 2020	<p>1) <input checked="" type="checkbox"/> Peer-reviewed: Case series <input type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Commentary, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input type="checkbox"/> Other: <specify></p> <p>2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p>
6.	Yu, 2020	<p>1) <input checked="" type="checkbox"/> Peer-reviewed: Case series <input type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Commentary, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input type="checkbox"/> Other: <specify></p> <p>2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p>
7.	Zou, 2020	<p>1) <input checked="" type="checkbox"/> Peer-reviewed: Letter <input type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Commentary, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input type="checkbox"/> Other: <specify></p> <p>2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p>
8.	Carver, 2020	<p>1) <input type="checkbox"/> Peer-reviewed: <specify study type> <input checked="" type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Letter, commentary, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input checked="" type="checkbox"/> Other: CEBM Rapid Review</p> <p>2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p>
9.	WHO, 2020	<p>1) <input type="checkbox"/> Peer-reviewed: <specify study type> <input checked="" type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Letter, commentary, editorial, preprint</p>

		<input checked="" type="checkbox"/> Guideline: WHO <input type="checkbox"/> Other: <specify> 2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)
10.	CDC, 2020a	1) <input type="checkbox"/> Peer-reviewed: <specify study type> <input checked="" type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Letter, commentary, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input checked="" type="checkbox"/> Other: RT-PCR Assay guidebook 2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)
11.	CDC, 2020b	1) <input type="checkbox"/> Peer-reviewed: <specify study type> <input checked="" type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Letter, commentary, editorial, preprint <input checked="" type="checkbox"/> Guideline: CDC <input type="checkbox"/> Other: <specify> 2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)
12.	Sheridan, 2020	1) <input type="checkbox"/> Peer-reviewed: <specify study type> <input checked="" type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Letter, commentary, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input checked="" type="checkbox"/> Other: Nature Biotechnology News 2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)
13.	Lin, 20202	1) <input type="checkbox"/> Peer-reviewed: <specify study type> <input checked="" type="checkbox"/> Not peer-reviewed <input checked="" type="checkbox"/> Letter, commentary, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input type="checkbox"/> Other: <specify> 2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)

		<p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p>
14.	Lo, 2020	<p>1) <input checked="" type="checkbox"/> Peer-reviewed: Case series <input type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Letter, commentary, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input type="checkbox"/> Other: <specify></p> <p>2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p>
15.	Corman, 2020	<p>1) <input checked="" type="checkbox"/> Peer-reviewed: Diagnostic test validation <input type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Letter, commentary, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input type="checkbox"/> Other: <specify></p> <p>2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p>
16.	Poljak, 2020	<p>1) <input checked="" type="checkbox"/> Peer-reviewed: Diagnostic test validation <input type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Letter, commentary, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input type="checkbox"/> Other: <specify></p> <p>2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p>
17.	Spencer, 2019	<p>1) <input checked="" type="checkbox"/> Peer-reviewed: Systematic review <input type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Letter, commentary, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input type="checkbox"/> Other: <specify></p> <p>2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p>

18.	Wölfel, 2020	<p>1) <input checked="" type="checkbox"/> Peer-reviewed: Case series <input type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Letter, commentary, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input type="checkbox"/> Other: <specify></p> <p>2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p>
19.	ECDC, 2020	<p>1) <input type="checkbox"/> Peer-reviewed: <specify> <input type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Letter, commentary, editorial, preprint <input checked="" type="checkbox"/> Guideline: European CDC <input type="checkbox"/> Other: <specify></p> <p>2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p>
20.	Broughton, 2020	<p>1) <input type="checkbox"/> Peer-reviewed: <specify> <input checked="" type="checkbox"/> Not peer-reviewed <input checked="" type="checkbox"/> Letter, commentary, editorial, preprint <input type="checkbox"/> Guideline: <specify> <input type="checkbox"/> Other: <specify></p> <p>2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (discard)</p>

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Search Strategy

Medline/PubMed

- 1 exp Coronavirus/ or exp Coronavirus Infections/ or coronavirus*.mp. or "corona virus*".mp. or ncov*.mp. or n-cov*.mp. or "novel cov".mp. or COVID-19.mp. or COVID19.mp. or COVID-2019.mp. or COVID2019.mp. or SARS-COV-2.mp. or SARSCOV-2.mp. or SARSCOV2.mp. or SARSCOV19.mp. or Sars-Cov-19.mp. or SarsCov-19.mp. or SARSCOV2019.mp. or Sars-Cov-2019.mp. or SarsCov-2019.mp. or "severe acute respiratory syndrome cov 2".mp. or "2019 ncov".mp. or "2019ncov".mp. (19365)
- 2 Middle East Respiratory Syndrome Coronavirus/ (986)
- 3 "middle east respiratory syndrome".mp. (1925)
- 4 mers.mp. (4091)
- 5 mers-cov.mp. (1521)
- 6 SARS Virus/ (2923)
- 7 Severe Acute Respiratory Syndrome/ (4489)
- 8 SARS.mp. (8939)
- 9 sars-cov.mp. (2555)
- 10 "severe acute respiratory syndrome".mp. (7042)
- 11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (24790)
- 12 Reverse Transcriptase Polymerase Chain Reaction/ (151137)
- 13 "reverse transcription polymerase chain reaction".mp. (40704)
- 14 RT-PCR.mp. (134344)

- 15 "polymerase chain reaction".mp. (567481)
- 16 PCR.mp. (496487)
- 17 exp "Sensitivity and Specificity"/ (576831)
- 18 sensitivity.mp. (1109665)
- 19 specificity.mp. (1025986)
- 20 exp Diagnostic Errors/ (115520)
- 21 "false negative".mp. (39118)
- 22 "false positive".mp. (63415)
- 23 "true positive".mp. (6168)
- 24 "true negative".mp. (2559)
- 25 "positive predictive value".mp. (40517)
- 26 "negative predictive value".mp. (33708)
- 27 "test validation".mp. (348)
- 28 validation.mp. (260046)
- 29 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (2829794)
- 30 nose.mp. (67398)
- 31 nasal.mp. (126578)
- 32 nares.mp. (2223)
- 33 nasopharyngeal.mp. (32741)
- 34 30 or 31 or 32 or 33 (192162)
- 35 11 and 29 and 34 (532)
- 36 limit 35 to yr="2019" (32)

CINAHL

- 1 exp Coronavirus/ or exp Coronavirus Infections/ or coronaviru*.mp. or "corona virus*".mp. or ncov*.mp. or n-cov*.mp. or "novel cov".mp. or COVID-19.mp. or COVID19.mp. or COVID-2019.mp. or COVID2019.mp. or SARS-COV-2.mp. or SARSCOV-2.mp. or SARSCOV2.mp. or SARSCOV19.mp. or Sars-Cov-19.mp. or SarsCov-19.mp. or SARSCOV2019.mp. or Sars-Cov-2019.mp. or SarsCov-2019.mp. or "severe acute respiratory syndrome cov 2".mp. or "2019 ncov".mp. or "2019ncov".mp. (19365)
- 2 Middle East Respiratory Syndrome Coronavirus/ (986)
- 3 "middle east respiratory syndrome".mp. (1925)
- 4 mers.mp. (4091)

- 5 mers-cov.mp. (1521)
- 6 SARS Virus/ (2923)
- 7 Severe Acute Respiratory Syndrome/ (4489)
- 8 SARS.mp. (8939)
- 9 sars-cov.mp. (2555)
- 10 "severe acute respiratory syndrome".mp. (7042)
- 11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (24790)
- 12 exp "Sensitivity and Specificity"/ (576831)
- 13 nose.mp. (67398)
- 14 nasal.mp. (126578)
- 15 nares.mp. (2223)
- 16 nasopharyngeal.mp. (32741)
- 17 13 or 14 or 15 or 16 (192162)
- 18 exp Specimen Handling/ (344704)
- 19 "specimen collect*".mp. (14662)
- 20 18 or 19 (346537)
- 21 11 and 17 and 20 (21)
- 22 limit 21 to yr="2019" (1)

- S1 (MH "Coronavirus+")
- S2 (MH "Coronavirus Infections+")
- S3 coronaviru*
- S4 "corona virus"
- Database - CINAHL Plus with Full Text Display
- S5 ncov*
- S6 n-cov*
- S7 COVID-19 OR COVID19 OR COVID-2019 OR COVID2019
- S8 SARS-COV-2 OR SARSCOV-2 OR SARSCOV2 OR SARSCOV19 OR SARS-COV-19 OR SARSCOV-19 OR SARSCOV2019 OR SARS-COV-2019 OR SARSCOV-2019
- S9 "severe acute respiratory syndrome cov 2" OR "severe acute respiratory syndrome coronavirus**"

Comparison of Sample Collection Methods • 17

S10	"2019 ncov" OR 2019ncov OR Hcov*	
S11	(MH "Middle East Respiratory Syndrome Coronavirus")	
S12	(MH "Middle East Respiratory Syndrome")	
Database - CINAHL Plus with Full Text Display		
S13	"middle east respiratory syndrome" OR MERS-COV OR MERS	
Database - CINAHL Plus with Full Text Display		
S14	(MH "SARS Virus")	
S15	(MH "Severe Acute Respiratory Syndrome")	
Database - CINAHL Plus with Full Text Display		
S16	"severe acute respiratory syndrome" OR SARS OR SARS-COV	
S17	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16	5,450
S18	(MH "Reverse Transcriptase Polymerase Chain Reaction")	14,348
S19	(MH "Polymerase Chain Reaction+")	49,523
S20	"reverse transcription polymerase chain reaction" OR RT-PCR OR PCR	
		35,745
S21	(MH "Sensitivity and Specificity")	87,879
S22	(MH "Diagnostic Errors+")	20,899
S23	(MH "Predictive Value of Tests")	51,142
S24	sensitivity OR specificity OR "false negative" OR "false positive" OR "true negative" OR "true positive" OR "positive predictive value" OR "negative predictive value" OR "test validation" OR validity	319,076
S25	S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24	
		420,733
S26	nasal OR nasopharyngeal OR nose OR nares	31,306
S27	S17 AND S25 AND S26	85
S28	S17 AND S25 AND S26	Limiters - Published Date: 20190101-20201231
		10
S1	(MH "Coronavirus+")	
S2	(MH "Coronavirus Infections+")	
Database - CINAHL Plus with Full Text Display		

Comparison of Sample Collection Methods • 18

S3	coronaviru*
S4	"corona virus"
S5	ncov*
S6	n-cov*
S7	COVID-19 OR COVID19 OR COVID-2019 OR COVID2019
Database - CINAHL Plus with Full Text Display	
S8	SARS-COV-2 OR SARSCOV-2 OR SARSCOV2 OR SARSCOV19 OR SARS-COV-19 OR SARSCOV-19 OR SARSCOV2019 OR SARS-COV-2019 OR SARSCOV-2019
S9	"severe acute respiratory syndrome cov 2" OR "severe acute respiratory syndrome coronavirus**"
S10	"2019 ncov" OR 2019ncov OR Hcov*
S11	(MH "Middle East Respiratory Syndrome Coronavirus")
S12	(MH "Middle East Respiratory Syndrome")
S13	"middle east respiratory syndrome" OR MERS-COV OR MERS
S14	(MH "SARS Virus")
S15	(MH "Severe Acute Respiratory Syndrome")
S16	"severe acute respiratory syndrome" OR SARS OR SARS-COV
S17	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 5,450
S18	nasal OR nasopharyngeal OR nose OR nares 31,306
S19	(MH "Specimen Handling+") Limiters - Published Date: 20190101-20201231 5,694
S20	"specimen collect*" Limiters - Published Date: 20190101-20201231 581
S21	S19 OR S20 5,729
S22	S17 AND S18 AND S21 1

TRIP Pro/Google Scholar/Google Advanced

("covid-19" OR coronavirus OR COVID19 OR "corona virus" OR ncov OR "n-cov" OR "covid-2019" OR covid2019 OR "SARS-COV-2" OR "sars-cov-19" OR sars-cov-2019" OR "severe acute respiratory syndrome) AND ("reverse transcription polymerase chain reaction" OR "polymerase chain reaction" OR RT-PCR OR PCR OR validity OR specificity OR sensitivity OR negative OR positive OR "predictive value" OR validation) AND (nasal OR nares OR nose OR nasopharyngeal) from:2019

("covid-19" OR coronavirus OR COVID19 OR "corona virus" OR ncov OR "n-cov" OR "covid-2019" OR covid2019 OR "SARS-COV-2" OR "sars-cov-19" OR sars-cov-2019" OR "severe acute respiratory syndrome) AND

(specimen OR "specimen collection" OR "specimen collecting" OR "specimen handling") AND (nasal OR nares OR nose OR nasopharyngeal) from:2019

LitCovid/WHO Global Research on COVID-19/CEBM/Elsevier/CDC/covid-evidence.org/evidence aid/Wolters Kluwer Coronavirus/Cochrane Library/NICE guidelines/BMJ Covid-19

("reverse transcription polymerase chain reaction" OR "polymerase chain reaction" OR RT-PCR OR PCR OR validity OR specificity OR sensitivity OR negative OR positive OR "predictive value" OR validation) AND (nasal OR nares OR nose OR nasopharyngeal)

"reverse transcription polymerase chain reaction" OR "polymerase chain reaction" OR RT-PCR OR PCR

nasal OR nares OR nose OR nasopharyngeal

specimen collection

RT-PCR