CHOICE OF SPECIMENS FOR RT-PCR

RECOMMENDATIONS

We recommend the use of the following specimens as alternative specimens to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 among symptomatic and asymptomatic patients suspected of COVID-19 in hospital and outpatient settings:.

- oropharyngeal swab *(Moderate quality of evidence; Strong recommendation)*
- saliva drool/spit and oral saliva *(Moderate quality of evidence; Strong recommendation)**
- nasal swab/wash *(Moderate quality of evidence; Strong recommendation)*
- throat swab *(Low quality of evidence; Strong recommendation)*

** Please see also separate evidence summary for saliva specimen.*

We recommend against the use of sputum as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19. *(Very low quality of evidence; Strong recommendation)*

There is no evidence to recommend the use of bronchoalveolar lavage as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19.

Consensus Issues

Currently, oropharyngeal and nasopharyngeal specimens are collected simultaneously. The use of oropharyngeal swab, oral saliva specimens, nasal swab/wash and throat swab were recommended as alternative clinical specimens to nasopharyngeal swab RT-PCR as the panel recognized the positive implication of single specimens on resource use. In addition, collection of single specimens will be less-time consuming.

The differences between oropharyngeal swab and throat swab samples were clarified. Although the two specimens are collected in the same area, they were considered by the panel as dissimilar specimens due to the differences in sample collection technique. The panel made a strong recommendation for using throat swab samples due to its relatively high sensitivity.

Despite the very low certainty of the evidence on the use of sputum specimens, the panel opted to strongly recommendation against using it as an alternative to nasopharyngeal swab samples due to the risk of viral transmission when obtaining such samples.

EVIDENCE SUMMARY

Which clinical specimen can be used as an alternative to nasopharyngeal swab RT PCR for the diagnosis of COVID-19?

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Key Findings

One cross sectional study on the use of oropharyngeal swab RT-PCR as an alternative clinical specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 showed that oropharyngeal swab had comparable sensitivity and specificity to nasopharyngeal swab RT-PCR.

A meta-analysis of 19 observational studies on the use of saliva as an alternative clinical specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 concluded that saliva had comparable sensitivity and specificity to nasopharyngeal swab RT-PCR.

Two cross sectional studies on the use of nasal swab/wash RT-PCR as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis showed that nasal swab/wash had comparable sensitivity and specificity to nasopharyngeal swab RT-PCR.

A cross sectional study on the use of throat swab RT-PCR as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 also showed that throat swab had comparable sensitivity and specificity to nasopharyngeal swab RT-PCR.

A cross-sectional study from a meta-analysis on the use of sputum RT-PCR as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 showed that sputum had lower sensitivity and specificity compared to nasopharyngeal swab RT-PCR.

All the above studies were assessed to have low risk of bias.

No studies were found that compared the sensitivity and specificity of bronchoalveolar lavage RT-PCR to nasopharyngeal swab RT-PCR. Hence, no conclusion and recommendation can be made for this particular clinical specimen.

Introduction

Nasopharyngeal swab is the current gold standard specimen used for RT-PCR. However, obtaining such swab samples is relatively invasive, uncomfortable, and may potentially trigger coughing which may consequently increase the risk of viral transmission to health care workers who lack sufficient personal protective equipment. In addition, the need to increase capacity for SARS-CoV-2 testing in a variety of settings along with shortages of sample collection supplies have motivated a search for alternative specimen types with equally high sensitivities. In line with this, the diagnostic performance of other specimens such as oropharyngeal swab, saliva, endotracheal aspirate, and bronchoalveolar lavage are currently being investigated.

A similar rapid review of 8 studies completed on May 2020 concluded that the pooled sensitivity of detecting SARS-CoV-2 RNA in non-respiratory tract specimens was high in saliva samples (77%, 95% CI 71-83%) and very low in stool/rectal swab (22%, 95% CI 22-37%), blood/serum 2% (95% CI 1-3%), and urine 22% (95% CI 18-25%) specimens [2]. In this review we summarize current evidence on the diagnostic accuracy of several types of clinical specimens.

Review Methods

A comprehensive literature search was done on January 23, 2021 in electronic databases MEDLINE, Cochrane CENTRAL, as well as www.medrxiv.org. We included observational studies or systematic reviews of observational studies which compared the sensitivity of at least two respiratory specimens against nasopharyngeal swab. Studies that did not have nasopharyngeal swab as the gold standard were excluded.

Results

Characteristics of included studies

We included a total of 21 observational studies in this review. Of these, 12 were cohort studies, 4 were case controls, 4 were cross-sectional studies and 1 is a prospective study included in this study. Nineteen of the 21 studies were previously included in 1 systematic review and meta-analysis [5], while 2 other cross-sectional studies were added [3,4]. The meta-analysis by Moreira et al. was appraised to have high methodological quality[1].

A total of 5,585 samples were evaluated across all 21 studies. Of these, 56 were nasal swab/wash [3,4], 29 were oropharyngeal swab [3], 36 were throat swab [4,5], 5,424 were saliva [5] and 40 were sputum samples [5]. All the specimens were analyzed using RT-PCR as reference standard [3,4,5]. The characteristics and the results of the included studies are summarized in Appendix 1.

Overall quality of the evidence

Majority of the included studies were rated as having low risk of bias. The included cross-sectional studies had a clearly defined inclusion criteria, reliable measurement of the exposure and outcome, used an objective criterion for measurement of the condition and used an appropriate statistical analysis [3,4]. However, most of the studies did not clearly state the interval between the reference and index specimen collection. The systematic review included was direct, used appropriate inclusion criteria and performed risk bias assessment [5].

The overall certainty of evidence for the sensitivity and specificity of nasal swab/wash, oropharyngeal swab was downgraded to moderate because of imprecision. Additionally, the specificities of the clinical specimens had wide confidence intervals.

The overall certainty of evidence for sensitivity of throat swab was downgraded to moderate because of imprecision due to small sample size. On the other hand, the quality of evidence of specificity of the said clinical specimen was further downgraded to low because of small sample size and wide confidence interval.

The quality of evidence for the sensitivity of saliva was downgraded to moderate because the inconsistency was rated serious due to the different point estimates across the observational studies. On the other hand, the quality of evidence for the specificity was high.

The risk of bias for sputum was rated as serious because the included study used a different dilution for sputum and the gold standard thereby lowering the quality of evidence to moderate. The quality of evidence for the sensitivity of throat swab was further downgraded to low because the imprecision was rated serious due to the wide confidence interval and small sample size. On the other hand, the specificity of the throat swab was downgraded to very low because the

[1] based on the Painless EBM criteria for appraising systematic reviews

imprecision was rated very serious due to the very wide confidence interval and small sample size.

Diagnostic accuracy

Among the included clinical specimens, oropharyngeal swab had the highest sensitivity and specificity of 100% ([95% CI 87 to 100%] studies, n=1) and 100% ([95% CI 16 to 100%], n=1), respectively. On the other hand, sputum had the lowest sensitivity at 63% ([95% CI 45 to 79%] studies, n=1) and specificity at 40% ([95% CI 5 to 85%], n=1). No study provided diagnostic accuracy measures for bronchoalveolar lavage samples. Results are summarized in Table 1.

Table 1. Sensitivities and specificities of the clinical specimens for RT-PCR.

Sample	No. of Studies	No. of samples	Quality of Evidence		Sensitivity (95%CI)	Specificity (95% CI)
			Sensitivity	Specificity		
Nasal Swab/ Wash	2	57	Moderate	Moderate	0.87 (0.74-0.95)	78% (0.40-0.97)
Oropharyngeal Swab	1	29	Moderate	Moderate	100% (0.87-1.00)	100% (0.16-1.00)
Throat Swab	1	36	Moderate	Low	93% (0.76-0.99)	89% (0.52-1.00)
Saliva	1	5424	Moderate	High	86% (0.84-0.88)	94% (0.93-0.94)
Sputum	1	40	Very Low	Very Low	63% (0.45-0.79)	40% (0.05-0.85)
Bronchoalveolar Lavage	N/A	N/A	N/A	N/A	N/A	N/A

Sources of heterogeneity

Since subgroup analysis was not done for this rapid review, the potential sources of heterogeneity cannot be ascertained; however, the succeeding statements may have influenced the computed estimates and must be considered whenever interpreting the conclusions.

Despite the generally low risk of bias across all the included studies, possible factors that may have still influenced the estimates of this study include the differences in the sample size per clinical specimen. For example, oropharyngeal swab had the highest sensitivity and specificity but there were only 29 patients included in the computation [3]. On the other hand, saliva had a lower sensitivity and specificity than oropharyngeal swab but there were 5,424 patients included in the computation of the sensitivity and specificity [5].

Another potential factor that may have influenced the estimate is the non-standardized timing of collection of clinical specimens. Some studies collected the clinical specimen days to weeks after symptoms have resolved while other studies have collected the specimen in the pre-symptomatic period [3,4,5]. However, since there was no subgroup analysis done for the timing of specimen collection, it is not clear how this factor could have influenced the diagnostic accuracy of these specimens.

The definition of clinical specimens varied in some studies. Some studies have equated throat swab to oropharyngeal swab while some have considered them as two different entities. In the

studies by Berenger et al and Moreira et al, the authors classified the swabs as throat swabs and not oropharyngeal swabs [4,5]. In the study by Berenger et al, it was mentioned that the throat swabs were collected from both sides of the oropharynx and the posterior pharyngeal wall under the uvula [4]. Conversely, the study by Moreira et al did not specify the exact method of collection [5]. For this review, the clinical specimens were analyzed according to how the authors have identified them.

Lastly, there were clinical specimen specific factors. For sputum, the sensitivity and specificity are difficult to ascertain as not all COVID-19 patients are able to produce sputum for testing. Additionally, the study that was included in the analysis of the sensitivity and specificity of sputum used different dilution for sputum and the gold standard [5]. This may explain why the computed sensitivity and specificity are low. On the other hand, the lack of data for bronchoalveolar lavage probably resulted from its relative invasiveness compared to the other clinical specimens used for the diagnosis of COVID 19.

Recommendations from Other Groups

Local interim guidelines (6 October 2020) from the Department of Health (DOH) identified nasopharyngeal swabs or lower respiratory tract specimens as the most reliable samples for RT-PCR. Combined oropharyngeal and nasopharyngeal swab samples were recommended to be collected and processed together. Nasopharyngeal swabs are preferred over oropharyngeal swabs alone because of the lower accuracy of the latter. At the time of publication of this guideline, the potential of using saliva samples was still being studied and validated by the Research Institute of Tropical Medicine [6].

Compared to the DOH, the US Centers for Disease Control and Prevention (CDC) (as of 06 January 2021) allows more upper respiratory specimen options for RT-PCR. CDC listed the following as acceptable specimens:

1. A nasopharyngeal (NP) specimen collected by a trained healthcare provider;
2. An oropharyngeal (OP) specimen collected by a trained healthcare provider;
3. A nasal mid-turbinate specimen collected by a trained healthcare provider or by a supervised or unsupervised onsite self-collection (using a flocked tapered swab), or self-collected at home following kit collection instructions;
4. An anterior nares specimen collected by a trained healthcare provider, or by a supervised or unsupervised onsite self-collection or self-collected at home following kit collection instructions (using a flocked or spun polyester swab);
5. Nasopharyngeal wash/aspirate or nasal wash/aspirate (NW) specimen collected by a trained healthcare provider; or
6. A saliva specimen (not specified if spit or swab) collected by the person being tested, either at home or at a testing site under supervision. Collect 1-5 mL of saliva in a sterile, leak-proof screw cap container. No preservative is required.

CDC also noted that an alternative to upper respiratory tract specimens is the testing of lower respiratory tract specimens. For patients who develop a productive cough, sputum can be collected and tested when available for SARS-CoV-2. However, they have recommended against the induction of sputum. Under certain clinical circumstances (e.g., those on invasive mechanical ventilation), a lower respiratory tract aspirate or bronchoalveolar lavage specimen should be collected and tested as a lower respiratory tract specimen [7].

Research Gaps

There are 3 ongoing studies listed in the NIH- U.S NLM's *ClinicalTrials.gov.* One is an RCT [8], 1 is a cross sectional study [9] and one is a prospective study [10]. One study is estimated to be completed in March 2021 [8]. The other one is estimated to be completed in June 2021 [9] and the last study is estimated to be completed in March 2023 [10]. The study description and status are summarized in Appendix 3.

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Appendix 1: Characteristics of Included Studies

First author Month-Year Country	Study Design	Sample Population	No. of Partici-pants	Sample size / specimen	Intervention		Outcome Measured
					Reference	Index	
Calame, Adrien Aug 2020 Switzerland	Cross sectional study	≥ 18 years old and hospitalized who had a positive SARS-CoV-2 rRT-PCR in a NPS specimen in the preceding one to six days. ICU patients were excluded.	29	Nasal wash: 20 Oropharyngeal: 29 Nasopharyngeal swab:29	Nasopharyngeal swab analyzed via RT-PCR Ct is arbitrarily defined at 45	Oropharyngeal swabs, Nasal wash, which were all analyzed via RT-PCR	compared the analytical sensitivity of SARS-CoV-2 real-time RT- PCR in nasal wash (NW), oropharyngeal swab (OPS) and NPS specimens.
Berenger, Byron May 2020 Canada	Cross sectional study	COVID 19 positive individuals. (41% female, mean age 44.6 (range 18-61)	30	Nasal swab, throat swab and nasopharyngeal swab: 36	Nasopharyngeal swab analyzed via RT-PCR Ct not specified	Nasal swab and Throat Swabwhich were all analyzed via RT-PCR	compared the sensitivity of NP, nasal and throat swabs to detect SARS-CoV-2
Moreira, Vania January 2021 Portugal	Systematic review and meta-analysis Case control, cohort, prospective study,cross sectional	COVID 19 positive and suspected individuals	Not stated	Saliva: 4739 Deep throat swab: 685 Sputum: 20	Nasopharyngeal swab analyzed via RT-PCR Ct not specified	sputum, saliva, deep throat swab	Sensitivity and specificity of RT-PCR among the samples

Appendix 2: GRADE Evidence Profile

Question: Should Nasal Swab RT-PCR be used to diagnose COVID 19 in the general population?

Sensitivity	0.87 (95% CI: 0.74 to 0.95)
Specificity	0.78 (95% CI: 0.40 to 0.97)

Prevalences	0%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 0%	
True positives (patients with COVID 19)	2 studies 47 patients	case-control type accuracy study	not serious	not serious	not serious	serious	none	0 (0 to 0)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having COVID 19)								0 (0 to 0)	
True negatives (patients without COVID 19)	2 studies 10 patients	case-control type accuracy study	not serious	not serious	not serious	serious	none	780 (400 to 970)	⨁⨁⨁◯ MODERATE
False positives (patients incorrectly classified as having COVID 19)								220 (30 to 600)	

Question: Should Oropharyngeal RT-PCR be used to diagnose COVID 19 in the general population?

Sensitivity	1.00 (95% CI: 0.87 to 1.00)
Specificity	1.00 (95% CI: 0.16 to 1.00)

Prevalences	0%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 0%	
True positives (patients with COVID 19)	1 studies 27 patients	case-control type accuracy study	not serious	not serious	not serious	serious	none	0 (0 to 0)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having COVID 19)								0 (0 to 0)	
True negatives (patients without COVID 19)	1 studies 2 patients	case-control type accuracy study	not serious	not serious	not serious	serious	none	1000 (160 to 1000)	⨁⨁⨁◯ MODERATE
False positives (patients incorrectly classified as having COVID 19)								0 (0 to 840)	

Question: Should Should Throat Swab RT-PCR be used to diagnose COVID 19 in the general population?

Sensitivity	0.93 (95% CI: 0.76 to 0.99)
Specificity	0.89 (95% CI: 0.52 to 1.00)

Prevalences	0%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 0%	
True positives (patients with COVID 19)	1 studies 27 patients	case-control type accuracy study	not serious	not serious	not serious	serious	none	0 (0 to 0)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having COVID 19)								0 (0 to 0)	
True negatives (patients without COVID 19)	1 studies 9 patients	case-control type accuracy study	not serious	not serious	not serious	very serious	none	890 (520 to 1000)	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having COVID 19)								110 (0 to 480)	

Question: Should Saliva RT-PCR be used to diagnose COVID 19 in the general population?

Sensitivity	0.86 (95% CI: 0.84 to 0.88)
Specificity	0.94 (95% CI: 0.93 to 0.94)

Prevalences	0%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 0%	
True positives (patients with COVID 19)	1 studies 1048 patients	case-control type accuracy study	not serious	not serious	serious	not serious	none	0 (0 to 0)	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having COVID 19)								0 (0 to 0)	
True negatives (patients without COVID 19)	1 studies 4376 patients	case-control type accuracy study	not serious	not serious	not serious	not serious	none	940 (930 to 940)	⨁⨁⨁⨁ HIGH
False positives (patients incorrectly classified as having COVID 19)								60 (60 to 70)	

Question: Should Sputum RT-PCR be used to diagnose COVID 19 in the general population?

Sensitivity	0.63 (95% CI: 0.45 to 0.79)
Specificity	0.40 (95% CI: 0.05 to 0.85)

Prevalences	0%		

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 0%	
True positives (patients with COVID 19)	1 studies 35 patients	case-control type accuracy study	serious	not serious	not serious	serious	none	0 (0 to 0)	⨁⨁◯◯ LOW
False negatives (patients incorrectly classified as not having COVID 19)								0 (0 to 0)	
True negatives (patients without COVID 19)	1 studies 5 patients	case-control type accuracy study	serious	not serious	not serious	very serious	none	400 (50 to 850)	⨁◯◯◯ VERY LOW
False positives (patients incorrectly classified as having COVID 19)								600 (150 to 950)	

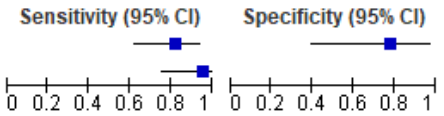
Appendix 3: Characteristics of Ongoing Studies

Study Setting	Study Type	Population	Intervention		Outcome/s	Status	Estimated Completion date
			Reference Standard	Index Test			
COVID-19: SARS-CoV-2 Detection in Saliva, Oropharyngeal and Nasopharyngeal Specimen Denmark NCT04715607	Randomized, double blind clinical trial (parallel assignment)	symptomatic and asymptomatic individuals tested for COVID-19 in a public test center during the COVID-19 pandemic n = 22,000	combined Saliva/OPS/NPS	Oropharyngeal swab Saliva	SARS-CoV-2 detection rates for OPS compared w/ NPS & saliva (48 hrs)	Recruiting	March 30, 2021
Saliva as Source of Detection for SARS-CoV-2 United States NCT04424446	Cross sectional	NIH staff members age 18 and older who are taking part in NIH CC SARS-CoV-2 surveillance. n = 5,000	Nasopharyngeal swab	Saliva (spit) Nasal swab	Saliva SARS-CoV-2 RT-PCR results	Recruiting	June 1, 2021
COVID-19 Biological Samples Collection (COLCOV19-BX) France NCT04332016	Prospective	Asymptomatic and symptomatic COVID-19 patients, patients who died from COVID-19, all sex, minors pregnant and breastfeeding women n = 2,000	Not stated	whole blood samples, urine and stool samples, upper respiratory samples, post-mortem biopsies	COVID-19 disease description from blood, URT, stool, urine samples	Recruiting	March 2023

Appendix 4: Forest Plots for the Sensitivities and Specificities of Different Clinical Specimens

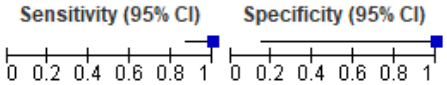
Nasal Swab/Wash

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Berenger 2020	22	2	5	7	0.81 [0.62, 0.94]	0.78 [0.40, 0.97]
Calame 2020	19	0	1	0	0.95 [0.75, 1.00]	Not estimable



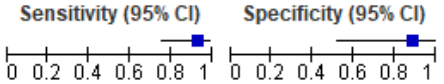
Oropharyngeal Swab

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Calame 2020	27	0	0	2	1.00 [0.87, 1.00]	1.00 [0.16, 1.00]



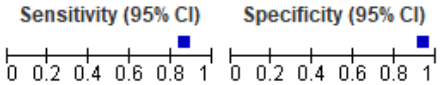
Throat Swab

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Berenger 2020	25	1	2	8	0.93 [0.76, 0.99]	0.89 [0.52, 1.00]



Saliva

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Moreira 2021	900	276	148	4100	0.86 [0.84, 0.88]	0.94 [0.93, 0.94]



Sputum

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Moreira 2021	22	3	13	2	0.63 [0.45, 0.79]	0.40 [0.05, 0.85]