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Evidence summary for accuracy of salivary samples in SARS-CoV-2 detection compared with nasopharyngeal, oropharyngeal or lower respiratory tract samples

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Key points

- The collection of nasopharyngeal and or oropharyngeal swabs involves an invasive technique with connotations for the patient and healthcare provider including discomfort, increased exposure for transmission, and the need for a relative degree of skill, alongside the potential for a shortage of swabs during large scale testing initiatives. Salivary samples present the potential to mitigate these limitations, with the additional benefit of potentially offering a 'self-collection' method by the patient.
- This evidence summary focussed on the accuracy of salivary samples in SARS-CoV-2 detection compared with nasopharyngeal, oropharyngeal or lower respiratory tract samples. Fifteen studies were identified by this review, including 14 unique populations.
- Eight studies included suspected SARS-CoV-2 cases and seven studies included patients known to be infected with SARS-CoV-2. All studies were conducted in adult, or likely to be adult, populations.
- The method of collection for salivary samples was inconsistent between studies with various procedures described, and often little detail provided.
- For suspected SARS-CoV-2 cases, positive detection by the comparators of interest to this review ranged from 79.3% to 100%; detection by saliva ranged from 64.7% to 100%. Positive agreement between samples for overall detection ranged from 57.4% to 100%. Negative agreement between samples ranged from 72.7% to 100%.
- For known SARS-CoV-2 infected cases, positive detection by the comparators of interest to this review ranged from 41.9% to 100%; detection by saliva ranged from 30.8% to 100%. Positive agreement of detection between samples ranged from 30.8% to 100%.
- The methodological quality of included studies was varied with important influencing factors such as time period between sample collection, time since symptom onset, sample sufficiency, and test parameters often poorly reported.

- Although positive cases were typically more frequently identified by the comparator (nasopharyngeal swab, oropharyngeal swab, or sputum), the results of this review indicate an inconsistency in the detection of SARS-CoV-2 by the samples included. Often with neither sample detecting all positive cases, and sometimes saliva testing positive for SARS-CoV-2 while the comparator was negative.
- Depending on the test environment and purpose, saliva may offer a viable alternative to traditional test samples. As additional studies are published in this rapidly emerging area, more robust conclusions may be drawn about the overall value of saliva as a clinical sample for the detection of SARS-CoV-2.

Evidence summary for accuracy of salivary samples in SARS-CoV-2 detection compared with nasopharyngeal, oropharyngeal or lower respiratory tract samples

The Health Information and Quality Authority (HIQA) has developed a series of 'Evidence Summaries' to assist the Clinical Expert Advisory Group (EAG) in supporting the National Public Health Emergency Team (NPHET) in their response to COVID-19. These summaries are based on specific research questions. This evidence summary was developed to address the following research question:

> **What is the accuracy of tests for the detection of SARS-CoV-2 using salivary clinical samples compared with nasopharyngeal, oropharyngeal or lower respiratory tract clinical samples?**

Background

The accurate and timely detection of SARS-CoV-2 facilitates public health surveillance, response, and control measures during the COVID-19 pandemic. Reverse transcription polymerase chain reaction (RT-PCR) is considered the gold standard in diagnostics for the detection of SARS-CoV-2 RNA in the acute phase of infection.[1, 2] A range of non-commercial laboratory diagnostic protocols for RT-PCR testing are published on the World Health Organization's COVID-19 webpage.[2]

The selection of sites for the retrieval of clinical samples to test for the presence of viral material has potential implications of the overall accuracy of the diagnostic test utilised.[3] A recent evidence summary from HIQA, published 15 April 2020, highlighted positive detection rates of SARS-CoV-2 through RT-PCR tests across a range of clinical samples and tests sites including nasopharyngeal, oropharyngeal, sputum, faecal matter, urine, blood, ocular, and blood.[4] The clinical sample sites were noted to be inconsistent in their detection of viral material for SARS-CoV-2, with discordance highlighted between clinical samples. Current guidance from the Health Protection Surveillance Centre (HSPC),[5] the WHO,[2] and the UK National Health Service (NHS)[6] endorse the collection of upper respiratory specimens through nasopharyngeal, combined with oropharyngeal swabs for the routine testing of SARS-CoV-2, with the collection of lower respiratory samples (bronchoalveolar lavage, endotracheal aspirate or sputum) in more severe illness. Recently updated guidance from the CDC has been extended to include nasal mid turbinate, anterior nares or nasopharyngeal/nasal aspirate or washes.[1]

The collection of nasopharyngeal and/or oropharyngeal swabs involves an invasive technique with connotations for the patient and healthcare provider including discomfort, increased exposure for transmission, and the need for a relative degree of skill, alongside the potential for a shortage of swabs during large scale testing initiatives.[3] In particular, anecdotal evidence has suggested that the collection of these clinical samples can be particularly problematic in paediatric populations. Salivary samples present the potential to mitigate these limitations, with the additional benefit of potentially offering a 'self-collection' method by the patient.

Methods

The processes as outlined in HIQA's *Protocol for evidence synthesis support - COVID-19* were followed throughout the conduct of this review.[7] Below is a summary of all relevant evidence comparing salivary samples with nasopharyngeal, oropharyngeal or lower respiratory tract specimens identified from December 2019 until 27 May 2020.

Results

A summary of the included studies is provided in Table 1. Fifteen relevant studies were identified within this review,[8-22] including fourteen distinct populations, with one population duplicated by To et al. in two studies.[18, 19] Of these fourteen distinct studies,[8-17, 19-22] five were case series,[8, 10, 11, 13, 21] four were cross-sectional studies,[14-16, 20] four were cohort studies,[9, 12, 19, 22] and one was a Food and Drug Administration (FDA) accelerated Emergency Use Authorization (EUA) summary for a SARS-CoV-2 assay.[17] Five of studies were from the United States,[9, 14, 15, 17, 21] with three from China,[10, 11, 22] and one each from Australia,[20] Canada,[13] Hong Kong,[19] Italy,[8] Japan,[12] and Thailand,[16] respectively. The median number of participants included by the studies was 76 and ranged from 23 to 622, although this latter large sample only analysed 89 matched samples.[20] Seven studies were conducted in adult populations,[8, 10, 11, 13, 16, 19, 21] four did not provide any demographic detail of the included participants,[9, 17, 20, 22] and the summary statistics of the remaining three studies would suggest the majority of, if not all, participants were adults.[12, 14, 15]

Seven of the studies included hospitalised patients,[8, 10, 11, 13, 15, 19, 21] of which six included severely ill patients within their sample,[8, 10, 11, 13, 19, 21] six were conducted in ambulatory settings,[9, 14, 16, 17, 20, 22] and one study included both hospitalised patients and those tested in an ambulatory setting.[12] Seven of the studies included participants tested due to suspicion of SARS-CoV-2 infection,[9, 14-17, 20, 22] five studies included patients known to be infected with SARS-CoV-2,[8, 10, 11, 13, 19] one study included cases of known and suspected SARS-CoV-2 infections,[12] and one study included SARS-CoV-2 infected patients and asymptomatic healthcare workers at risk

of exposure.[21] Eight of the included studies compared salivary samples with nasopharyngeal swabs,[8, 9, 11-15, 20] two with oropharyngeal swabs,[10, 22] two with both swab types,[16, 21] one with either swab type,[17] and one with nasopharyngeal swab or sputum specimens.[19]

Salivary sample collection method

The included studies varied in the methods used to collect salivary samples. Seven studies collected samples by participants expelling saliva into a sterile container,[12, 13, 15-17, 20, 21] two studies used a deep throat collection method where participants were asked to cough and swirl contents in their mouths before expelling into a container or onto a swab,[14, 19] one study used a drooling technique for non-ventilated patients and intraoral collection using a pipette for ventilated patients,[8] one study used salivary gland massage,[10] and one study used lingual swabs.[22] Two studies did not provide any detail on method of collection.[9, 11] Four studies included a statement regarding cessation of oral intake and hygiene for a period of time prior to sample collection.[10, 15, 19, 21]

Self-collection alone was reported by two studies,[12, 14] five studies reported self-collection with clinician supervision,[13, 14, 17, 19, 21] three studies used clinician collection,[8, 10, 22] and four studies did not provide detail on who the sample was collected by.[9, 11, 16, 20]

Detection in suspected SARS-CoV-2 cases

Eight studies included within this review presented results regarding the accuracy of saliva samples for the detection of SARS-CoV-2 in suspected cases.[9, 12, 14-17, 20, 22] As shown in Table 2, detection by nasopharyngeal and/or oropharyngeal swabs ranged from 79.3% to 100% relative to all positive samples. Detection by saliva relative to all positive samples ranged from 64.7% to 100%. A graphical representation of the sensitivity of each sample type for the detection of positive cases is provided in Figure 1. Positive agreement of detection by the salivary sample relative to the reference samples ranged from 60% to 100%, with positive agreement between samples for overall detection ranging from 57.4% to 100%. Negative agreement between samples ranged from 72.7% to 100%.

Becker et al.[9] noted higher detection of SARS-CoV-2 with nasopharyngeal swabs compared with salivary samples from 85 participants within a community testing environment (88.2% vs 64.7%). Positive agreement of saliva relative to nasopharyngeal swabs was 60% (9/15), with 52.9% (9/17) overall positive agreement between samples. Negative agreement of samples was 86.1%. The samples were collected simultaneously but no details were provided regarding population or clinical characteristics.

Kojima et al.[14] highlighted a higher overall detection of SARS-CoV-2 by salivary samples compared with nasopharyngeal swabs (89.7% vs 79.3%) in 45 adults tested in the community, with simultaneous collection. The agreement between saliva and nasopharyngeal samples was 86.9% (20/23), with 69% (20/29) overall positive agreement between samples and 72.7% overall negative agreement. Of note, the authors further reported higher detection rates in salivary samples collected while supervised by clinicians (26/29) versus unsupervised collection (19/29).

McCormik-Baw et al.[15] highlighted comparable rates of detection between nasopharyngeal and salivary samples (98% vs 96%) in 155 suspected cases tested within a hospital setting. The overall positive agreement between samples was 94% (47/50) with a similarly high negative agreement of 98.1%. No demographic or clinical detail was provided, and the time between sample collections was not specified by the study.

An Australian study conducted by Williams et al.[20] of testing within an ambulatory care setting presented matched results for 89 suspected SARS-CoV-2 cases. Overall, a higher number of infections were detected with nasopharyngeal swabs compared with salivary samples (97.5% vs 85%). Positive detection of saliva relative to the reference sample was 84.6% (33/39), with an overall positive agreement of 82.5% (33/40) and negative agreement of 89.1% between samples. No demographic or clinical detail was provided, however consecutive collection of samples was noted.

Using consecutive sampling, Pasomsub et al.[16] note higher rates of detection with nasopharyngeal and oropharyngeal swabs compared with salivary samples in 200 adults tested at an acute respiratory clinic in Thailand (90.4% vs 85.7%). Salivary detection relative to the reference was 84.2% (16/19), overall positive agreement between samples 76.2% (16/21) and negative agreement was 98.3%. The median time since symptom onset was three days prior to testing.

In an EUA study for a SARS-CoV-2 assay, the Rutgers Clinical Laboratory[17] noted complete agreement between either nasopharyngeal or oropharyngeal, and salivary samples with 30 positive and 30 negative tests from suspected cases, with simultaneous collection in three ambulatory care settings. No demographic or clinical detail was provided. Similarly, Iwasaki et al.[12] presented a negative agreement of 100%, with all 66 suspected cases tested returning negative results in nasopharyngeal and salivary samples collected simultaneously.

Comparing lingual swabs with oropharyngeal swabs in fever clinics, Ye et al.[22] noted higher detection with oropharyngeal samples overall (85.1% vs 70.2%), with a positive detection by saliva relative to the reference of 67.5% (27/40). Overall positive agreement between samples was 57.4% (27/47), and negative agreement

87.9% (51/58). No demographic or clinical details were provided by the study and the time period between sample collections was unclear.

Detection in SARS-CoV-2 infected patients

Seven studies included known SARS-CoV-2 infected patients, with a lack of clarity on whether the reference sample was for the purpose of diagnosis, monitoring or both, and on the timing between tests of different samples.[8, 10, 11, 13, 15, 19, 21] All of the included studies were conducted with hospitalised adult patients, with six noted to include participants with severe disease within their sample.[8, 10, 11, 13, 19, 21] As shown in Table 2, detection by the comparators of interest to this review ranged from 41.9% to 100% relative to all positive samples. Detection by saliva relative to all positive samples ranged from 30.8% to 100%. A graphical representation of the sensitivity of each sample type for the detection of positive cases is provided in Figure 1. Positive agreement of detection between samples ranged from 30.8% to 100%.

Three studies reported 100% detection of SARS-CoV-2 with the reference samples of interest to this review.[8, 11, 19] Azzi et al.[8] highlighted complete agreement (100%) between saliva and nasopharyngeal swabs with SARS-CoV-2 detected in all samples from 25 participants with severe or very severe disease. The time between samples or time since symptom onset was not reported. Fang et al.[11] noted detection of SARS-CoV-2 in 78.1% (25/32) salivary samples in a population of ICU and non-ICU patients, of whom 28/32 were symptomatic. The time between sample collection and symptom onset was not reported. To et al.[19] noted detection of SARS-CoV-2 in 87% (20/23) salivary samples of cases of mild and severe disease, with the duration of symptoms prior to testing and timing between samples not reported.

Four studies reported discordance between the reference sample and salivary samples.[10, 12, 13, 21] Jamal et al.[13] noted an overall positive agreement between nasopharyngeal and salivary samples of 66% (31/47) with nasopharyngeal samples identifying 89.4% (42/47) of cases and saliva detecting 76.6% (36/47) of cases. Samples were collected consecutively at a median time since symptom onset of 11 days. Iwasaki et al.[12] reported positive agreement between samples of 80% (8/10) with nasopharyngeal swabs and saliva samples both detecting 90% of cases (9/10). Samples were collected consecutively at a median of nine days since symptom onset. Wyllie et al.[21] reported a higher detection of SARS-CoV-2 by saliva samples compared with nasopharyngeal and/or oropharyngeal swabs in 38 hospitalised patients (92.1% vs 78.9%). The overall positive agreement between samples was 71.1% (27/38). Of note, the authors also report the detection of SARS-CoV-2 in the saliva of two asymptomatic healthcare workers who had tested negative with nasopharyngeal swabs. The time periods between sample collection, and between

symptom onset and testing were not reported. Chen et al.[10] reported low rates of detection by both oropharyngeal and salivary samples in 31 inpatients (41.9% vs 30.8%). The overall positive agreement between tests for 13 paired samples were 30.8% (4/13). Neither the time from symptom onset or the time between the different sample collections were reported. Of note, the rates of detection within this study are considerably lower than the other studies raising concerns about these factors in particular.

Sample sufficiency and spoilage

Details regarding sample sufficiency were reported by one of the 14 studies within this review,[14] with one insufficient sample noted for unsupervised oral fluid collection, and no insufficient samples for clinician supervised oral fluid collection or nasopharyngeal swab samples.

Becker et al.[9] noted six nasopharyngeal and two salivary samples as indeterminate, respectively, but did not provide reasoning for these results.

Study quality and quality of the evidence

Of the fourteen included studies, seven were preprints which have not yet been peer-reviewed,[9, 10, 12-14, 16, 21] raising concerns about overall quality.

Seven of the studies included SARS-CoV-2 confirmed inpatients (either the entire sample or a proportion of the sample),[8, 10-13, 19, 21] with five not peer-reviewed as yet.[10-13, 21] These studies were quality assessed using a generalised case series tool as described in the protocol. Overall, the majority of studies had a clearly stated objective, provided appropriate statistical analysis and most provided some description of patient demographics and clear inclusion criteria. Only two clearly stated consecutive inclusion of participants,[13, 19] and therefore the other studies may have been open to spectrum bias. One study used a mixed group of known and suspected SARS-CoV-2 patients.[12] In most studies both the condition and the outcome were measured in a standard and reliable way.[8, 11-13, 19]

Seven studies included patients who were suspected to have COVID-19,[9, 14-17, 20, 22] with three having been peer reviewed;[15, 20, 22] one was an EUA summary from the FDA.[17] These studies were assessed using a modified version of the QUADAS-2. Overall, the applicability of the studies to the research question was considered good. However, due to a lack of clarity around patient selection and specific details of collection and analysis for the reference and salivary samples, many studies were judged to be at an unclear risk of bias overall. For patient selection, only one study stated that consecutive patients were enrolled with a low risk of bias for patient selection.[16] While most had an unclear risk of bias for this domain due to a lack of

information on the inclusion/exclusion criteria, one study only included a subset of the enrolled patients,[20] and another study included a mixture of emergency department suspected patients and patients from a COVID-19 ward,[15] placing them at an unclear to high risk of bias. For the RT-PCR test using saliva, it was generally unclear if the test results were interpreted without knowledge of the comparator test, and vice versa. One study sent the tests out to different laboratories, and used separate primers for analysis. However, this study had a high risk of bias in this domain as they used two different collection devices for the saliva, which their own analysis suggested may affect the outcome of the test.[9] Only one study was deemed to have a low risk of bias in this domain.[16] The comparator sample test had an unclear risk of bias in four studies;[14, 15, 17, 22] in one of these studies two different sample sites (nasopharyngeal or oropharyngeal) for the tests were used.[17] In terms of flow and timing it was not always clear what interval existed between collection of the samples within the included studies, the time of sample collection relative to symptom onset, or disease severity.

Overall, the quality of the included studies was varied. Certain factors which could affect test performance such as thresholds used, real time RT-PCR assay used including details of limit of detection, location of tests, preservation fluid used for sample, viral load, time since symptom onset, and time between sample collections were often poorly reported.

Discussion and conclusion

The results of this review highlight that there are variable rates of SARS-CoV-2 detection with salivary samples and the comparators of interest (nasopharyngeal, oropharyngeal, or lower respiratory tract samples).

Although typically higher detection rates were seen with the comparators, the rates of positive detection and discordance between samples highlight inconsistencies in detection of the virus between sample types. The included studies used a variety of methods to collect salivary samples which were not always well described. The overall quality of the studies included within this review was typically low. Important variables such as symptom duration, time between sample collection, and test parameters were often poorly reported. Additionally, seven of the 14 included studies are preprints, which have not yet been peer-reviewed, seven were conducted in known SARS-CoV-2 infected patients, and all were in adult, or likely to be adult, populations which may limit generalisability of results.

The collection methods for the reference sample were typically reported as being a standardised procedure with clinician collection. However, the collection of salivary samples varied in procedure, including expelling into a sterile container, swab use, drooling, and deep throat collection methods. Furthermore, the description of these

procedures often lacked detail, as did specifications on whether they were self-collected by the participants, collected under direction/supervision by the clinician, or collected by the clinician. The variety of collection methods has connotations for the specificity of the specimen collected, ease of collection, equipment required, and required experience level of the clinician.[3] Furthermore, little detail was provided by the included studies with regards to sample sufficiency or test spoilage. This may reflect a retrospective approach whereby only samples which were analysed in full were eligible for inclusion, however these considerations would provide meaningful information for decision-making overall.

For the majority of included studies (9/14), the reference sample was shown to detect a greater number of positive cases of SARS-CoV-2 than the salivary samples. However, it is worth noting that nine of the included studies noted detection of SARS-CoV-2 in at least 85% of positive cases using salivary samples.[8, 12, 14-17, 19-21] Of studies reporting lower rates of detection, specific concerns were raised with regard to a lack of reporting of time between sample collection,[11, 22] time between symptom onset and sample collection,[10, 13] and variation in test parameters.[9] Although these variables were typically poorly reported across studies, they may serve as important considerations for the discrepancies seen in the results of this review.

All studies included within this review used a form of RT-PCR testing, therefore, an assumption was made that a positive test indicates a positive case regardless of the sample used. This reflects the view that false positive results using this test for the detection of SARS-CoV-2 are rare and typically represent technical errors or contamination rather than accuracy.[23-25] However, false negatives with RT-PCR testing for SARS-CoV-2 are well-documented with a range magnitude of influencing factors including timing of sample collection relative to symptom onset, sufficiency of collected samples, and test parameters.[23-25] For example, sensitivity of nasopharyngeal swabs tested with RT-PCR compared with chest CT was estimated to be 71% in a retrospective analysis by Fang et al..[26] For this reason, the WHO and ECDC recommend caution in terms of a negative test if a person meets the clinical case definition with a re-test advised a number of days later,[2, 27] given notable increases in viral load particularly in the early stages of infection.[24] Such factors are important considerations within this review, particularly in studies of known infected SARS-CoV-2 patients, where it was often unclear if the reference sample was used for initial diagnostics and the salivary sample as a follow up test raising concerns about the timing between samples and the duration of illness at the point of each sample collection.

Furthermore, differences in detection rates have been noted dependent on the clinical specimen tested and timing of the sample.[4] A study by Wang et al. notes

that lower respiratory tract specimens typically show higher positivity than upper respiratory tract samples.[28] Similarly, viral load has been noted to peak and reduce at different rates depending on the sample used.[28, 29] Hence, false negative test results may occur if samples are tested during the early period or late convalescent phase of infection, when virus levels may be undetectable depending on the sample used. Of note, although not the premise of this review, viral loads reported by studies were typically higher in nasopharyngeal than saliva samples,[12, 20] with generally longer viral shedding times.[9, 11, 12, 20] Such considerations may be important in terms of decision-making for the timing of use of salivary samples in testing for COVID-19 and appear to indicate, in particular, that they may not be suitable for monitoring of the disease once confirmed.

In conclusion, the studies included within this review typically displayed an overall higher rate of detection of SARS-CoV-2 with the reference samples than salivary samples. However, variability in the detection rates of all positive samples and in the agreement between samples highlights that neither sample type consistently detects all cases. Depending on the testing environment, population, and available resources, the benefits of salivary sample collection may offer a viable alternative to more traditional approaches. However, there was a lack of consistency in methods used to collect the salivary samples, the quality of included studies was generally low, and there was poor reporting of important influencing factors such as timing of sample collection relative to symptom onset, time period between sample collection, sufficiency of collected samples, and test parameters which limit the overall findings of this review. More robust conclusions may be drawn about the overall value of saliva as a clinical sample for the detection of SARS-CoV-2 as additional studies are published in this rapidly emerging area.

Table 1. Summary of identified studies

Author **Country** **Sample size** **Study design** **Status: DOI**	**Patient demographics** **Setting** **Clinical characteristics** **Time between samples**	**Salivary sample** **Test** **Gene target** **Threshold** **Collection method** **Self- or provider- collected**	**Reference sample** **Test** **Gene target** **Threshold** **Collection method**	**Primary outcome results**
Azzi 2020 **Italy** **N=25** **Case series** **Published:** https://doi.org/10.1016/j.jinf.2020.04.005	*Population:* SARS-CoV-2 infected patients *Population demographics:* Mean age: 61.5 years (SD= 11.2, range= 39 to 85), 17 males (68%), 15 (65%) were affected by cardiovascular and/or dysmetabolic disorders. *Setting:* Single hospital, hospitalised in ICU or in the Unit of Infectious and Tropical Diseases *Clinical characteristics:* Severe or very severe disease *Time between samples:* NR	*Index sample:* Salivary sample *Test:* rRT-PCR *Threshold:* Ct value < 33 *Gene target:* NR *Collection method:* 1. Drooling technique 2. Patients with endotracheal intubation and mechanical ventilation, saliva was collected intraorally. *Self- or provider- collection:* 1. Drooling technique: NR 2. Intubated/mechanically ventilated: Physician collected with pipette.	*Reference sample:* Nasopharyngeal swabs *Test:* RT-qPCR *Threshold:* NR *Gene target:* NR *Collection method:* NR	*Detection rate:* SARS-CoV-2 was detected in all 25 patients' first salivary swab (100%).
Becker 2020 **United States** **N=88** **Cohort study** **Preprint:** https://doi.org/10.1101/2020.05.11.20092338	*Population:* Suspected SARS-CoV-2 cases *Population demographics:* No information provided *Setting:* Community testing environment *Clinical characteristics:*	*Index sample:* Salivary sample *Test:* RT-PCR in two separate labs with different primers used. *Threshold:* NR *Gene target:*	*Reference sample:* Nasopharyngeal swabs *Test:* RT-PCR *Threshold:* NR *Gene target:*	*Detection rate:* • 9/88 positive in both samples • 6/88 positive nasopharyngeal and negative saliva sample • 6/88 indeterminate with nasopharyngeal, 2/88 indeterminate with saliva sample • 62/88 negative in both samples • Nasopharyngeal sensitivity:

	NR ***Time between samples:*** Simultaneous collection	ORF1ab (RdRp) ***Collection method:*** 33 and 55 saliva specimens were collected using Orasure OM-505 Microbiome and OGD-610 DNA collection kits, respectively. No further detail provided. ***Self- or provider- collection:*** NR	ORF1ab (RdRp) ***Collection method:*** NR	98.9% (95% CI: 67.6%- 99.7%) • Saliva sensitivity: 69.2% (95% CI: 38.6%-97.6%). Note: saliva results from Primerdesign v1 and UCSD taqpath.
Chen 2020 **China** **N= 31 (paired sample n=13)** **Case series** **Preprint:** https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3557140	***Population:*** SARS-CoV-2 infected patients ***Population demographics:*** Median age: 60.6 years, ranging from 18 to 86 years, 15 males. ***Setting:*** Single hospital ***Clinical characteristics:*** Five critically ill, ventilated patients. 26 ordinary or heavy illness. ***Time between samples:*** Saliva and oropharyngeal samples collected at the same time.	***Index sample:*** Salivary sample ***Test:*** rRT-PCR ***Threshold:*** CT value < 35 ***Gene target:*** ORF1ab ***Collection method:*** After cessation of eating or drinking for 30 minutes, oral cavity was cleaned. Gentle massage of the salivary gland below tongue. About 1.5ml of midstream salivary fluid with cotton swabs. Placed into sterile dry containers immediately. ***Self- or provider- collection:*** Provider collected	***Reference sample:*** Oropharyngeal swabs ***Test:*** rRT-PCR ***Threshold:*** CT value < 35 ***Gene target:*** ORF1ab ***Collection method:*** Synthetic fibre swab inserted into the patient's throat and the posterior pharynx swabbed, avoiding the tongue. Placed immediately into a sterile tube.	***Detection rate:*** • 13/31 (41.9%) positive oropharyngeal swab. • 4/13 detected by matched saliva samples (30.7%).
Fang 2020 **China** **N=32** **Case series** **Published:**	***Population:*** SARS-CoV-2 infected patients ***Population demographics:*** Age range: 34 to 54 years, 16 males (50%), 13 (41%) had underlying health conditions.	***Index sample:*** Salivary sample ***Test:*** RT-PCR ***Gene target:*** NR	***Reference sample:*** Nasal swab* ***Test:*** RT-PCR ***Gene target:*** NR	***Detection rate:*** SARS-CoV-2 was detected in 25 (78.1%) of the 32 patients using salivary samples. All patients previously confirmed to have SARS-CoV-2 on the basis of nasal swabs

https://doi.org/10.1016/j.jinf.2020.03.013	***Setting:*** Patients admitted to a single hospital. 8 ICU and 24 non-ICU patients. ***Clinical characteristics:*** 28 symptomatic, 4 asymptomatic. ***Time between samples:*** NR	***Threshold:*** NR ***Collection method:*** NR ***Self- or provider- collection:*** NR	***Threshold:*** NR ***Collection method:*** NR	
Iwasaki 2020 **Japan** **N=76** **Cohort study** **Preprint:** https://doi.org/10.1101/2020.05.13.20100206.	***Populations:*** 1. SARS-CoV-2 infected patients (n=10) 2. Suspected SARS-CoV-2 cases (n=66) ***Population demographics:*** Median age: COVID-19 patients was 70.5 years-old (range 30 to 97). No demographic detail for suspected cases ***Setting:*** Single hospital ***Clinical characteristics:*** Most COVID-19 patients had mild-moderate disease. Median day of sampling was 9 days (range 3-19 days) after symptom onset. ***Time between samples:*** Simultaneous collection	***Index sample:*** Salivary sample ***Test:*** RT-qPCR ***Gene target:*** NR ***Threshold:*** NR ***Collection method:*** Spit into sterile container ***Self- or provider- collection:*** Self-collected with the exception of one patient.	***Reference sample:*** Nasopharyngeal swab ***Test:*** RT-qPCR ***Gene target:*** NR ***Threshold:*** NR ***Collection method:*** The swab was passed through the nostril until reaching the posterior nasopharynx and slowly removed while rotating.	***Detection rate:*** • SARS-CoV-2 detected in in 9/10 (90%) saliva samples and 9/10 nasopharyngeal samples (authors note the single case that did not test positive had samples taken 19 days after symptom onset). • Negativity was concordant between nasopharyngeal and saliva samples; the virus was not detected in either sample from 66 COVID-19 suspicious patients.
Jamal 2020 **Canada** **N= 53** **Case series**	***Population:*** SARS-CoV-2 infected patients ***Population demographics:*** Median age: 63 years (Range 27-106), 32 males (60%), 38 (72%) had at least 1	***Index sample:*** Salivary sample ***Test:*** RT-PCR ***Threshold:***	***Reference sample:*** Nasopharyngeal swab ***Test:*** RT-PCR ***Threshold:***	***Detection rate:*** Of 53 patients with paired samples 47 (89%) had at least one positive specimen: • 31/47 (66%) both

Preprint: https://doi.org/10.1101/2020.05.01.20081026	comorbidity. ***Setting:*** Inpatients from 6 hospitals consecutively enrolled ***Clinical characteristics:*** Median time from illness onset to hospital admission was 6 days (interquartile range 3-8) and 18 (34%) required intensive care. Median time from illness onset to collection of the tested specimens was 11 days (interquartile range 7-15). ***Time between samples:*** Samples collected on the day of enrolment.	NR ***Gene target:*** RdRp, N, and E ***Collection method:*** Patients were asked to spit into a sterile specimen container and then 2.5 ml of phosphate buffered saline were added. ***Self- or provider- collection:*** Unclear if directed or supervised by clinician.	NR ***Gene target:*** RdRp, N, and E ***Collection method:*** Collected as per standard procedures.	nasopharyngeal swab and saliva were positive • 11/47 (23%) only the nasopharyngeal swab was positive • 5/47 (11%) only saliva was positive. Using nasopharyngeal swabs only would have detected 42/47 (89%). Using salivary samples only would have detected 36/47 (77%).
Kojima 2020 **United States** **N= 45** **Cross-sectional** **Preprint:** https://doi.org/10.1101/2020.04.11.20062372	***Population:*** Suspected SARS-CoV-2 cases ***Population demographics:*** Median age 42 years (Interquartile range 31 to 52 years). ***Setting:*** Samples collected in participant homes. ***Clinical characteristics:*** 29 positive for SARS-CoV-2 from at least one specimen type collected (Oral fluid, nasal swab, nasopharyngeal swab). 21 reported active symptoms. Range 2-21 days from symptom onset to sample collection.	***Index sample:*** Oral fluid sample ***Test:*** RT-qPCR ***Threshold:*** NR ***Gene target:*** N ***Collection method:*** Participants were instructed to cough deeply 3-5 times collecting any phlegm or secretions in their mouth, rub the swab on both cheeks, above and below the tongue, both gums, and on the hard palate for a total of 20 seconds to ensure the swab was saturated with oral	***Reference sample:*** Nasopharyngeal swab ***Test:*** RT-qPCR ***Threshold:*** NR ***Gene target:*** N ***Collection method:*** Posterior using the recommended medical technique.	***Detection rate:*** 16 (35.6%) participants negative with both samples. 29 (64.4%) participants identified as positive by at least one specimen. No single specimen type detected all those with infection: • Clinician-supervised oral fluid swab specimens detected 26/29 (90%) • Unsupervised self-collected oral fluid swab specimens detected 19/29 (66%) • Clinician-collected posterior nasopharyngeal swab specimens detected 23/29 (79%). ***Sample insufficiency:*** One unsupervised oral fluid No supervised oral fluid

	Time between samples: All samples collected within a 30 minute window.	fluid ***Self- or provider- collection:*** 1. Unsupervised self-collected oral fluid sample 2. Clinician supervised oral fluid sample.		No nasopharyngeal samples.
McCormik-Baw 2020 **United States** **N= 156** **Cross-sectional** **Published:** 10.1128/JCM.01109-20	***Population:*** Suspected SARS-CoV-2 cases ***Population demographics:*** Mean age 47.8 years, 90 males (58%) ***Setting:*** Emergency department and inpatients from COVID positive hospital unit ***Clinical characteristics:*** Unventilated participants. ***Time between samples:*** NR	***Index sample:*** Salivary sample ***Test:*** rRT-PCR (Cepheid Xpert Xpress SARS-CoV-2 PCR test) ***Gene target:*** E and N2 ***Threshold:*** Detection of both targets or N2 alone is considered positive and detection of E alone is considered presumptive positive. ***Collection method:*** Recommended that patients not have any food, drink, tobacco or gum for 30 minutes prior to collection. Saliva was collected in sterile urine cups or sterile 50 ml conical tubes. 5 ml of saliva was requested; however, specimens were considered acceptable if approximately 1 ml saliva was submitted. ***Self- or provider- collection:*** Clinician present but uncertain if clinician collected or supervised. Encouraged to collect saliva not sputum collection.	***Reference sample:*** Nasopharyngeal swab ***Test:*** rRT-PCR (Cepheid Xpert Xpress SARS-CoV-2 PCR test) ***Gene target:*** E and N2 ***Threshold:*** Detection of both targets or N2 alone is considered positive and detection of E alone is considered presumptive positive. ***Collection method:*** Collected in a standard fashion.	***Detection rate:*** • 50 samples tested positive with either sample • 47/49 (96%) were positive in saliva compared to nasopharyngeal (95% CI 86.02 to 99.5%). • 105/106 (99%) had a negative saliva and nasopharyngeal sample. • A single sample was positive for saliva, but negative for nasopharyngeal swab. Note: community rate positivity 11.1% during study time period.

Pasomsub 2020 **Thailand** **N=200** **Cross-sectional study** **Preprint:** https://doi.org/10.1101/2020.04.17.20070045	***Population:*** Suspected SARS-CoV-2 cases ***Population demographics:*** Patients >18 years. Median age 36 (Interquartile range 28-48), 69 males (34.5%). ***Setting:*** Acute respiratory infection clinic at a single hospital ***Clinical characteristics:*** Median onset of symptoms before testing 3 days (interquartile range 2 to 7). ***Time between samples:*** Consecutively with saliva first.	***Index sample:*** Salivary sample ***Test:*** RT-PCR ***Gene Target:*** ORF1AB and N ***Threshold:*** Both target genes Ct value < 38 ***Collection method:*** Patients were asked to provide a saliva sample, void of coughing, in a sputum collection container. ***Self- or provider- collection:*** Unclear	***Reference sample:*** Nasopharyngeal and throat swabs ***Test:*** RT-PCR ***Gene Target:*** ORF1AB and N ***Threshold:*** Both target genes Ct value < 38 ***Collection method:*** Collected as per standard protocol.	***Detection rate:*** • Positive detection in 21 cases ○ 19/21 by nasopharyngeal ○ 18/21 by saliva. • Using nasopharyngeal as reference standard authors report: ○ sensitivity 84.2% (95% CI: 60.4% to 96.6%)[¥] ○ specificity 98.8% (95% CI: 96.1% to 99.9%).[¥] ○ 97.5% agreement between the two specimens.
Rutgers Clinical Genomics Laboratory **United States** **N=60** **Accelerated Emergency Use Authorization published by Food and Drug Administration** https://www.fda.gov/media/136875/download	***Population:*** Suspected SARS-CoV-2 cases ***Population demographics:*** No demographic information provided ***Setting:*** Three ambulatory care centres. ***Clinical characteristics:*** Symptomatic patients ***Time between samples:*** Both sample sites collected within 10 minutes of each other.	***Index sample:*** Salivary sample ***Test:*** rRT-PCR ***Gene target:*** N, S and, ORF1ab ***Threshold:*** Two of three Ct value <37 ***Collection method:*** Each patient was provided with instructions for self-collection of saliva using a commercial saliva collection device. ***Self- or provider- collection:*** Self-collected under supervision of clinician	***Reference sample:*** Nasopharyngeal or oropharyngeal swab ***Test:*** rRT-PCR ***Gene target:*** N, S and, ORF1ab ***Threshold:*** Two of three Ct value<37 ***Collection method:*** Collected in a standard fashion	***Detection rate:*** • Positive agreement: 100% (30/30) (95% CI 88.7 to 100%). • Negative agreement: 100% (30/30) (95% CI 88.7 to 100%).

To 2020a **Hong Kong** **N=23** **Cohort study** **Published:** https://doi.org/10.1016S1473-3099(20)30196-1 Includes results from To 2020b[18]	***Population:*** SARS-CoV-2 infected patients ***Population demographics:*** Median age: 62 years (Range 37-75), 13 males (57%), 11 (48%) had chronic medical conditions. ***Setting:*** Hospitalised patients from two hospital sites. ***Clinical characteristics:*** 10 participants has severe disease, 13 had mild disease. 5 patients were admitted to ICU. Median interval between symptom onset and hospitalisation was 4 days (range 0 to 13). ***Time between samples:*** NR	***Index sample:*** Salivary sample ***Test:*** RT-qPCR ***Gene target:*** RNA polymerase helicase gene region ***Threshold:*** NR ***Collection method:*** Early morning saliva sample from the posterior oropharynx (i.e., coughed up by clearing the throat) before tooth brushing and breakfast. ***Self- or provider- collection:*** Self-collection instructed and supervised by nurses.	***Reference sample:*** Nasopharyngeal or sputum specimens ***Test:*** RT-qPCR ***Gene target:*** RNA polymerase helicase gene region ***Threshold:*** NR ***Collection method:*** NR	***Detection rate:*** SARS-CoV-2 RNA was detected in the saliva of 20/23 (87%) patients.
Williams 2020 **Australia** **N= 622 (n=89 matched samples analysed)** **Cross-sectional** **Published:** 10.1128/JCM.00776-20	***Population:*** Suspected SARS-CoV-2 cases ***Population demographics:*** No demographic information provided ***Setting:*** Ambulatory screening clinic at a single hospital. ***Clinical characteristics:*** NR ***Time between samples:*** Consecutive	***Index sample:*** Salivary sample ***Test:*** RT-PCR ***Threshold:*** NR ***Collection method:*** Patients were asked to pool saliva in their mouth for 1-2 minutes prior to collection, and gently spit 1-2 ml of saliva into a 25ml collection pot. ***Self- or provider- collection:*** Unclear	***Reference sample:*** Nasopharyngeal swab ***Test:*** RT-PCR ***Threshold:*** NR ***Collection method:*** NR	***Detection rate:*** 39/622 tested positive through nasopharyngeal samples: • 33/39 tested positive with salivary samples (84.6%; 95% CI 70.0 to 93.1). • 1/50 (2%; 95% CI 0.1 to 11.5) positive which had tested negative with nasopharyngeal swabs.

Wyllie 2020 **United States** **N= 142 (n=44 SARS-CoV-2 infected patients [n=38 paired samples], n=98 asymptomatic healthcare workers)** **Case series** **Preprint:** https://doi.org/10.1101/2020.04.16.20067835	***Populations:*** 1. SARS-CoV-2 infected patients (n=44) 2. Asymptomatic healthcare workers at moderate-high risk of exposure (n=98) ***Population demographics:*** Aged > 18 years • SARS-CoV-2 inpatients: Mean age 61 years (Range 23-92), 23 males (52%) • Asymptomatic healthcare workers: Mean age 36 years (Range 22-67), 16 males (16%). ***Setting:*** COVID-19 inpatients and asymptomatic healthcare workers from a single hospital ***Clinical characteristics:*** Of COVID-19 inpatients 19 (43%) required intensive care, 10 (23%) required mechanical ventilation, and 2 (5%) deceased ***Time between samples:*** NR	***Index sample:*** Salivary sample ***Test:*** RT-PCR ***Gene target:*** N ***Threshold:*** Ct value < 38 ***Collection method:*** Patients were asked to avoid food, water and brushing of teeth until the sample was collected. Patients were asked to repeatedly spit into a sterile urine cup until roughly a third full of liquid. Obtained every three days. ***Self- or provider- collection:*** COVID-19 inpatients: Self-collected with instruction. Asymptomatic healthcare workers: Self-collected	***Reference sample:*** Nasopharyngeal and/ or oropharyngeal swab ***Test:*** RT-PCR ***Gene target:*** N ***Threshold:*** Ct value < 38 ***Collection method:*** The flexible, mini-tip swab was passed through the patient's nostril until the posterior nasopharynx was reached, left in place for several seconds to absorb secretions then slowly removed while rotating. Obtained every 3 days. Asymptomatic healthcare workers were asked to collect a self-administered nasopharyngeal swab and a saliva sample every 3 days for a period of 2 weeks. ***Self- or provider- collection:*** COVID-19 inpatients: Collected by nurses Asymptomatic healthcare workers: Self-collected	***Detection Rate:*** Paired samples for 38 participants. • Detected from the saliva but not the nasopharyngeal swabs in 8/38 patient matched samples (21%) • Detected from nasopharyngeal swabs and not saliva from 3/38 patient matched samples (8%) • Detected in 2 healthcare workers saliva samples which were negative with nasopharyngeal swabs.
Ye 2020 **China** **N= 91** **Cohort** **Published:** https://doi.org/10.1016/j	***Population:*** Suspected SARS-CoV-2 cases ***Population demographics:*** Patients with suspected COVID-19. No further demographic formation provided.	***Index sample:*** Lingual swab^ ***Test:*** RT-PCR ***Gene target:*** NR	***Reference sample:*** Throat swab ***Test:*** RT-PCR ***Gene target:*** NR	***Detection rate*** Throat swabs: 40/91 (44.0%) Lingual swabs: 33/91 (36.3%) *Hospital 1 (1 experienced nurse)* • Positive: 25/46 (54.3%) • Throat swabs: 25/46 (54.3%)

.jhin.2020.03.012	***Setting:*** Fever clinic in 2 hospital sites: • Hospital one (n=46) • Hospital two (n=45). ***Clinical characteristics:*** NR ***Time between samples:*** NR	***Threshold:*** NR ***Collection method:*** NR ***Self- or provider- collection:*** Clinician collected. Hospital 1 was by 1 experienced nurse. Hospital 2 was by several nurses.	***Threshold:*** NR ***Collection method:*** NR ***Self- or provider- collection:*** Clinician collected. Hospital 1 was by 1 experienced nurse. Hospital 2 was by several nurses.	• Lingual swabs: 17/46 (36.9%) • All patients with positive lingual swabs also had positive throat swabs. *Hospital 2 (several nurses)* • Positive: 22/45 (48.9%) • Throat swabs: 15/45 (33.3%) • Lingual swabs: 16/45 (35.6%) • 10/22 (45.5%) of the positive patients were detected by both methods.

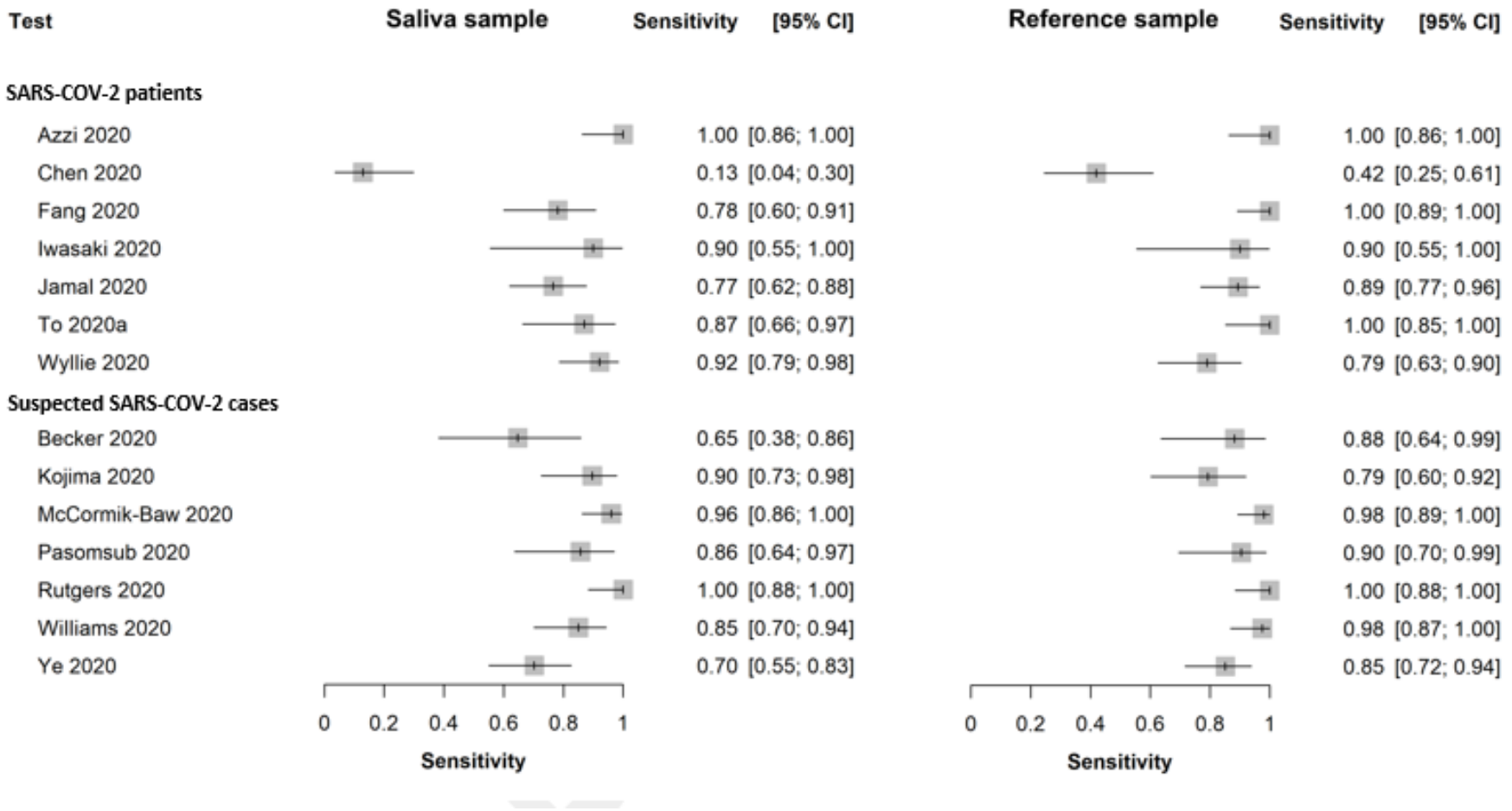
*Study describes nasal swabs which may not be nasopharyngeal
^Lingual swabs- method of collection on or around the tongue, may not be indicative of salivary
¥ Estimates recalculated using binomial distribution due to low counts

Table 2. Detection rates of SARS-CoV-2 reported by included studies

Study Reference sample(s)	Positive (any specimen)	Positive (reference)	Positive (saliva)	Detection by saliva relative to reference (%)	Positive agreement between samples	Negative (reference)	Negative (saliva)	Negative agreement between samples
Suspected SARS-COV-2 cases								
Becker (n=85)* Nasopharyngeal	17	15 (88.2%)	11 (64.7%)	9/15 (60%)	9/17 (52.9%)	64*	72*	62/72 (86.1%)*
Iwasaki (n=66)^ Nasopharyngeal	0	0	0	-	-	66	66	66/66 (100%)
Kojima (n=45) Nasopharyngeal	29	23 (79.3%)	26 (89.7%)	20/23 (86.9%)	20/29 (69%)	22	19	16/22 (72.7%)
McCormik- Baw (n=156) Nasopharyngeal	50	49 (98%)	48 (96%)	47/49 (96%)	47/50 (94%)	106	107	105/107 (98.1%)
Pasomsub (n=200) Nasopharyngeal and oropharyngeal	21	19 (90.4%)	18 (85.7%)	16/19 (84.2%)	16/21 (76.2%)	181	182	179/182 (98.3%)
Rutgers Clinical Laboratory (n=60) Nasopharyngeal or oropharyngeal	30	30 (100%)	30 (100%)	30/30 (100%)	30/30 (100%)	30	30	30/30 (100%)
Williams (n= 89) Nasopharyngeal	40	39 (97.5%)	34 (85%)	33/39 (84.6%)	33/40 (82.5%)	50	55	49/55 (89.1%)
Ye (n=91) Oropharyngeal	47	40 (85.1%)	33 (70.2%)	27/40 (67.5%)	27/47 (57.4%)	51	58	51/58 (87.9%)
SARS-COV-2 infected patients								
Azzi (n=25) Nasopharyngeal	25	25 (100%)	25 (100%)	25/25 (100%)	25/25 (100%)			
Chen (n=31, 13 paired samples) Oropharyngeal	31	13 (41.9%)	4 (30.8%)	4/13 (30.8%)	4/13 (30.8%)			
Fang (n=32) Nasopharyngeal	32	32 (100%)	25 (78.1%)	25/32 (78.1%)	25/32 (78.1%)			
Iwasaki (n=10)^ Nasopharyngeal	10	9 (90%)	9 (90%)	8/9 (88.9%)	8/10 (80%)			
Jamal (n=53) Nasopharyngeal	47	42 (89.4%)	36 (76.6%)	31/42 (73.8%)	31/47 (66%)			
To (n=23) Nasopharyngeal or sputum	23	23 (100%)	20 (87%)	20/23 (87%)	20/23 (87%)			
Wyllie (n=38) Nasopharyngeal and/or oropharyngeal	38	30 (78.9%)	35 (92.1%)	27/30 (90%)	27/38 (71.1%)			

*Six indeterminate samples by nasopharyngeal, two indeterminate samples by saliva
^separate groups reported by study

Figure 1. Sensitivity of saliva and reference samples for the detection of SARS-CoV-2



Note: For confirmed SARS-CoV-2 patients reference samples included nasopharyngeal swabs and/or oropharyngeal swabs or sputum

For suspected SARS-CoV-2 cases reference samples included nasopharyngeal and/or oropharyngeal swabs

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