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Norwegian Institute of Public Health

memo

COVID-19-EPIDEMIC :

Saliva sample for testing SARS-CoV-2 infection – a rapid review

Title	Saliva sample for testing SARS-CoV-2 infection – a rapid review
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Key messages

This memo is based on rapid searches in PubMed, LitCov and supplementary searches for pre-prints. One researcher assessed the relevance of each reference and summarized the findings. Another researcher supplied information and summarized the findings, read and provided feedback on the review. In the current situation, there is an urgent need for identifying the most important evidence quickly. Hence, we opted for this rapid approach despite an inherent risk of overlooking key evidence or making misguided judgements.

The aim of this rapid report is to investigate if there are studies supporting the use of salivary samples for detection of SARS-CoV-2, and if there are studies that can be used to calculate the diagnostic accuracy of salivary testing compared to nasopharyngeal or oropharyngeal swab samples.

We selected studies focusing on testing for SARS-Cov-2 in saliva. We excluded studies that had not used SARS-CoV-2 testing with samples from nasopharyngeal and/or oropharyngeal swabs as reference standard. This rapid review does not include a formal quality assessment of included papers, nor does it include a grading of the certainty of evidence. The results should therefore be interpreted with caution.

We identified 32 new papers from the database search and by manual searching of reference lists. From these, we include 8 studies comparing SARS-Cov-2 nucleic acid detection from salivary samples compared to nasopharyngeal or oropharyngeal swab samples. Two of the included studies had not been through peer review. The sample sizes range from 4-82 patients. Two of the studies could be used to assess diagnostic accuracy. The results indicate that the correlation between diagnostic accuracy of symptomatic patients tested with reverse transcription polymerase chain reaction (rRT-PCR) using self- collected saliva samples, compared to health care worker administrated nasopharyngeal or oropharyngeal swabs is good, corresponding to a sensitivity of 97-100 % and a specificity of 89-100%. The results should be considered with caution as further studies may change the estimates. Additionally, six of the studies are indicative of various types of salivary sampling as appropriate for detection of SARS-Cov-2 nucleic acid. These findings are highly relevant in the face of shortages of both swabs and personal protective equipment for health care workers. Self-collection of saliva is comfortable for patients as well as being easy, cheap, and non-invasive with minimal equipment required.

In conclusion, the results indicate that the correlation between diagnostic accuracy of symptomatic patients tested with rRT-PCR using self- collected saliva samples compared nasopharyngeal or oropharyngeal swabs is good. The results should be considered with caution as further studies may change the estimates.

Hovedfunn (Norwegian)

Dette notatet baserer seg på raske søk i PubMed, LitCov og pre-print databaser. Én forsker gikk gjennom søketreff, to forskere valgte ut og oppsummerte resultatene. Ettersom det har vært viktig å få fram forskningsresultatene raskt, valgte vi denne framgangsmåten selv om det innebærer risiko for at vi kan ha oversett viktig dokumentasjon og kan ha gjort feilvurderinger underveis.

Hensikten med denne hurtigoversikten er å oppsummere hva som finnes av studier om påvisning av SARS-CoV-2 i spytt, og om diagnostisk nøyaktighet ved bruk av spyttprøver sammenlignet med bruk av dyp nese- og/eller halsprøver kan beregnes.

Vi ekskluderte studier som ikke hadde bekreftet SARS-CoV-2 fra dyp nese- eller halsprøve som referanse standard. Denne hurtigoppsummeringen inkluderer ikke en kvalitetsvurdering av studiene, ei heller en gardering av tiltroen til studiene. Så resultatene bør tolkes med forsiktighet.

Etter søk i databaser og manuelle søk i referanselister, identifiserte vi 32 nye originalpublikasjoner. Av disse inkluderte 8 studier som sammenlignet SARS-CoV-2 nukleinsyrer deteksjon fra spyttprøver med dyp nese- eller halsprøve. To av de inkluderte studiene var pre-prints som ikke har vært gjennom fagfellevurdering, og mange av studier hadde veldig få deltakere (fra 4 til 82 pasienter). I to av studiene kunne en sammenligne den diagnostisk nøyaktigheten. Resultatet av sammenligningen viste til god diagnostisk nøyaktighet på pasienter med symptomer testet med rRT-PCR på spytt-prøver pasienten tok selv sammenlignet med dyp nese eller halsprøve. Studiene viste sensitivitet på mellom 97 til 100 % og spesifisitet på 89 til 100%. Resultantene må tolkes med forsiktighet da nye studier sannsynligvis vil endre estimatene. I tillegg inkluderte vi seks studier som også antyder at spytt-prøver kan være en formålstjenlig måte å bruke for å påvise SARS-CoV-2 nukleinsyrer ved mistanke om infeksjon.

Disse forskningsresultatene er relevante da det er en mangel på både prøvetakingsutstyr og beskyttelsesutstyr til helsepersonell i denne epidemien. Spytt-prøver, i tillegg til å ikke være smertefull, er en ikke-invasiv prøvetakning, som både er billigere og hvor behovet for prøvetakingsutstyr er mindre. I tillegg vil den minske risiko for nosokomial spredningen av SARS-CoV-2 til helsepersonell.

For å konkludere, indikerer studiene at det er godt samsvar mellom prøvene tatt i spytt av pasienten selv og ved dyp nese-halsprøve tatt av helsepersonell. Estimater for diagnostisk nøyaktighet må tolkes med forsiktighet siden ny forskning kan påvirke disse.

Content

Introduction

In relation to the Norwegian Institute of Public Health's role in handling the COVID-19 epidemic, we have been asked to produce a rapid summary of the available research on saliva test for testing SARS-CoV-2 infection.
Diagnostic tests for SARS-CoV-2 can broadly be grouped into two categories, those aimed at:

- pathogen (virus) detection (acute infection)
- detection of immune response to the pathogen (past exposure).

Pathogen detection tests, mainly reverse transcription polymerase chain reaction (rRT-PCR) to detect viral nucleic acid, and tests to detect an immune response to the virus (development of SARS-CoV-2-specific antibodies) should not be considered competing alternatives. Both testing approaches are clinically relevant, but must be deployed at different time points during the clinical course of infection taking consideration of their relevant diagnostic windows (1).

Nasopharyngeal and oropharyngeal swabs are the recommended specimen types for Covid-19 diagnostic testing. The collection of these specimen types requires close contact between healthcare workers and patients and poses a risk of transmission of the virus, causes discomfort and may cause bleeding, especially in patients with condition such as thrombocytopenia (2). Saliva has a potential as a diagnostic fluid and offers an edge over other biological fluids as its collection method does not require invasive procedure or health personal (2).

RT-PCR facilitates direct detection of SARS-CoV-2 RNA. It is characterised by high sensitivity and specificity and is regarded as the gold standard for clinical diagnostics of SARS-CoV-2. The initial identification of the SARS-CoV-2 virus was based on non-commercial RT-PCR laboratory protocols which were published on the World Health Organization (WHO) website. Now, rRT-PCR test kits, many of which work off existing platforms already deployed in hospital and diagnostic virology laboratories, are also available. The diagnostic window for using RT-PCR to detect acute infection with SARS-CoV-2 ranges from approximately three days following exposure to the virus until two weeks following symptom onset (1).

Saliva specimens can be obtained by different techniques, including self-sampling were the patient is asked to spit into a sterile bottle. Recent research has suggested that

SARS-CoV-2 can be detected in saliva at high titers, and salivary diagnostics has the potential to be incorporated as part of disease diagnosis, clinical monitoring of systemic health and to make clinical decisions for patient care (2).

An Irish rapid HTA has summarized twenty-seven studies reported on positive detection rates across sample sites (including sputum, faecal, urine, blood, saliva, lingual, ocular, BALF and vaginal) in patients with laboratory-confirmed COVID-19, as per oropharyngeal and nasopharyngeal swabs (table 1) (3).

Table 1. Different sample sites for test of SARS-CoV-2 (3).

Sample	Studies	Positive rate
Spuntum	6	77% to 100%*
Faecal	12	3% to 100%*
Urine	14	No detection (11 studies) or 7% to 11%
Blood	14	1% to 87%
Saliva	2	78% and 92%
Lingual	1	36%
Ocular	3	1% to 16%
BALF	2	79% and 100%*
Vaginal	1	no positive

*However, it should be noted that the 100% detection rate was based on a studies with few patients.
BALF=bronchoalveolar lavage fluid

The aim of this report is to investigate if there are studies supporting the use of salivary samples for detection of SARS-CoV-2 and if there are studies that can be used to calculate the diagnostic accuracy of salivary testing compared to nasopharyngeal or oropharyngeal swab samples.

Methods

The main objective of this rapid review update was to summarise current evidence concerning saliva as a sample for SARS-CoV-2 testing. More specifically we wanted to address how saliva sampling performed compared to nasopharyngeal and/or oropharynges swab sampling.

We searched in PubMed and LitCov, using the search strategy combining Saliva with Coronavirus/SARS-CoV-2/Covid-19 and diagnostic search filters. Searches were limited to the period from December 2019 to 04 May 2020, as SARS-CoV-2 was first identified in December 2019. We also search in Norwegian Institute of Public Health's systematic and living map on COVID-19 evidence (4). For pre-prints we search in medRxiv with this searching term "Saliva and diagnosis and SARS-Cov-2". All referenced were imported to EndNote-database and duplicates removed.

We selected studies focusing on diagnostic accuracy using SARS-Cov2 tests on saliva samples. We excluded studies that not included patients with confirmed SARS-CoV-2 from nasopharyngeal and oropharyngeal swabs as a gold standard. This rapid review does not include a formal quality assessment of included papers, nor does it include a grading of the certainty of evidence. The results should therefore be interpreted with caution.

One researcher (Lene K Juvet) assessed the relevance of each reference and summarized the findings. Another researcher (Vigdis Lauvrak) supplied information and summarized the findings, read and provided feedback on the review. One other researchers Karolin Bragstad, Norwegian Institute of Public Health) initiated the review, read and provided feedback on the review before publication.

Results

The update-search resulted in 32 unique records, 13 studies were read in full text, and we ended up including 8 primary clinical studies (5-11). Two of the included studies were conducted in China (6, 7) , two in USA (11, 12), two in Hong Kong (8, 10), one in Italy (5), on in Australia (9). Four of the included studies were published or accepted for publication in peer reviewed journals (5-10), two (6, 12) was an unpublished pre-prints and one was information supplied with a commercial assay for SARS-CoV-2 for saliva Enhanced Emergency Authorisation (EUA) by FDA in the USA (12).

Summary of included studies

Sample sizes of the included studies ranged from 4 to 82 patients tested with rRT-PCR using both saliva samples and reference samples (nasopharyngeal and/or oropharyngeal swabs). The identification and selection of cases for inclusion was not always adequately described. Timing of the collection of saliva samples relative to the reference samples varied, as did the information on number of replicates and excluded samples. Saliva was collected through different techniques with variable information on the details provided. In most studies the saliva sampling was stated to be performed by the patient (self-sampling) under instructions of health-care workers.

We considered that two of the studies (9, 12) can be used to calculate diagnostic accuracy of saliva samples compared to the reference sample. In both these studies the included patients were symptomatic, but not necessarily critically ill patients, providing self-administrated samples. In the other studies, mainly samples from hospitalised patients were analysed in a retrospective manner and diagnostic accuracy could not be calculated. All the eight included studies are shortly described in table 2. Details on the individual studies is presented below.

Table 2. Included studies

Study Country	Age, sex	Patient setting	Sample/ test	Reference sample/ test	N	TP	FP	TN	FN
Williams 2020 (9), Australia	NI	Ambulatory care setting	Pool saliva in their mouth and spit/ rRT-PCR	Nasopharyngeal swabs or sputum/	82	33	6	49	1
FDA EUA (12), USA	NI	Ambulatory care setting	Self-administrated saliva test/ rRT-PCR	Nasopharyngal or oropharyngal swab/ rRT/PCR	60	30	0	30	0
Azzi L 2020 (5), Italy	Mean age of 61.5 ±11.2 years. 68% males	Hospitalized, severe disease	Drooling/ rRT-PCR	Nasopharyngeal swab/ rRT-PCR	25	25	0	NA	NA
Wyllie 2020 (11) USA	Over 18 years	Hospitalized, severe disease	Saliva, no details/ rRTPCR	Nasopharyngeal swab/ rRT-PCR	38	30	5	3	0
Chen 2020 (6) China	Mean age of 60.6 (18-81) years. 52% males	Hospitalized, severe disease. Only 4 had both tests.	Massage of the salivary gland/ rRT-PCR	Oropharyngeal swab/ rRT-PCR	4	3	1	NA	NA
Fang 2020 (7) China	Mean age of 41 (34-54) years. 50% males	Hospitalized	N/A	Nasal swab	32	25	7	NA	NA
To KK 2020 (10) Hong Kong	Mean age of 62 (range 37-75) years. 58% males	Hospitalized	Self-administrated cough out saliva, 2 days after hospitalization/ rRT-PCR	Nasopharyngal swab or sputum at admission/ rRTPCR	12	11	NA	*NA*	*1*
To KK 2020 (8) Hong Kong	Mean age of 62 (range 37-75) years. 57% males	Hospitalized	Archieval samples as above 4-20 days after hospitalization/ rRT-PCR	.Nasopharyngal or sputum at admission/ rRTPCR	23	20	NA	NA	3

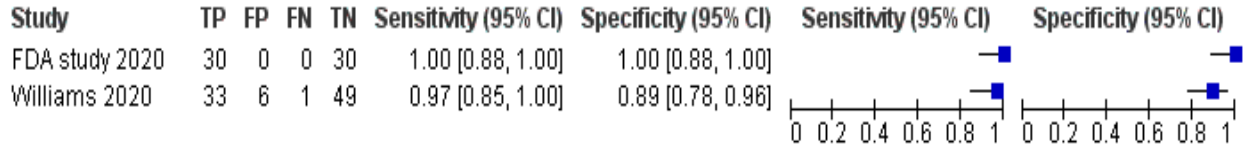
rRT-PCR =, NA = Not applicable, NI = No Information, N = Total number of patients, TP = True Positive relative to reference, FP = False positive relative to reference, TN= True Negative relative to reference, FN = False negative relative to reference

Diagnostic accuracy

Two studies (9, 12) were included for calculation of diagnostic accuracy. In the largest, performed in Australia (9), 622 patients were screened for Covid-19 using nasopharyngeal swabs and 522 of these also provided patient self-sampled saliva samples. Patients were asked to pool saliva in their mouth for 1-2 minutes prior to collection of spit into a 25 ml collection pot. Neat saliva was transported to a laboratory where it was mixed with liquid Amies media (1:1). The median time from sample collection to addition of media was 180 minutes. All reference samples underwent rRT-PCR. Samples from patients testing positive with the reference were also analysed by rRT-PCR. Following nucleic acid extraction (extraction volume of 200uL of the sample was used, 33 with RNA eluted in 60uL in Qiagen 32 EZ1 platform). In total 39 of 622 (6.3%; 95% confidence interval [CI] 4.6%-8.5%) patients were positive for the reference test, and 33 of these (84.6%; 95% CI 70.0%-93.1%) were positive with the saliva test. To assess specificity, a subset of saliva specimens from 50 patients with PCR negative swabs was also tested. One in 50 (2%; 95% CI 0.1%- 45 11.5%) of these saliva samples was positive.

In the FDA EUA study (12) samples from 30 symptomatic patients at three ambulatory care centres were included. The patients were provided with instructions for self-collection of saliva. Self-collection was performed under the observation of a healthcare provider who subsequently (within 10 minutes) also collected either a nasopharyngeal or oropharyngeal swab from each patient for parallel testing. The samples were placed in viral transport medium. Details on how the saliva sampling was performed is not described. Both the saliva and swabs were transported at ambient temperature, nucleic acid was extracted (PerkinElmer Chemagic 360 automated specimen processing system), and the samples were analysed by the same RT-PCR test within 48 hours of collection. A total of 30 positive and 30 negative samples were included in the study. There was 100% (95% two-sided score CI 88.7-100) positive and negative agreement between the results obtained from testing of saliva and those obtained from nasopharyngeal and oropharyngeal swabs. No information on the total number of samples screened, nor the number of inconclusive samples was provided in the document available to us.
Diagnostic accuracy based on these two studies are revealed in figure 1.

Figure 1. Summary of diagnostic accuracy (sensitivity and specificity) of two studies (9, 12)



In conclusion, the results indicate that the correlation between diagnostic accuracy of symptomatic patients tested with rRT-PCR using self- collected saliva samples compared to health care workers administrated nasopharyngeal or oropharyngeal swabs is good (9, 12) . The results should be considered with caution as further studies may change the estimates.

Detection of SARS-Cov-2 in saliva

Six studies of salivary sample being an appropriate sample for detection of SARS-Cov-2 nucleic acid in a diagnostic setting were included.

In an American study (11), samples were collected from 44 hospitalized patients with severe disease with 19 requiring intensive care unit (ICU) care, 10 ventilation. 121 self-collected saliva or nasopharyngeal swab samples from these patients were retrospectively analysed. For saliva sampling the patients, upon waking 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 (excluding bubbles), before securely closing it. All samples were stored at room temperature and transported to the research lab at the Yale School of Public Health within 5 hours of sample collection. There were 38 patients with matched saliva and nasopharyngeal samples. Of these 35 were saliva positive and 30 were nasopharyngeal positive. The authors claim to see a higher viral count in the saliva samples. We have not assessed this in detail as the timing of the samples relative to each other was not presented.

The same study (11) also reported on self-collected saliva samples and/or nasopharyngeal samples from 98 asymptomatic hospital workers and analysed these with rRT-PCR. A total of 33 had both type of samples taken (matched samples) at the same time. Nucleic acid was extracted using the MagMAX Viral/Pathogen Nucleic Acid Isolation kit (ThermoFisher Scientific). Two health-care workers with matched samples tested positive on saliva samples, not on nasopharyngeal samples. Based on rRT-PCR data viral load in the positive samples was low. Data was not presented to assess these results in detail.

In the Italian study (5), 25 hospitalized patients were included. All patients were affected by severe or very severe Covid-19 confirmed by rRT-PCR on nasopharyngeal samples. Saliva was collected by the drooling technique, excluding mucus from the oropharynx or lower respiratory tract. In intubated patients or patients with mechanical ventilation saliva was collected by a physician with a pipette. Information on time between reference sample is not provided. Following nucleic acid extraction (QIAmp Viral RNA mini kit (Qiagen)), rRT-PCR was performed. Samples were run in four replicas. All samples from all patients tested positive. CT values were not influenced by age or com-

morbidity. Two patients with matched samples tested positive on saliva samples, not on nasopharyngeal samples.

In one Chinese study (6), 31 Covid-19 patients confirmed positive patients were included. Of these four were critically ill and saliva samples were compared to oropharyngeal swab samples taken at the same time. Details on methods for sampling was not provided. The salivary samples were all positives. We conclude that this study reveals that viral nucleic acid can be detected in saliva samples of SARS-CoV-2 infected patients but based on this study we cannot conclude regarding diagnostic accuracy (sensitivity and specificity).

In a second Chinese study (7) 32 Covid-19 suspected hospital admitted patietns were included. Of these eight were intensive care unit patients (ICU) and 24 were non-ICU. Nasal, blood, fecal, urine saliva and tear samples were taken from each patient. Details on methods for sampling are not provided. All included patients tested positive on nasal swab samples. No information is provided to whether this was an inclusion criteria. Following nucleic acid extraction, rRT-PCR was performed. The positive rate of saliva was 25 out of 32 (78.1%) compared to 5 out of 32 in tears (15,6%). We conclude that this study reveals that viral nucleic acid can be detected in saliva samples of Covid-19 infected patients but based on this study we cannot conclude regarding diagnostic accuracy (sensitivity and specificity).

The two Honk Kong studies (8, 10) overlapped in patients included. In the first study, 12 patients with laboratory confirmed Covid-19 based on nasopharyngeal or sputum analysed with RT-PCR were included. For oropharynhgal saliva samples patients were asked to produce an early morning (before, fluid intake, meal and toothbrush) cough up sample by clearing the throat. This self-sampling procedure was done under supervision of nurses. Saliva sampling was performed after admission at a median of day two. After nucleic acid extraction, the saliva samples were analysed by rRT-PCR. Eleven out of 12 patients (91.7%) tested positive for SARS-CoV-2. In the second Hong Kong study (8) 30 consecutive patients (including the 12 from the first (10)) with laboratory confirmed Covid-19 were screened for inclusion, 23 were included. Archival samples of blood, urine, posterior oropharyngeal saliva, and rectal swabs were analysed. Patients were excluded if insufficient sample of saliva or serum was available. For viral load analysis in saliva the same self-sampling procedure as described above was used unless the patient was intubated. From intubated patients, endotracheal aspirates were used as the saliva sample. A total of 173 samples were collected at different time points, with an average of 7.5 for each patient. The samples were analysed by rRT-PCR as in the first study. Three out of 23 patients had no positive saliva samples. Seven of 21 surviving patients had positive samples at 20 days or longer following symptom debut. No correlation between viral load in saliva and severity of disease was detected.

In conclusion, these six studies reveal that viral nucleic acid can be detected in saliva samples of Covid-19 infected patients but based on these studies we cannot conclude regarding diagnostic accuracy (sensitivity and specificity).

Discussion and conclusion

We included 8 original studies in this rapid review of research related to saliva test for testing SARS-CoV-2 infection. Two studies were conducted in China, and two studies in USA and in addition studies were conducted in Italy, Hong Kong and Australia (5-9, 11, 12). In most of the studies included the sample had been taking in a hospital setting, only one study had a screening setting that is comparable to community settings (9). Most of the studies were retrospective and had small sample sizes. Results from an EUA approved FDA test was also included (12).

According to Cochrane Handbook a study should include at least 200 participants to be able to conclude about diagnostic accuracy (13). We conclude that the level of evidence on clinical samples and collection sites suitable for SARS-CoV-2 testing overall is low. The limited number of participants in the studies identified here mainly included patients with laboratory-confirmed SARS-CoV-2, as per PCR testing of oropharyngeal and nasopharyngeal swabs. The absolute number of false positive and false negative test results observed in a population will depend on the prevalence of the disease being studied: as prevalence decreases the absolute number of false negatives decreases and the absolute number of false positives increases (13). This could be of relevance if saliva diagnostics should be used in the community with relative low numbers of SARS-CoV-2 infected people. Although FDA has recently approved saliva as a possible way of sampling for COVID-19 (12). Larger studies will come, we identified a protocol for an ongoing study including larger sample size of patient self-collection of saliva samples (14).

Some of the studies found in the search (5, 11, 15) show positive salivary samples but negative respiratory swabs samples at the same time. There has been concerns of the findings of some patients with symptoms of Covid-19 with having a negative nasopharyngeal swab in hospital. There may be several explanations for any apparent discordance between test results based on discordance between test results and clinical findings which are unrelated to the test itself. Firstly, there is a potential for pre-analytical errors including issues such as insufficient sampling, contamination of specimens, and inappropriate storage and transport conditions. Secondly, the analytical process can affect results with the use of different sample preparations and varying levels of analyst skills. Thirdly, the viral dynamics of SARS-CoV-2 across the time course of the infection are still not fully understood. Hence, false negative test results may occur if samples are

tested during the early incubation period or else during the late convalescent phase, when virus levels may be undetectable.

It is still not understood why the virus is detectable in the oral cavity. It may appear in the mouth because it migrates from the nasopharynx or the lower respiratory tract to the oral cavity, but it can't be excluded that a role may be played by the secretory activity of the salivary glands. It has been suggested that the oral cavity may play an active role in the pathogenesis of COVID-19, and this was highlighted by a Chinese study that showed a high expression of ACE2 receptors on the epithelial cells of the oral mucosa (5) . However, it should be noted that saliva specimens not only contain saliva secreted from major or minor salivary glands but also contain secretions coming down from the nasopharynx or coming up from the lung via the action of cilia lining the airway. Further studies are required to delineate the sources of SARS-CoV-2 in saliva (10).

The sensitivity of saliva as a diagnostic specimen seems high and comparable to nasopharyngeal or oropharyngeal samples. Saliva testing may therefore be a suitable alternative for first-line screening test in several environments, including low resource settings reserved for patients with an ongoing high clinical index of suspicion. These findings are highly relevant in the face of shortages of both swabs and personal protective equipment in many settings (9). An advantage of saliva is sampling comfortability in an epidemic situation. By using saliva as a collection sample, healthcare providers, doctors, nurses, dentists and paramedic staff will be safe from the transmission of disease. Saliva collection is quite comfortable for patients as well as being easy, cheap, and non-invasive with minimal equipment required. It should also minimize the nosocomial transmission of SARS-CoV-2 to healthcare workers.

One study was excluded (16), the study was a retrospective cohort study with 3497 respiratory samples (688 sputum and 1178 deep cough saliva) as well as stool, serum and urine samples were collected from patients after hospitalisation. Infection was confirmed by testing sputum and saliva samples with rRT-RCT. 96 patients had confirmed covid-19. The study was excluded as the deep cough saliva samples were not tested with the relevant a reference test. However, the study reveals that viral nucleic acid can be detected in sputum and in deep cough saliva samples of Covid-19 infected patients.

In conclusion, the results indicate that the correlation between diagnostic accuracy of symptomatic patients tested with rRT-PCR using self- collected saliva samples compared to health care workers administrated nasopharyngeal or oropharyngeal swabs is good. The results should be considered with caution as further studies may change the estimates.

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