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Accuracy of SARS-CoV-2 Detection in Saliva for COVID-19 Diagnosis: A Systematic Review and Meta-Analysis

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Abstract

Context: There is an unmet clinical need to develop simple, easy, rapid, and accessible testing for the detection of SARS-CoV-2. Recent reports suggested that saliva may be a host for the virus. The existence of SARS-CoV-2 in saliva can be associated with oral manifestations in infected patients. A systematic review was conducted as well as a meta-analysis to evaluate the diagnostic accuracy of detecting SARS-CoV-2 in saliva and investigate the association between positive saliva test and oral manifestations of COVID-19.

Evidence acquisition: A literature search in MEDLINE via PubMed, Scopus, Web of Science, and Cochrane was done in June 2020 and updated in February 2021 using relevant keywords. We screened studies for eligibility. The extracted data were analyzed using Meta-Disc software.

Results: Eighteen studies were included. Pooled data from eligible studies showed that the sensitivity of diagnosis of SARS-CoV-2 in saliva was 0.86 (95% CI, 0.83–0.89), and the specificity was 0.98 (95% CI, 0.96–0.98). COVID-19 was associated with oral diseases as amblygeustia, dry mouth, dryness, inflammation of the mouth, and enlargement of lymph nodes in the submandibular regions.

Conclusions: Our results showed that the saliva has a high accuracy in the detection of SARS-CoV-2.

Key words: COVID-19; Meta-analysis; Saliva; SARS-CoV-2

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CONTEXT

Since the outbreak of COVID-19, the configuration of the clinical picture and mode of transmission has become a global requirement. The initial diagnosis of COVID-19 is routinely made by a nasopharyngeal swab and Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR) of the respiratory specimen (1, 2).

The nasopharyngeal swab has many drawbacks, for it is a sensitive and bothersome technique for the patient. Other drawbacks include coughing, sneezing, or even gaging, which puts the medical staff at a higher risk of infection, another reason why there has been an increasing demand to develop new methods for COVID-19 screening and diagnosis (3, 4).

Detection of the virus in saliva could present a lower risk rate and straightforward procedure for diagnosis (5). The presence of severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) in the oral cavity could be due to many reasons: through droplets from the respiratory tract, through blood, or from the salivary gland (6). Angiotensin-converting enzyme 2 (ACE2) receptors, the main target receptor of COVID-19, are widely present in lungs and also the salivary glands (7). And it is reported that the virus can be detected in the saliva up to one month after the infection (8).

This review aimed to evaluate the diagnostic accuracy of detecting SARS-CoV-2 in saliva rather than nasopharyngeal specimen, and further, investigate the possible association between positive saliva test and oral manifestations of COVID-19.

Evidence acquisition

Search strategy

We searched the following databases: MEDLINE via PubMed, Scopus, Web of Science, and Cochrane Central Register until the date of June 2020, and updated in February 2021. The following search strategy has been used: ("2019 novel coronavirus disease" OR covid19 OR "COVID-19 pandemic" OR

"SARS-CoV-2 infection" OR "COVID-19 virus disease" OR "2019-nCoV infection" OR "coronavirus disease 2019" OR "coronavirus disease-19" OR "2019-nCoV disease" OR "COVID-19 virus infection" OR "Wuhan coronavirus" OR "Wuhan seafood market pneumonia virus") AND (Saliva OR "nasopharyngeal swab" OR "or pharyngeal swab").

Eligibility criteria and study selection

We included all relevant articles about the detection of SARS-COV-2 without restriction on age or medical conditions. Studies evaluated the accuracy of virus detection by RT-PCR in the saliva compared to the standard diagnosis of SARS-CoV-2 by RT-PCR in nasopharyngeal swabs.

We excluded animal, conference, non-English studies, reviews, and studies with unreliable data for extraction. Screening for eligibility was performed in two steps: firstly, abstracts were screened. Secondly, full-text articles of eligible abstracts were retrieved to meta-analysis.

Data Extraction

We extracted the following data from the included studies using a formatted data extraction sheet for summary and baseline of the included studies, including study ID, country, sample size, age, sample source, and the number of patients who were positive by detection of the virus in saliva.

Quality assessment

The quality of included studies was performed by two authors using the "QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies". QUADAS-2 tool is applied in 4 phases: summarize the review question, tailor the tool and produce review-specific guidance, construct a flow diagram for the primary study, and judge bias and applicability (9).

Statistical analysis

We analyzed the data using Meta-Disc (version 1.4), and a P-value<0.05 was considered statistically significant. Heterogeneous data was analyzed by random model. We calculated the sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (dOR), the summary receiver operating characteristic (sROC) curve, and the area under the ROC, and corresponding 95% confidence intervals (CIs) from true positive, false positive, false negative, and true negative cases. A random effects model was applied to summarize the sensitivity, specificity, PLR, and NLR.

RESULTS

Literature search

The primary literature search retrieved 2683 citations, and after the removal of duplication, 2210 studies were eligible for screening. Following title and abstract screening, 61 articles were retrieved for full-text evaluation. Eighteen studies that match our criteria were included in the meta-analysis (See PRISMA flow diagram; Figure 1).

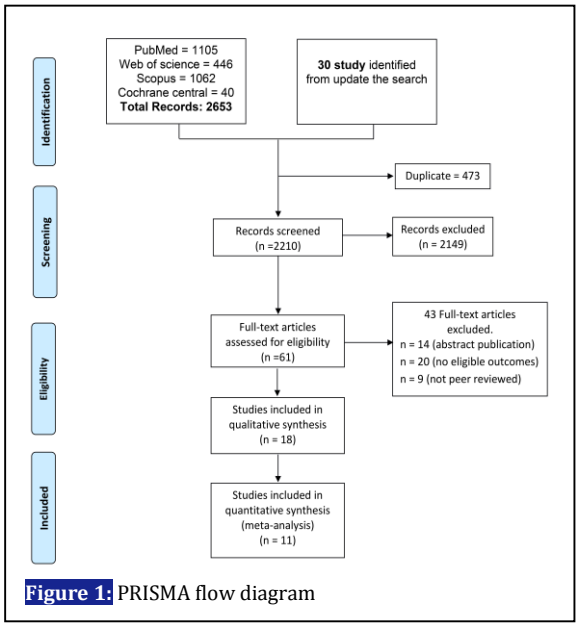

Figure 1: PRISMA flow diagram

Characteristics and quality of included studies

The summary and baseline characteristics of enrolled patients are shown in appendix 1. According to QUADAS-2 Quality Assessment tool, the quality assessment of the included studies ranged from moderate to high quality as showed in figure 2; the summary of quality assessment of each study is shown in table 1.

Qualitative evidence

Chen 2020 et al. (10) reported that SARS-CoV-19 was positively detected in the saliva of 4/13 cases; three of them were critically ill while one was an ordinary patient. This result confirmed the possibility of 2019-nCoV being present in saliva. It was also reported that oral-associated symptoms might be related to COVID-19, including amblygeustia (47.2%), dry mouth (46.3%), dryness, and inflammation of mouth (11.1%), and enlargement of lymph nodes in the submandibular regions (0.9%). Azzi 2020a et al. (5) reported that saliva is a reliable biological fluid that could be a candidate for SARS-COV-2, the virus may appear in mouth during migration from nasopharynx or the lower respiratory tract. Caly 2020 et al. (11) reported a case report of a 58-year-old man from Wuhan, who showed that SARS-COV-2 significantly detected in nasopharyngeal swab and sputum on RT-PCR. The viral load daily testing showed a gradual decline in sputum after eight days of

Table 1: Quality assessment by QUADAS-II checklist

Study ID	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Caulley 2020[13]	High	Low	Unclear	Low	Low	Low	Unclear
Hanson 2020[14]	Unclear	Low	Low	Low	Low	Low	Low
Iwasaki 2020[15]	Unclear	Low	Low	High	Low	Low	Low
Kojima 2020[16]	High	Low	Low	Unclear	Low	Low	Low
Landry 2020[17]	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Unclear
McCormick-Baw 2021[18]	Unclear	Low	Low	Unclear	Unclear	Low	Low
Pasomsub 2020[19]	Unclear	Low	Low	Low	Unclear	Low	Low
To 2020a[3]	Unclear	low	low	low	low	Unclear	Low
Vaz 2020[20]	Unclear	Low	Low	Low	Low	Low	Low
Williams 2020[21]	Unclear	Unclear	Low	Low	Low	Low	Low
Wong 2020[22]	Unclear	Low	Low	Unclear	Unclear	Low	Low
Chen 2020[10]	Unclear	Unclear	Low	Unclear	Low	Low	Low
To 2020b[23]	Unclear	Low	Low	Unclear	Unclear	Unclear	Low
Azzi 2020a[5]	Unclear	Low	Low	Low	Low	Low	Low
Azzi 2020b[12]	Unclear	Unclear	Unclear	low	Unclear	Unclear	Unclear
Caly 2020[11]	Unclear	Unclear	Unclear	low	Unclear	Unclear	Unclear
Zheng 2020[24]	Unclear	low	low	low	low	Unclear	Low
Cheng 220[25]	Unclear	Unclear	Low	Unclear	Unclear	Low	Low

Table 2: SARS-COV-2 Diagnostic indices based on Saliva detection.

Parameter	Test of association		Test of heterogeneity			Model
	Estimate	95% CI	chi-squared	P-value	I-square (%)	
Sensitivity	0.86	0.83 - 0.89	37.69	<0.001	73.5	Random
Specificity	0.98	0.96 - 0.98	292.24	<0.001	96.6	Random
PLR	29.56	3.33 - 262.27	845.13	<0.001	98.8	Random
NLR	0.15	0.08 - 0.29	58.41	<0.001	82.9	Random
dOR	194.12	37.06 - 1016.7	131	<0.001	92.4	Random

CI = Confidence interval, NLR = negative- likelihood ratio, PLR = positive-likelihood ratio, and dOR = diagnostic odds ratio

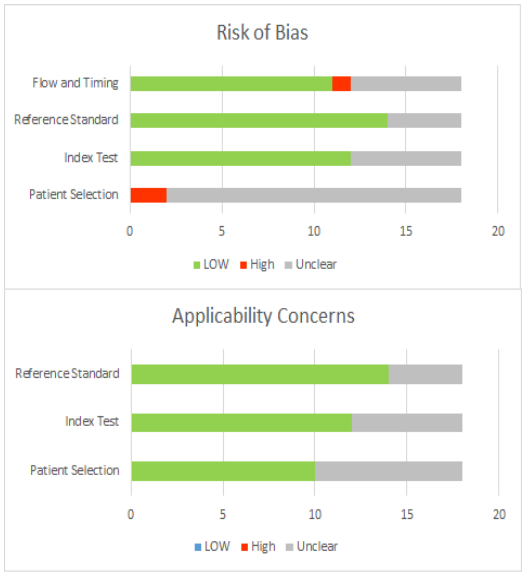

Figure 2: The quality assessment of the included studies

admission. They reported that the virus was not detected in urine, plasma, and fecal samples. Azzi 2020b et al. (12) reported that the salivary sample collected from the 64-year-old man was positive after the first and second swabs after two days, while the two bronchoalveolar swabs were negative. To 2020b et al. (23), Zheng 2020 et al. (24), and Cheng 2020 et al. (25) recommended the saliva as a noninvasive procedure, also it associated with reducing nosocomial transmission of SARS-CoV-2.

Quantitative evidence on the accuracy of SARS-CoV-2 detection in the saliva

The overall diagnostic measurements for detecting SARS-Cov-2 in saliva specimen was summarized in figure 3. The pooled sensitivity was 0.86 (95% CI, 0.83–0.89), and the pooled estimation showed significant heterogeneity (p=0.001, chi-square =37.69, I2=73.5%) (Figure 3A). Meanwhile, the summary specificity was 0.98 (95% CI, 0.96–0.98), and the pooled estimation also showed noticeable heterogeneity (p=0.001, chi-square = 292.24.40, I2=96.6%) (Figure 3B). The pooled dOR was 194.12 (95% CI, 37.06–1016.7), with significant heterogeneity (p=0.001, chi-square=131, I2=92.4%) (Figure 3C). The pooled AUC value was 0.95 ± 0.021 (Figure 3D). All extracted data are reported in table 2.

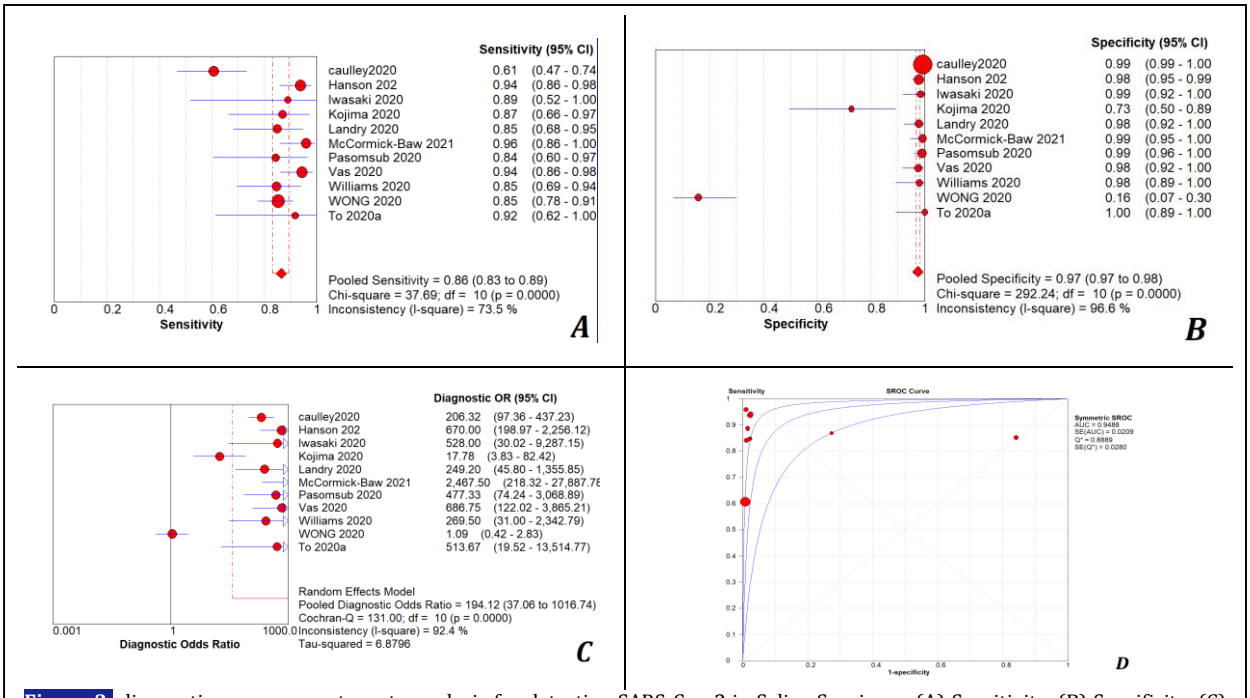

Figure 3: diagnostic measurements meta-analysis for detecting SARS-Cov-2 in Saliva Specimen. (A) Sensitivity, (B) Specificity, (C) Diagnostic odds ratio (D) sROC curve

Discussion

Summary of finding

This study provides evidence that SARS-CoV-2 detection in the saliva gives an 86% sensitivity, and 98% specificity compared to nasopharyngeal specimen which is the gold standard of COVID-19 diagnosis. The included studies reported the reliability of saliva to detect the virus through the percentage of true positive patients in all truly infected patients.

Explanation of the study findings

Saliva is a potential source of the transmission of SARS-CoV-2 (26). Human saliva is a fluid produced by salivary glands, contains many components as proline-rich proteins, mucins MG1 and MG2, and gp340 (27). These components can interact with different pathogens, causing changes in their biological behavior (28). We can detect more than 700 microbial specie in saliva, these microorganisms are related to oral and systemic diseases, saliva has a role in the colonization of oral microorganisms; it also prevents the overgrowth of these microorganisms (29).

Diagnosis of SARS-CoV-2 can be performed with the usage of saliva through a nasopharyngeal, oropharyngeal swab, or blood samples (30). Salivary diagnosis has many advantages as it can be extracted easily without invasive processes; also, it has a low risk of nosocomial 2019-nCoV transmission to healthcare workers (23). It has prolonged detection time which is 20 days or more. Transmission of SARS-CoV-2 from human-to-human occurs directly by cough, or sneeze of droplets, or indirect contact transmission as saliva, or mucous membranes of the nose (31). SARS-CoV-2 reaches saliva through three routes: infection of salivary gland with virus release through salivary ducts, virus in the upper and lower respiratory tract that reaches the oral cavity through droplets, and virus in blood that can reach saliva through the gingival crevicular fluid (32).

Previous studies

Previous studies demonstrate that saliva has a high viral load, especially in posterior oropharyngeal saliva samples (33). A recent study indicates that SARS-CoV-2 can be easily detected in either in bronchoalveolar lavage fluid (93%), sputum (72%), nasal swabs (63%), fibro bronchoscope brush biopsy (46%), pharyngeal swabs (32%), faeces (29%), or blood (1%). No one can however detect it in urine specimens (34). A previous diagnostic meta-analysis that included non-peer reviewed paper reported converging results 83.2% for sensitivity and 99.2% for specificity (35).

Chen 2020 et al. reported an association between oral manifestation and COVID-19 as amblygeustia, dry mouth, dryness and inflammation of the mouth, and enlargement of lymph nodes in the submandibular regions (10). The previous study

reported an association between COVID-19 and oral manifestation, including oral pain, gingivitis, ulcers, and blisters (36).

Dentists should take caution while treating patients during the pandemic when using mouth rinse, and local nasal products that include beta-cyclodextrins in conjunction with flavonoid agents and provide an adjuvant cate to reduce SARS-CoV-2 transmission (37).

Strength points & Limitations

The main strengths of our study are that we included only peer reviewed studies while our search study and methodology was sensitive. The quality of the studies made was high to moderate and included quantities evidence. However, we have some limitations; a relatively small sample of included studies and patients; a heterogenetic of results; we included only observational studies, which in general, have a high risk of bias and low quality of evidence.

Conclusions

In summary, salivary detection of SARS-CoV-2 is reliable and provides high sensitivity and specificity.

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None.

Authors' contribution

DME and AH conceived of the presented idea, WA, MA and AK conducted database searching and screening; All authors participated in data extraction, risk of bias, and writing; AH analyzed the data; DME and AH revise the final manuscript; All the authors met the standards of authorship based on the recommendations of the International Committee of Medical Journal Editors.

Conflict of interest

None declared.

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Appendix 1: Demographic factors and clinical signs of patients with migraine headache history by sex

Study ID	Country	Sample size	Gender Male (%)	Age, mean years (SD)	Sample source	True detection number TP (%)	False detection number TN (%)	conclusion
Chen 2020 [10]	China	31	15 (48)	52.0 (16.28)	The opening of the salivary gland canal of the cleaned oral cavity	4 (31)	9 (69)	This study concluded that ACE2 expressed in the salivary gland, and SARS-COV-2 can be detected in saliva; also, oral symptoms may be frequently manifested by COVID-19 patients. These findings suggest that saliva may carry a risk of 2019-nCoV transmission.
To 2020a [3]	Hong Kong	23	Sever 6 (60) Mild 7 (54)	Sever 61.5 (10.7) Mild 56 (10.96)	posterior oropharyngeal saliva samples	18 (78)	15 (22)	This study reported that Posterior oropharyngeal saliva samples are a non-invasive specimen more acceptable to patients and healthcare workers. This finding emphasizes the importance of stringent infection control and early use of potent antiviral agents, alone or in combination, for high-risk individuals. The serological assay can complement RT-qPCR for diagnosis.
Azzi 2020a [5]	Italy	25	17 (68)	61.5 (11.20)	Saliva was collected through the drooling technique or with a pipette, depending on the patient's clinical condition;	25 (100)	0 (0)	This study reported that saliva is a reliable tool to detect SARS-CoV-2; it also may inform about the clinical evolution of the disease.
Azzi 2020b [12]	Italy	2	2 (100)	71/ 64	drooling technique collected with a pipette	2 (100)	0 (0)	This study concludes that saliva is more reliable than bronchoalveolar swabs.
To 2020b [23]	Hong Kong	12	7 (58)	54.75 (7.30)	cough out saliva from their throat into a sterile container	11 (92)	1 (8)	These results demonstrated the potential for saliva for the diagnosis and viral load monitoring of SARS-COV-2. Also, saliva specimens will reduce the risk of nosocomial transmission of the virus to health workers.
Williams 2020 [21]	Australia	89	-	-	pool saliva in their mouth for 1-2 minutes before collection, and gently spit	33 (37)	49 (55)	This study demonstrated that saliva as a non-invasive specimen for the detection of SARS-CoV-2.
Caly 2020 [20]	Australia	1	1 (100)	58	the viral burden was greatest in sputum specimen	1 (100)	0 (0)	this study reported that SARS-COV-2 significantly detected in nasopharyngeal swab and sputum on RT-PCR
Pasomsub 2020 [19]	Thailand	200	69 (35)	37.33 (14.93)	Nasopharyngeal and throat swabs in a tube and saliva samples from the collection container were treated with lysis buffer	16 (8)	179 (89)	This study concluded that saliva might be an alternative specimen for the diagnosis of COVID-19. This method could facilitate the diagnosis of the disease, given the simplicity of specimen collection and good diagnostic performance
Zheng 2020 [24]	China	65	40 (62)	52.38 (6.56)	Throat swabs, nasal swabs and saliva or sputum.	37 (57)	28 (43)	SARS-CoV-2 highly detected in saliva more than other respiratory samples. The convenience methods reduce the risk of infection among medical stuff.
McCormick -Baw 2021 [18]	USA	156	90 (58)	average age 47.8 years	Saliva specimens for the diagnosis of COVID-19 using PCR test.	47 (30)	105 (67)	Saliva is more acceptable than nasopharyngeal swab for detecting SARS-CoV-2 nucleic acids. Also, it is more favorable for patient as it is noninvasive.
Vaz 2020 [20]	Brazil	155	46 (31)	40.37 (4.47)	Saliva samples were collected into 30 ml sterile cups.	67 (43)	82 (53)	Self-collected saliva samples are an easy, convenient, and low-cost alternative to conventional nasopharyngeal swab based molecular tests.
Cheng 2020 [25]	China	42	20 (48)	59 (17.25)	Nasopharyngeal flocked swab, throat swab, and saliva of this patient.	27 (64)	(36)	Appropriate hospital infection control measures were able to prevent nosocomial transmission of SARS-CoV-2.

Appendix 1 (in continued): Demographic factors and clinical signs of patients with migraine headache history by sex

Study ID	Country	Sample size	Gender Male (%)	Age, mean years (SD)	Sample source	True detection number TP (%)	False detection number TN (%)	conclusion
Caulley 2020 [13]	Canada	1939	-	-	Standard Swab and Saliva Sample, Standard Swab Alone, or Saliva Sample Alone.	34 (2)	1869 (96)	The study reported the feasibility of saliva as anon invasive tool to detect SARS-CoV-2.
Hanson 2020 [14]	USA	368	195 (53)	35 (14.2)	Nasopharyngeal flocked swab or saliva from mouth without coughing.	75 (20)	268 (73)	This study reported that more than one specimen needed to detect SARS-CoV-2.
Iwasaki 2020 [15]	Japan	76	-	69 (16.7)	Nasopharyngeal swab through the nostril until reaching the posterior nasopharynx, and Saliva were self-collected by the patients and spit into a sterile tube.	8 (11)	66 (87)	This result estimate that the viral load in saliva was equivalent at earlier time, but lower than nasopharyngeal samples.
Kojima 2020 [16]	USA	45	-	42 (5.3)	unsupervised self-collected oral fluid swab specimens, clinician-supervised self-collected oral fluid swab specimens, clinician-supervised self-collected anterior nasal swab specimens, and clinician-collected posterior nasopharyngeal swab specimens	20 (44)	16 (36)	Supervised self-collected oral fluid and anterior nasal swab specimens performed similarly to clinician-collected nasopharyngeal swab specimens for the detection of SARS-CoV-2. No sample type captured all infections.
Landry 2020 [17]	USA	124	-	-	Saliva spit into sterile containers, or Nasopharyngeal swab.	28 (23)	89 (72)	Saliva had an overall sensitivity for SARS CoV-2 RNA detection of 85.7 % when compared to simultaneously collect Nasopharyngeal swab.
WONG 2020 [22]	China	166	60 (63)	36 (22)	Posterior oropharyngeal saliva or nasopharyngeal specimen.	104 (63)	7 (4)	Posterior oropharyngeal saliva is an acceptable alternative specimen to nasopharyngeal specimen for the detection of SARS-CoV-2.