NIPH
Norwegian Institute of Public Health

memo

COVID-19-EPIDEMIC :

Saliva sample for testing SARS-CoV-2 infection, 1st update on diagnostic accuracy

Title	Saliva sample for testing SARS-CoV-2 infection, 1st update on diagnostic accuracy
Norwegian title	Spyttprøver for testing av SARS-CoV-2 infeksjon, første oppdatering om diagnostisk nøyaktighet
Institution	Norwegian Institute of Public Health
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Memo	Desember – 2020
ISBN	978-82-8406-151-1
Publication type	Systematic Review, COVID-19 rapid response
Number of pages	25 (46 including appendix)
Commisioner	Norwegian Institute of Public Health
Citation	Lauvrak V, Juvet LK. Saliva sample for testing SARS-CoV-2 infection, 1st update on diagnostic accuracy. Systematic review, COVID-19 rapid response 2020. Oslo: Norwegian Institute of Public Health, 2020.

Key messages

The aim of this review was to investigate the diagnostic accuracy of reverse transcription real time polymerase chain reaction (rRT-PCR) for detection of SARS-CoV-2 in saliva specimens compared to upper airway samples. We performed a systematic literature search focusing on COVID-19 and saliva. The search provided 501 titles and abstracts, from which we inspected 70 records in full text and included 23 studies. From the included studies, we extracted data from 27 sets of comparative analysis of in total 7065 paired samples to calculate sensitivity[1] and specificity[2].

- In five studies with a total of 4299 paired samples from screening a mainly asymptomatic population, we found that sensitivity in the analysis ranged from 61% to 100 % (GRADE certainty of the evidence[3] moderate, ⊕⊕⊕◯). The specificity, ranged from 95% to 100% (GRADE certainty of the evidence high, ⊕⊕⊕⊕).
- In 11 studies with a total of 1612 paired samples from screening mainly symptomatic persons, we found variable, but predominantly good concordance between saliva samples and upper airway samples. Due to risk of bias we have low confidence in estimates based on these studies (GRADE certainty of evidence low ⊕⊕◯◯).
- In 9 studies with a total of 1154 paired samples from re-testing patients with known Covid-19 status, we likewise found variable, but predominantly good concordance. Due to high risk of bias, we have very low confidence in estimates based on these studies(GRADE certainty of evidence very low ⊕◯◯◯).

The results indicate that the diagnostic accuracy of rRT-PCR on saliva samples, compared to upper airway samples, probably is somewhat lower regarding sensitivity, but high regarding specificity. Variations between the analysis may be related to publication bias (more positive results published), risk of bias in the included studies, technical and clinical factors. The studies do not allow conclusions to be made about what factor may have the largest impact on the results.

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[1] Sensitivity is the likelihood that a person with a condition (diseased/infected) is correctly diagnosed using the index test compared to the reference test.
[2] Specificity is the likelihood that a person without a condition (healthu/non-infected) is correctly identified as negative by the index test compared to the reference test.
[3] GRADE certainty of evidence reflects our certainty that the estimate is close to a true estimate. The lower the certainty, the higher is our anticipation that new evidence may change the estimates.

Hovedfunn (Norwegian)

Hensikten med denne oversikten var å undersøke diagnostisk nøyaktighet av revers transkriptase sanntid polymerasekjedereaksjon (rRT-PCR) for påvisning av SARS-CoV-2 i spyttprøver sammenlignet med øvre luftveisprøver. Vi utførte et systematisk litteratursøk med fokus på covid-19 og spytt. Søket ga 501 titler og sammendrag. Etter gjennomgang av disse, inspiserte vi 70 referanser i fulltekst og inkluderte 23 studier. Fra studiene ekstraherte vi data fra 27 sammenliknende analyser av totalt 7065 parede prøver og beregnet sensitivitet[4] og spesifisitet[5].

- I fem studier, med totalt 4299 parede prøver fra screening av en hovedsakelig asymptomatisk populasjon, varierte sensitiviteten mellom analysene fra 61 % til 100 % (GRADE tillit til resultatet[6] moderat ⊕⊕⊕◯). Spesifisiteten varierte fra 95 % til 100 % (GRADE tillit til resultatet høy ⊕⊕⊕⊕).
- I 11 studier, med totalt 1612 parede prøver fra screening av hovedsakelig symptomatiske personer, fant vi noe variasjon, men overveiende godt samsvar mellom spyttprøver og øvre luftveisprøver. På grunn av risiko for skjevhet, har vi lav tillit til estimater basert på disse studiene (GRADE tillit til resultatet lav ⊕⊕◯◯).
- I 9 studier, med totalt 1154 parede prøver fra re-testing av pasienter med kjent Covid-19-status, fant vi også noe variasjon, men overveiende godt samsvar. På grunn av høy risiko for skjevhet, har vi svært lav tillit til estimater basert på disse studiene (GRADE tillit til resultatet svært lav ⊕◯◯◯).

Resultatene indikerer at den diagnostiske nøyaktigheten av rRT-PCR på spyttprøver, sammenlignet med øvre luftveisprøver, sannsynligvis er noe lavere med hensyn til sensitivitet, men høy med hensyn til spesifisitet. Den observerte variasjonen mellom analysene kan være relatert til både publikasjonsskjevhet (mer positive resultater publisert), risiko for skjevhet i inkluderte studier, tekniske og kliniske faktorer. De inkluderte studiene tillater ikke konklusjoner om hvilken faktor som kan ha størst innvirkning på resultatene.

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[4] Sensitivitet er sannsynligheten for at en person med en gitt tilstand (syk/smittet) får tilstanden påvist med indeks testen sammenliknet med en referanse testen, dvs positiv test.
[5] Spesifisitet er sannsynligheten for at en person uten tilstanden (frisk/ikke smittet) får riktig svar med indeks testen sammenliknet med referanse testen, dvs negativ test.
[6] GRADE tillit til resultatet reflekterer vår tillit til at estimatet er nært en sann verdi. Jo lavere tillit vi har jo mer sannsynlig anser vi at der at nye studier vil kunne endre estimatet.

Preface

This review has been commissioned by the Director of Infection Prevention and Control at The Norwegian Institute of Public Health (NIPH). The review is an update of a rapid report on saliva samples for rRT-PCR detection of SARS-CoV-2 from May 2020 focusing solely on diagnostic accuracy. The review has been produced without a published protocol and we have used a simplified review process with only one external reviewer. 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.

We would like to thank the following for valuable contribution:

- Elisabet Hafstad, Senior Advisor and information specialist, Division for Health Services, NIPH. Literature search
- Karoline Bragstad, Head of Section for Influenza and other respiratory viruses, Department of Virology, Division of Infection Control and Environmental Health, NIPH. Feedback during the assessment and read a draft of the review before publication
- Kjetil Gundro Brurberg, Department Director Division for Health Services, NIPH. Read a draft of the report before publication
- Einar Nilsen, Avdelinsgssjef. Overlege Avdeling for medisinsk mikrobiologi, Helse Møre og Romsdal. External review

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Content

Introduction

In relation to the Norwegian Institute of Public Health's role in handling the COVID-19 epidemic, we have updated a rapid report on saliva samples for rRT-PCR detection of SARS-CoV-2 from May 2020 (1). While our first review had included studies reporting on the identification of SARS-CoV-2 by rRT-PCR and saliva specimens as such, this update is restricted to available research on diagnostic accuracy of rRT-PCR for SARS-CoV-2 using saliva sampling as index test, compared to using upper airway sampling as reference test. The update has been actualised by the recent recommendations on test strategies made by the European Centre for Disease Control (ECDC) were saliva is considered a suitable sample for SARS-CoV-2 testing (2).

Current test strategy

Diagnostic testing of virus can be considered to be a three step process:

1. Sampling, transport and storage
2. Sample preparation
3. Analytical testing

Nasopharyngeal upper airways samples taken by health care workers, followed by laboratory viral nucleic acid extraction and detection of viral RNA by rRT-PCR analysis is characterised by high sensitivity and specificity and considered to be the gold standard of SARS-CoV-2 detection and confirmation of COVID-19 disease. The initial identification of the SARS-CoV-2 virus was based on non-commercial rRT-PCR laboratory protocols published on the World Health Organization (WHO) website (3). According to the FINDS SARS COV19 Diagnostic pipeline listing (4) there are (per 12th of October 2020) 157 commercial SARS–CoV-2 nucleic acid manual test kits, and 67 kits classified as automated lab-based, point of care (POC) or near POC labelled kits with a CE-In Vitro Diagnostic label (IVD) label marketing in Europe.

Recommended test procedures in Norway are found on the web page of the Norwegian Institute of Public health (5). According to the current Norwegian recommendations on sampling procedure for rRT-PCR, health care workers or trained staff should collect upper airway specimens. If possible, the sampling should be performed by combining a nasopharyngeal and an oral deep throat swab in the same test tube, alternatively a swab from only one of the sample sites can be collected (6).

The samples are usually transported to a Norwegian hospital or commercial diagnostic virology laboratory were in most cases the samples undergo nucleic acid extraction protocols. Analysis by rRT-PCR for detection of SARS-CoV-2 RNA are performed according to procedures determined and validated by each laboratory. The Norwegian laboratories have deployed a range of in-house and commercial nucleic acid extraction and rRT-PCR test systems, many of which work on existing platforms for automatic handling and analysis of airway samples. In addition some test-sites have deployed rapid rRT-PCR test kits working on specific analytical small scale platforms (7).

The collection of upper airway samples requires close contact between healthcare workers and patients, and poses a risk of transmission of the virus, causes discomfort for the patient and may cause bleeding, especially in patients with condition such as thrombocytopenia. Also, it might be difficult to get good upper airway samples from small children, the elderly and disabled. Saliva has a potential as a diagnostic fluid, and it may offer an edge over other biological fluids as its collection method does not require an invasive procedure and self-sampling may be an option (8).

Self-sampling of saliva

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 titres, 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 (1;8). The anticipated diagnostic window for using rRT-PCR to detect acute infection with SARS-CoV-2 in nasopharyngeal samples ranges from approximately two days following viral exposure until two weeks following symptom onset (5). Less is known about what the viral detection tells about the severity of disease and how viral load in nasopharyngeal samples relate to risk of transmission. Furthermore, it is still disputed how well viral titres in nasopharyngeal and saliva samples correlate.

Research question of this review

In this review we have focused on diagnostic accuracy expressed as sensitivity and specificity of the index test compared to the reference test. Sensitivity is a measure of the likelihood that a person with a positive reference test result, in this case rRCT – PCR result on NPS and/or OPS specimen, is identified as positive by the index test, in this case rRT-PCR on a saliva specimen. Specificity is a measure of the likelihood that a person with a negative reference test result is identified as negative by the index test. The review is restricted to clinical studies that have reported results from at least 20 paired reference and index samples taken from the same person the same day.

Methods

For the systematic database search, we retrieved RIS-files from the Stephen B Thacker CDC Library COVID-19 Research Articles Downloadable Database (CDC database) (9). This was done on August 26th 2020. The CDC database is updated daily by systematically searching more than 20 bibliographic databases and hand searching selected grey literature sources. The identified 92439 records from CDC files were uploaded to EndNote (10). We then searched within the EndNote database for relevant references using either the word saliva, salivary or sputum, keeping only references added to the database since May 2020. In addition, we inspected the INAHTA database as well as the websites of World Health Organization (WHO), European Centre for Disease Control and Prevention (ECDC), Centers for Disease Control and Prevention (CDC), Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Care Excellence (NICE), Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) and the European Network for Health technology Assessment (EUnetHTA). Reference lists of identified systematic reviews and Health Technology assessments were checked for additional references. All referenced were imported to EndNote-database and duplicates removed. The authors (VL, LKJ), independent of each other, assessed the relevance of each reference based on the title and abstract. Inclusion criteria are revealed in table 1.

Table 1 Inclusion criteria

Population	Persons tested for SARS-CoV-2. Main subgroups: 1. Screening population: Asymptomatic or symptomatic persons with unknown SARS-CoV-2 and COVID-19 status 2. Test population: Patients with known COVID-19 status upon enrolment (re-testing)
Index test	rRT-PCR on saliva specimens
Comparator/ Reference test	rRT-PCR on Nasopharyngeal (NPS) and/or oropharyngeal (OPS) specimens
Outcomes	Data to populate a 2 x 2 table reflecting true and false positives as well as true and false negatives; Differences in rRT-PCR threshold Cycle (Ct) values in paired samples
Study design	Primary studies reporting relevant data; Systematic reviews*, rapid reviews* and Health Technology Assessment reports*

*Only the most updated of these were used as additional sources of primary studies

We selected for full-text inspection studies, systematic reviews and HTA reports focusing on diagnostic accuracy using rRT-PCR SARS-CoV2 as the analytical test on saliva samples (index test) compared to NPS and/or OPS (reference test). Systematic reviews and HTA reports were only used to identify additional primary studies not detected by our search strategy.

We excluded studies that did not report on paired samples of index and reference test taken from the same person on the same day. We also excluded studies with less than 20 paired samples, and studies were data for calculation of diagnostic accuracy using a 2x2 table could not be extracted or calculated. In addition, we excluded data that were only available as Food and Drug Administration (FDA) accelerated Emergency Use Authorization (EUA) summaries without a scientific publication record.

Disagreements were solved by consensus. The full-text version of each identified reference was read by one author who extracted data, using a data-extraction form prepared for the purpose, and summarized the findings. The extracted data, relative to the full-text version of the reference, was checked by the other author. Notably, we only extracted data relevant for the research question of this report.

The true positive, true negative, false positive and false negative rate of the index test relative to the reference test, was extracted or calculated by one author and checked by the other. The diagnostic test accuracy analytical program in Review Manager 5.4 was used to calculate sensitivity and specificity and present the results as forests plots. The analysis was performed by one author (LKJ) and checked by the other (VL). As diagnostic accuracy is anticipated to be highly variable in different settings and using different approaches to sampling, sample preparation and analysis, meta-analysis to calculate a common estimate of diagnostic accuracy across the analysis was not attempted. The risk of bias in studies included for data-extraction was evaluated by the QUADAS2 protocol for diagnostic accuracy studies (11). Confidence in the estimates of diagnostic accuracy and was evaluated by GRADEpro (https://gradepro.org/).

Ongoing relevant studies were identified in the database search and an additional non-comprehensive search in clinical.trials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) using the search words (Covid or SARS) and Saliva.

Results

The database search resulted in 401 unique references to published articles and 97 preprints. In addition, three references were included from searching websites providing a total of 501 references. After screening titles and abstracts 66 studies were included. In addition, two references from our rapid review from May (1), one references from inspection of an identified systematic review (12) and one reference from an HTA report (13) were included for full-text inspection. Based on this, 70 references were read in full text, and we ended up including 23 primary clinical studies for data-extraction. The inclusion process is revealed in figure 1.

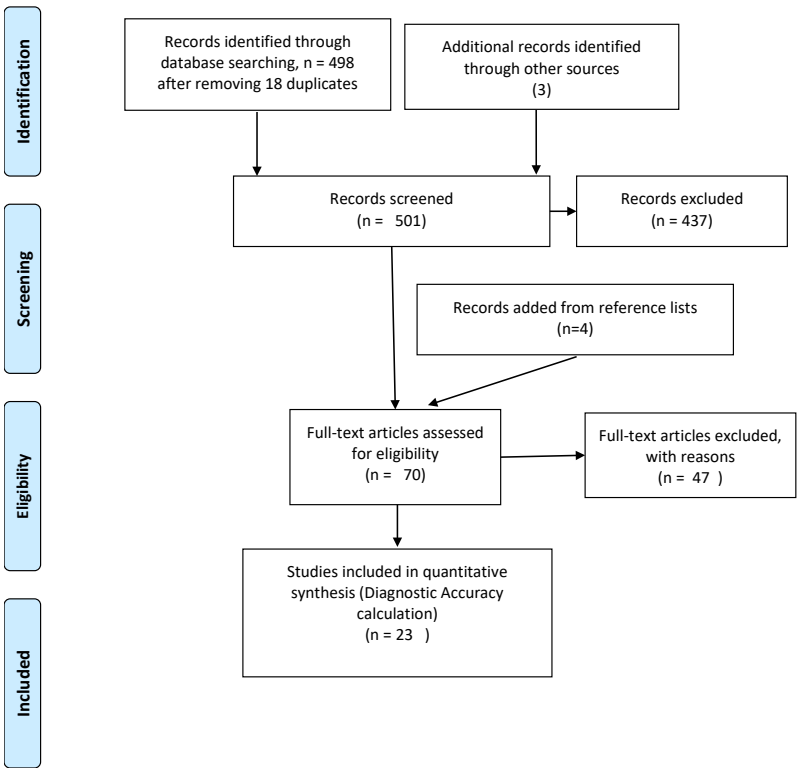

Figure 1. *Flow-chart Inclusion process, adapted from The PRISMA Statement (14).*

Characteristics of each included study, such as population, sampling techniques, sample preparation, and analytical assays are revealed in Appendix 1. The risk of

bias analysis for the included studies is provided in Appendix 2. A list of excluded studies and reasons for exclusion is provided in Appendix 3.

Diagnostic accuracy

A total of 23 studies were included for assessment of diagnostic accuracy. At the time of inclusion, 12 studies were only available as preprints, eight were letters to editors or short communications and three were peer-reviewed published scientific journal articles. Five studies were conducted in Europe, ten in USA or Canada, seven studies in Asia, and one in Australia (see appendix 1 for more details on each study).

The number of comparisons performed on paired index test and reference test samples in these studies ranged from 51 to 1939 with a total of 7065 paired samples across the included studies. In some cases, more than one paired sample was taken from the same patient/person at different time points, and in some cases the same sample was handled or compared by different approaches (15;16).

The populations tested in the included studies can be grouped according to their SARS-CoV-2 and/or COVID-19 status upon enrolment. Those with unknown SARS-CoV-2 and COVID-19 status upon enrolment were either mainly asymptomatic persons subjected to screening for COVID-19 including persons in quarantine and health care workers (HCWs) or mainly symptomatic persons suspected to have COVID-19x. Those with known SARS-CoV-2 status upon enrolment were either hospitalised patients with confirmed COVID-19, patients with mild symptoms of COVID-19 or asymptomatic persons identified through screening and re-tested. In two studies (17;18) there was two cohorts. See table 2 for details.

Table 2. *Population groups and number of paired sample comparisons across the included studies*

Population	No of comparative analysis* (Cohorts)	No of paired samples
Screening mainly asymptomatic	5 (5)	4299
Screening mainly symptomatic	12 (11)	1612
Re-testing confirmed COVID-19	10 (9)	1154
Total	27 (25**)	7065

*Some studies had performed more than one set of comparisons (15;16), **Two studies had included two different cohorts (17;18), the number of included studies is 23.

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 HCWs. In most cases, the reference test sample was collected by HCWs. The use of viral transport media, addition of viral inhibiting substances, storage conditions and the time of storage before analysis was variable. In most studies, the samples were subjected to nucleic acid extraction before analysis. However, there are also studies (see appendix 1 for details) were no extraction was used, and in one study three different extraction protocols were compared (19). In one study, a protocol with extraction was compared to a protocol without extraction (16).

The rRT-PCR test deployed by the included studies was highly variable including both commercially available tests and in-house tests. In most studies, the rRT-PCR test used for the index samples and for the reference standard were the same. In one study (15) one type of rRT-PCR test was compared with another using the same samples. A list of the included studies, patient settings, the number of true positives, false positives, false negatives and true negatives, extracted or calculated to assess diagnostic accuracy for each included study is provided in table 3.

Table 3. *Data extracted, or calculated to assess diagnostic accuracy (more details on characteristics of each study is provided in Appendix 2)*

Study ID and Country	Patient setting	No of paired samples	TP	FP	FN	TN
Akgun 2020 (20), Tyrkey	Testing of symptomatic hospitalized patients with moderate COVID-19 symptoms.	98	30	5	25	38
Azzi 2020 (21), Italy	Screening of symptomatic and asymptomatic patients and HCW in a hospital setting.	119	24	49	2	38
Becker 2020 (15), USA	Screening of symptomatic and asymptomatic persons – rRT-PCR variant 1	77	9	0	6	62
	– rRT-PCR variant 2	58	4	1	6	47
	Re-testing confirmed COVID-19 cases	24	Limited details, only sensitivity reported: 89% for NPS and 77% for saliva			
Byrne 2020 (22), UK	Testing symptomatic patients hospital setting	110	12	0	2	96
Caully 2020 (23), Canada	Screening symptomatic or asymptomatic persons	1939	34	14	22	1869
Chen 2020 (24), China	Re-testing archival samples from confirmed COVID-19 patients	58	49	0	6	3
Cheuk 2020 (25), Hong Kong	Re-testing patients with confirmed COVID-19	229	104	18	37	70
Fernández-Pittol 2020 (16), Spain	Re-testing of patients with **confirmed** primary diagnosis of COVID-19 - 1. With RNA extraction of saliva sample	51	30	1	7	13
	- 2. With heat inactivation of saliva sample	51	31	1	6	13
Griesemer 2020 (18), USA	Screening asymptomatic persons, low frequency cohort	236	6	6	0	224
	Screening symptomatic and asymptomatic persons, high frequency cohort	227	79	2	12	134
Hanson 2020 (26), USA	Screening symptomatic persons	354	78	6	5	265
Iwasaki 2020 (27), Japan	Testing symptomatic hospital admitted persons and re-testing (10) patients with confirmed COVID-19-	76	8	1	1	66
Jamal A 2020 (28) Canada	Re-testing hospitalized patients with confirmed COVID-19	53	31	5	6	11
Landry 2020 (29), USA	Screening symptomatic persons	124	28	2		89
Leung 2020 (30), Hong Kong	Re-testing hospital admitted patients with known SARS CoV-2 test results	95	38	13	7	37

Study ID and Country	Patient setting	No of paired samples	TP	FP	FN	TN
McCormick 2020 (31), USA	Screening symptomatic persons and re-testing hospitalized patients with confirmed COVID-19	156	47	1	2	105
Miller 2020 (19), USA	Re-testing samples from symptomatic and asymptomatic persons with confirmed COVID-19 status or known SARS-CoV-2 status. RNA extraction type 1	91	33	2	1	55
	RNA extraction type 2	91	33	1	1	56
	RNA extraction type 3	91	33	2	1	55
Pasomsub 2020 (32), Thailand	Screening of symptomatic persons.	200	16	2	3	179
Rao 2020 (33), Malaysia	Testing confirmed COVID-19 in quarantine center	217	73	11	76	57
Skolimowska 2020 (34), UK	Screening symptomatic persons	131	15	1	3	112
Vogels 2020 (35), USA	Re-testing paired samples (unclear setting) known to be SARS CoV-2 positive or negative (clinical validation of a kit)	67	32	3	2	30
Williams 2020 (36), Australia	Re-testing paired samples known to be positive or negative from screening population	82	33	6	1	49
Wyllie 2020 (37) USA	Re-testing paired samples from hospitalized patients with confirmed COVID-19	70	50	7	0	13
Yokota 2020 (17), Japan	Screening of asymtomatic airport travelers (quarantine cohort)	1763	4	0	1	1758
	Screening of mainly asymptomatic contacts	161	38	6	3	114

rRT-PCR = reverse transcription real time polymerase chain reaction, HCW=health care workers, 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

We analysed the extracted or calculated data (table 3) to provide forest plots revealing diagnostic accuracy expressed as sensitivity and specificity of rRT-PCR for SARS-CoV-2 detection in saliva samples compared to NPS and/or OPS specimens. A total of 27 comparative analysis was performed.

Diagnostic accuracy across all analysis

Sensitivity across all analysis ranged from 0.40 [95% CI, 0.12 to 0.74] to 1 [95% CI, 0.54 to 1.00] (see figure 2, 3 and 4 below). Notably, Becker 2020 (15) the study for which we calculated the lowest sensitivity, had compared two different rRT-PCR tests on the same samples. This could reflect that that the choice of analytical test may influence the results (see figure 3: Becker -1: sensitivity 0.60 [0.32 to 0.84] and Becker-2: sensitivity 0.40 [95% CI, 0.12 to 0.74]).

Twenty-one out of the 27 analysis gave sensitivities above 0.80, and nine gave sensitivities above 0.90. The highest sensitivity rates were seen in smallest studies with higher prevalence and re-testing. Most of these studies are associated with unclear risks of bias as information such as blinding of the laboratory personal is only exceptionally reported and risk of publication bias (more positive than negative results published) cannot be excluded. Specificity was, with one exception of 0.44 [0.33 to 0.55] of data extracted from Azzi 2020 (21), high with the remaining analysis revealing a range from 0.88 [95% CI, 0.75 to 0.96] to 1.00.

Diagnostic accuracy in screening populations

The sensitivity for screening a mainly asymptomatic population ranged from 0.61 [95% CI, 0.47 to 0.74] to 1 [95% CI, 0.54 to 1.00] and the specificity ranged from 0.95 [0.89 to 0.98] to 1.00 (figure 2). The sensitivity in the two largest screening studies including 1869 (23) and 1758 (17) paired samples of mainly asymptomatic persons was 0.61 [95% CI, 0.47 to 0.74] and 0.80 [95% CI, 0.28 to 0.97], respectively. Notably, the prevalence in this setting is low resulting in large uncertainty connected to the sensitivity data.

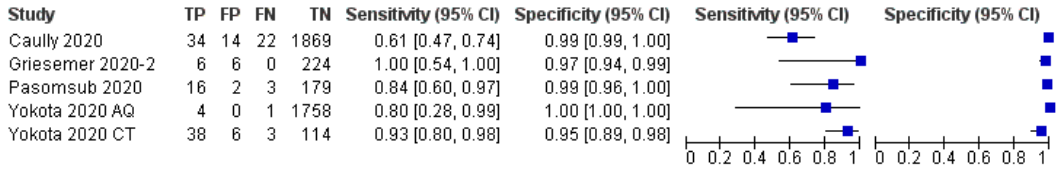

Figure 2. *Summary of diagnostic accuracy (sensitivity and specificity) in a screening setting of (mainly asymptomatic) persons with unknown SARS-CoV-2 status upon enrolment.*

Our confidence in the estimates for sensitivity of using rRT PCR on saliva samples for screening mainly asymptomatic persons to be within the range is moderate, for and specificity our confidence is high (see appendix 2). The reason for the difference in confidence is related to the variation in sensitivity as well as large confidence intervals for sensitivity in the studies. I contrast, there is less variation in specificity and narrower confidence intervals. Estimates for expected number of true positives and negatives when testing 1000 persons at prevalences of 0.5%, 3% and 10% is revealed in table 4.

Table 4 *Summary of findings for using rRT PCR on saliva samples compared to rRT PCR on NPS/OPS when screening a mainly asymptomatic population based on the range of included analysis*

Test result	Estimated number of results per 1 000 patients tested			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 0.5% Low prevalence screening	**Prevalence 3%** Medium prevalence screening	**Prevalence 10%** High prevalence screening		
True positives	3 to 5	18 to 30	61 to 100	4299 (5)	⨁⨁⨁◯ **MODERATE** [a]
False negatives	0 to 2	0 to 12	0 to 39		
True negatives	945 to 985	922 to 960	855 to 891	4299 (5)	⨁⨁⨁⨁ **HIGH**
False positives	10 to 50	10 to 48	9 to 45		

a. Variation and large confidence intervals for sensitivity

The sensitivity for screening a mainly symptomatic population ranged from 0.40 [95% CI, 0.12 to 0.74] to 97% [95% CI 0.85 to 1.00] (figure 3). Our confidence in estimates from these studies are low (see appendix 2).

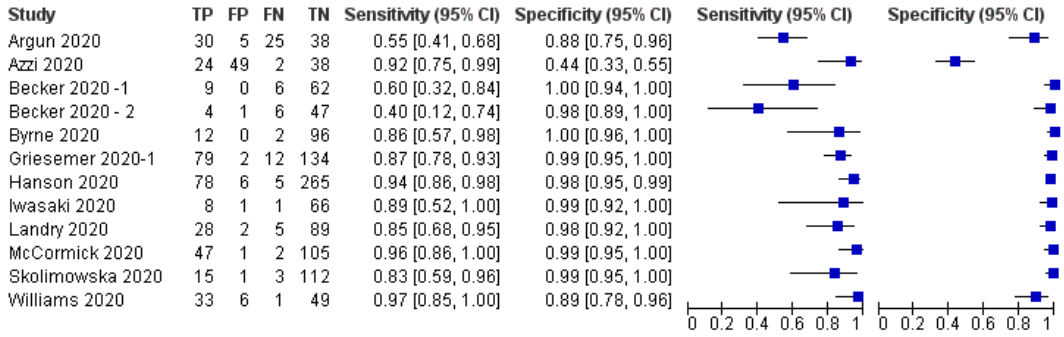

Figure 3. *Summary of diagnostic accuracy (sensitivity and specificity) in a screening setting of (mainly) symptomatic persons with unknown SARS-CoV-2 status upon enrolment.*

Diagnostic accuracy in re-testing patients with known SARS-CoV-2 status

In the analysis including paired samples from patients with known SARS-CoV-2 status up-on enrolment, sensitivity ranged from 0.49 [95% CI, 0.41 to 0.57] to 1.00 (figure 4). Specificity in these studies ranged from 0.74 [95% CI 0.60 to 0.85] and 0.96 [95% CI, 0.88 to 1.00]. Our confidence in estimates from these studies are very low (see appendix 2).

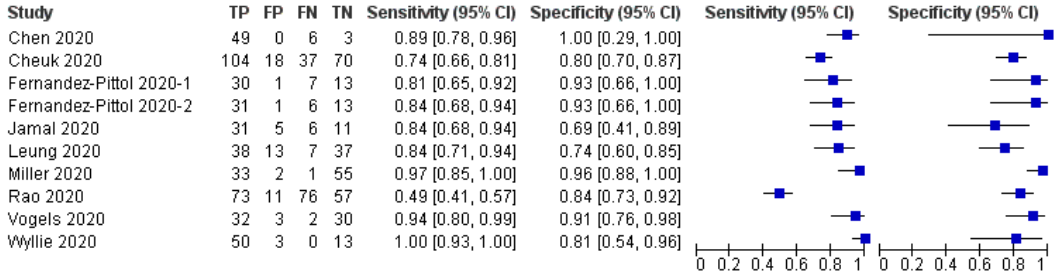

Figure 4. *Summary of diagnostic accuracy (sensitivity and specificity) of known SARS-CoV-2 or COVID-19 status upon enrolment.*

In conclusion, the overall results of our analysis indicate that the diagnostic accuracy of rRT-PCR on saliva samples, compared to NPS and/or OPS, probably is somewhat lower regarding sensitivity, but high regarding specificity. The observed variation may be related to both publication bias (more positive results published), risk of bias in the included studies, technical and clinical factors. The included studies do not allow conclusions to be made about what factor may have the largest impact on the results.

Differences in Ct values

Test results using rRT-PCR rely on multiple cycles of amplification to produce a detectable amount of product above background values. The threshold cycle value (Ct) is defined as the cycle number at which the PCR product crosses a threshold of detection, beyond this threshold positive signals are likely to be negative (noise). This threshold line is either automatically set by the software algorithm of the real-time PCR instrument, or can be manually adjusted. The Ct values are essential for quantitation since a standard curve is generated by plotting the Ct values versus the logarithmic nucleic acid concentration. A positive unknown sample will be assigned a specific Ct value and by comparison with the standard curve the concentration of viral RNA in the sample can be calculated. The same sample can give different Ct values on different RT-PCR instruments and different analytical tests. Different sampling and preparation procedures will influence the RNA concentration in the analysed sample. Therefore, the Ct values are not an absolute scale and cannot directly be used to estimate viral load in different clinical specimens. However, when comparing two samples with the same analytical test and instrument, the concentration of nucleic acid in the prepared samples can be estimated. A low Ct value indicates a higher concentration of viral RNA in the analysed sample.

For some studies the Ct values were not presented (16;21;23;32) or in some studies the mean Ct values were not given specifically for index or reference tests (15;20;22;34;36). However, in some of the included studies the mean or average Ct values for the positive samples was stated. The measurement given in table 5 are data extracted from studies that presented mean values of positive samples for both the index and reference tests.

Table 5. *Median cycle threshold value (average in all pair samples or in only positive pair samples)*

Cycle threshold value	**Sample (Target)**	Nasopharyngeal	Saliva	significance
Chen 2020 **(24)**	All (N2 target Ct)	29.3, IQR 23.3– 36.5	2.3, IQR: 29.9–38.6	p = 0.0002
Cheuk 2020 **(25)**	Positive (n/a)	mean diff 0.26 (range: 12.63 to −14.74) higher in NPS		Pearson's R 0.579
Hanson 2020 **(26)**	Positive (TMA assay)	27.0 (range 19.7–32.7)	28.2 (range 18.3–7.5)	n/a
Iwasaki 2020 **(27)**	n/a (n/a)	26.5 ± 8.1	30.6 ± 4.6	p =0.206
Jamal 2020 **(28)**	Positive (N gene Ct)	32 (IQR 28-35)	27 (IQR 28-35)	p =0.6

Cycle threshold value	Sample (Target)	Nasopharyngeal	Saliva	significance
Landry 2020 **(29)**	Positive (N1 target Ct)	34 (IQR 33-38)	38 (IQR 37-38)	p = 0.0331
Leung 2020 **(30)**	Positive (N gene Ct)	Range 33.7 to 37.9	Range 23.9 to 35.9	p> .05
McCormick 2020 **(31)**	All (N2 gene Ct)	26.70 ± 7.61	30.49 ± 9.67	p = 0.73
Miller 2020 **(19)**	Positive (N1 target Ct)	34.5 (SD 5.0)	33.2 (SD 3.9)	n/a
Rao 2020 **(33)**	Positive (E-gene Ct)	32.2 ± 3.5	29 ± 4.5	n/a
Vogels 2020 **(35)**	Positive (N1 gene Ct)	higher using SalivaDirect (median difference of 3.3 Ct)		p < 0.01
Yokota 2020 **(17)**	Six pair positive on saliva and negative on NPS (Ct 33.7 to 37.2)			κ=0.87

IQR =inter quartile range, n/a not available, κ=Kendall's coefficient

Based on the extracted results, most of the studies revealed the lowest Ct values, indicative of higher SARS-Cov-2 nucleic acid concentrations in the reference test samples. However, this was not the case for all (see table 3) and no firm conclusions on SARS-Cov-2 nucleic acid concentration in saliva samples compared to upper airway samples can be made based on the included studies.

Ongoing studies

Based on the database search and a non-comprehensive search in the WHO ICTRP database and Clinical Trials.gov we screened 109 records of registered ongoing studies and identified seven of relevance for the research question of this review. Study ID and details are revealed in table 6. As the search was not comprehensive, we cannot exclude that additional relevant ongoing trials exist. The results reveals that several studies with planned comparisons on saliva as index test will be available in the future. No published results from the studies were identified.

Table 6. Registered ongoing clinical trials

Study ID, Study Country	Status/ Final completion date	Population	N planned	Index	Reference	Main outcomes
NCT04424446, USA	Ongoing-recruiting, start July 2020/ June 2021	NIH staff undergoing standard NIH COVID-19 screening	5000	Saliva RT PCR	Nasal swab RT-PCR	Saliva SARS-CoV-2 RT-PCR test results; Saliva and nasal swab SARS-CoV-2 RT-PCR test results
NCT04386551, France	Ongoing-recruiting, start July 2020/December 2020	Adult ambulatory patients screened for SARS Cov 19	225	Saliva RT PCR	NPS RT PCR	Detection of SARS-CoV-2 RNA in the saliva sample; Concordance between the saliva and nasopharyngeal sample SARS-CoV-2 RT-PCR results

Study ID, Study Country	Status/ Final completion date	Population	N planned	Index	Reference	Main outcomes
NCT04517682, USA	Ongoing, recruiting start May 21. 2020, Completion December 2020)	Symptomatic or high risk (unknown and known)	300 planned	Saliva RT PCR	NPS RT PCR	Detection of COVID-19 SARs-CoV-2 in saliva samples versus nasopharyngeal samples
NCT04468217, Chile	Ongoing, start June 2020/ December 2020	Subjects with positive test to SARS-COV2 and Staff with negative test to SARS-COV2 (employees of critical service companies)/	150 planned	Saliva; Oropharyngeal swab, Buccal swab, and nasal swab RT-PCR	NPS RT-PCR	Evaluation of samples in AAA-Safe proprietary transport medium, alternative method of extraction and qPCR
NCT04531501, USA	Recruiting, start June 2020, September 2020	Patient suspected to have COVID-19; Patients tested positive for COVID-19	400 planned	Chronomic saliva sample and test workflow; Chronomic NPS sample and test workflow	NHS Sample and test workflow	Test result (positive/negative/ indeterminate)
NCT04578509, France	Recruiting, start October 2020/ April 2021	Ambulatory adults or children attending screeing	2700 planned	Saliva sample RT-PCR	NPS RT PCR	Positivity of samples
NCT04561102, USA	Enrolling, start September 2020/ December 2020	Asymptomatic, adults	2500 planned	Saliva COVID-Seq Test	Nasal swab, EUA Covid test	Diagnostic accuracy (Positive and Negative predictive values of index/comparator)

N= Number of planned participants to include

Discussion and conclusion

In this rapid review of diagnostic accuracy of rRT-PCR testing for SARS-CoV-2 in saliva samples compared to NPS and/or OPS, we included 23 original studies. Using data from the studies, we performed 27 sets of comparative analysis of 7065 paired samples. Based on our findings, the sensitivity of rRT-PCR on saliva as a diagnostic specimen is variable, but in most instances (21 out of 27 analysis) 80% or more compared to NPS or OPS. Specificity was above 88% in 21 out of 27 analysis.

Our review is based on systematic screening of all records in the CDC COVID-19 database concerning SARS-CoV-2/COVID-19 and saliva. To avoid risk of bias in the inclusion process the screening, eligibility assessments, and risk of bias assessments (QUADAS-2 (11)) were performed independently by both authors. Data extraction was performed by one author using a predefined extraction template. All extracted data was checked by the other author. We have reasonable confidence in the completeness and accuracy of the findings up until the search date (August 26th 2020). We also checked for registered ongoing studies and found no results from these published per November 12th, 2020. However, as the review is produced under strict timelines with limited external peer review, we cannot exclude that we have missed some studies and that there might be flaws in our interpretation of the extracted data.

In our first review from May 2020 (1), only two studies (36;38) were identified from which we could extract data to calculate diagnostic accuracy, implicating a considerable rise in evidence in only 4 months. One of the studies included in our first review (38) has been excluded from this review. The reason for this is that it is an FDA EUA assay application not published in other formats. Information on diagnostic accuracy in FDA EUA assays can be found at the FDA web site (38). The clinical evaluation documented on these web pages are in line with the evaluation reported by Miller 2020 (19), as they are generally small studies were samples with known SARS CoV-2 status are re-tested in pairs. Inclusion of further documentation of this kind would not have changed the conclusions of this report. Furthermore, we are uncertain to which extent the FDA EUA assays are available in Norway. However, for those interested in performance of a particular procedure or kit, it might be of value to also search for information in these sources. We have also excluded studies that only reported data to calculate sensitivity (see list of excluded studies). Other

rapid reviews, including those checked for references (12;13) updated in June and late May, respectively have included more broadly. This could be because, at the time these were produced, the number of studies were both sensitivity and specificity could be calculated was restricted to four studies with few participants. None of the studies we excluded were large screening studies and most were early clinical validations. Mainly these studies report sensitivities in the upper level, however due to in-particular risk of publication bias associated with these small studies, their inclusion would not have impacted our overall conclusion. Rather there is a need for larger studies investigating the use of a saliva-based screening or testing-strategy with pre-validated procedures. At least three ongoing clinical studies with a high N will be able to address this in the future (see table 5).

We have not calculated predictive values of test results. The predictive value of a test result will depend on the diagnostic accuracy and 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 (39). Notable, this could be of relevance if saliva diagnostics should be used in a screening setting with relative low numbers of SARS-CoV-2 infected people. Lower sensitivity will influence the predictive value of the test. However, based on our assessment we do not know if the reference test (NPS) or saliva provides the most clinically relevant number of test positives or negatives. If indeed, as some argue, rRT-PCR on NPS provides many clinically irrelevant positives (persons that might have been positives, but are no longer contagious), saliva with a lower sensitivity might be more clinically relevant with regard to detection of those that should be isolated. However, our review does not provide results to conclude regarding this.

We found variations in diagnostic accuracy. The observed variations may theoretically be associated with all process steps ranging from differences in population, sampling, sample preparation to analytical rRT-PCR assays and instruments. We did observe high sensitivity in several small studies and in studies with high prevalence or known COVID-19 status. However, as we cannot exclude that this is relatable to risk of bias, we cannot make any generalizable conclusion about prevalence or testing of symptomatic versus asymptomatic. The result of one study (15), investigating the influence of using different rRT-PCR assays and two studies comparing different extraction procedures (19), or no extraction versus heat inactivation extraction (16), illustrates that any test needs to be carefully validated with regard to all steps. However, based on the included studies we cannot make generalizable conclusions with regard to factors related to extraction that may have influenced the variation. Differences in sampling techniques were not studied in any of the included studies, and since information on the sampling techniques was limited, we are not able make generalizable conclusions on how variations in sampling may have influenced the outcomes.

Based on our findings, the sensitivity of saliva as a diagnostic specimen is variable, but in most instances (21 out of 27 analysis) 80% or more compared to NPS or OPS. The specificity is probably higher (88% or more in 26 out of 27 analysis,). These findings could be relevant in face of shortages of both swabs and personal protective equipment (36). Another advantage is the safety of those performing sample collection. By using saliva as a collection sample HCWs will be safe from the transmission of disease during sampling. A third advantage is sampling comfortability. Saliva collection is quite comfortable for patients as well as being easy and non-invasive. However, one needs to assure that the sample container does not represent a safety risk for laboratory personnel.

However, it should be noted that changing test-procedures requires considering several factors not assessed in this review such as most relevant setting for a potential change, availability of test tubes for saliva self-sampling, compatibility of test tubes with established sample transport, storage procedures, automated laboratory procedures and risks of contamination during sample handling. Before a recommendation can be made to change procedures or implement a new test-strategy, these factors need to be assessed. In addition, each laboratory needs to perform its own validation of any new specimen and change in procedures. It should be noted that this may be substantial work and require substantial costs.

We have not assessed diagnostic accuracy of self-sampling by alternative procedures such as OPS compared to HCW sampling. In some circumstances, this might be equally relevant as saliva self-sampling. In a recently collaborative assessment by the European Network of Health Technology Assessment (EUnetHTA), the diagnostic accuracy of nucleic acid based tests has been assessed (40). In the protocol of this assessment it is stated that sampling techniques if possible, will be subjected to sub-group analysis. During the process of writing this review, we contacted the authors, who could inform that they had not identified studies that allowed sub-group analysis based on self-sampling compared to HCW sampled specimens (personal communication). This is also stated in the publication. In conclusion, there are probably no studies currently available to answer questions regarding self-sampling versus HCW sampling.

It should be noted that other tests for SARS-CoV-2 than rRT-PCR have been developed and are under development. These tests can broadly be grouped into three categories, those aimed at:

- pathogen (virus) RNA detection (acute infection diagnostic) using isothermal procedures such as loop mediated isothermal amplification (LAMP)
- pathogen (virus) antigen detection (acute infection diagnostic) such as antigen lateral flow (LFA) tests
- detection of immune response to the pathogen (past exposure).

The alternatives to rRT-PCR such as LAMP and LFA have as far as we know, mainly been validated using nasopharyngeal sample specimens, and there are still limited studies available to show how these tests perform with saliva as the specimen. The benefit of LAMP and LFA is that they may be deployed as point of care tests. The inclusion of studies to assess the diagnostic accuracy of these tests was out of the scope for this review, and we did exclude some studies that could have been relevant to answer research questions related to these tests. Diagnostic accuracy of nucleic acid based tests including LAMP has recently been in depth assessed (40). We are not aware of any systematic review or recent HTA report on LFA tests, but according to the most recent update of NIPHs web site, several studies have been published revealing lower sensitivity, but comparable specificity of LFA compared to rRT-PCR on upper airway samples (7).

The benefit of using pathogen detection tests 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 (41).

In conclusion, the results of our analysis indicate that diagnostic accuracy of rRT-PCR on saliva samples compared to NPS and/or OPS probably is slightly lower regarding sensitivity, but high regarding specificity. Notably, variation is expected and may be related to both technical and clinical factors, risk of bias in the included studies, publication bias (more positive results published), and to low prevalence in the largest studies. The included studies do not allow conclusions to be made about what factor may have the largest impact on the results. The results should be considered with caution as further studies may change the estimates. These findings are relevant in setting with a great need for exploring test strategies in testing SARS-CoV-2.

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Appendix 1. Characteristics of included studies

Notably, the table only reveals characteristics extracted as relevant for the research question of this review. Additional information and outcomes are reported in most of the studies.

Study ID [Type of publication]	No patients included/ No paired samples*	Population	Sampling	Sample preparation	Analytical assay	Outcome reported relevant for this review
Akgun 2020, Turkey [Preprint]	200/ 200 at day 0, 56 at day 5	**Setting:** Hospitalised with moderate Covid-19 symptoms; **Age:** 54.9 (+/- 16.1); **Sex:** 106/94 (53% Male)	**Index:** Saliva self-collection instructed drooling technique, 1ml into Falcon tubes with viral transport medium (Innomed VTM001). Samples refrigerated within 1 hour. **Reference:** NPS dacron swab and OP cotton taken by HCW, refrigerated within 1h.	**Index:** No extraction **Reference:** As for index test	**Index:** rRT PCR, ORF1ab and N gene, Direct Detection of SARS-CoV-2 Detection Kit (Coyote Bioscience Co., Ltd) **Reference:** As for index test	Test concordance
Azzi 2020b, Italy [Letter to editor]	122 / 114	**Setting:** Hospitalized patients or HCW mixed symptomatic and asymptomatic; **Age:** Mean 53 +/- 19.8; **Sex:** Male female ratio 1:2	**Index:** Saliva self-collection (in the morning) 1ml, drooling technique **Reference:** NPS taken by HCW, refrigerated within 1h.	**Index:** RNA extraction by QIAmp Viral RNA mini kit (Qiagen) **Reference:** RNA extraction by Abbott mSample Preparation System and automated extraction (Extraction m2000SP, Abbott Molecular).	**Index:** One step rRT-PCR Luna® Universal qPCR Master Mix (New England BioLab), QuantStudio 5 Real-Time PCR System (ThermoFisher Scientific). **Reference:** GeneFinderTM COVID19 Plus RealAmp PCR kit (ELITechGroup), one-step rRT-PCR	Diagnostic accuracy of index compared to reference

Study ID [Type of publication]	No patients included/ No paired samples*	Population	Sampling	Sample preparation	Analytical assay	Outcome reported relevant for this review
Becker 2020, USA [Preprint]	88 Diagnostic Cohort (DC) and 24 Covalescent Cohort (CC)/ DC, 77 and 58 two different analytical assays; CC, 24	**Setting:** DC Community setting mixed symptomatic and asymptomatic, CC confirmed cases recalled **Age:** ND **Sex:** ND	**Index:** Saliva self-collection using the Oragene OM-505 and OGD-610 kit (DNAgenotek) **Reference:** NPS in Viral Transport Media (no further details)	**Index:** RNA extraction, MagMax Viral/Pathogen RNA purification kit (ThermoFisher CAT: A42352) **Reference:** As for Index test	**Index:** 1. TaqPath Multiplex RT-PCR COVID-19 Kit (Thermo), Quantstudio 7 qRT-PCR instrument (Thermo) and 2. PrimerDesign COVID-19 assay on Roche LightCycler 480 II or Thermofisher Quantstudio 7 **Reference:** As for index	Diagnostic accuracy of index compared to reference, One rRT-PCR test compared to another (TaqPath vs PrimerDesign COVID-19 assay)
Byrne 2020, UK [Preprint]	110/ 110 at Day 0), 14 at Day2 and 6 at Day 7 (Day 2 and 7, only available from positive hospitalised participants)	**Setting:** Patients with Covid 19 symptoms; **Age:** >18 years **Sex:** 45% male	**Index:** Saliva, self-collection under instruction (except one using swab) into a funnel in sterile cryotube collection tube (SARSTEDT, Germany). Transported on ice and frozen at -80oC until processing. **Reference:** Combined nasal and throat (NT) swabs (Copan, Italy) were taken by a research nurse delegated to the study.	**Index:** RNA extraction, QIAamp Viral RNA Mini Kit (Qiagen, Germany) with an internal extraction control incorporated at the lysis stage (Genesig, UK). Stored on ice during PCR setup. **Reference:** As for index test	**Index:** rRT-PCR Gnesig® Real-Time Coronavirus COVID-19 PCR assay (Genesig, UK) in a RGQ 6000 thermocycler (Qiagen, Germany). **Reference:** As for index test	Proportion of positive and negative samples

Study ID [Type of publication]	No patients included/ No paired samples*	Population	Sampling	Sample preparation	Analytical assay	Outcome reported relevant for this review
Caulley 2020, Canada [Brief research report]	1969/ 1939	**Setting:** Consecutive, screening at one test Centre, mixed symptomatic asymptomatic **Age:** >18 years **Sex:** ND	**Index:** Saliva, self-collection under instruction according to kit instructions (OMNIgene•ORAL, OM- 505 [DNA Genotek]). **Reference:** NPS (n=272) or OS collected by HCWs, transported in universal viral transport medium.	**Index:** Total nucleic acid extraction, STARMag Universal cartridge kit (Seegene) on a Nimbus (Seegene) or Starlet (Seegene) extractor. **Reference:** As for index test	**Index:** rRT-PCR Allplex 2019-nCoV assay (Seegene) to detect the presence of nucleoprotein (N), envelope (E) and ribonucleic acid (RNA)-dependent RNA polymerase (RdRp) gene targets of SARS-CoV-2. **Refrerence:** As for index test	Diagnostic accuracy index compared to reference
Chen 2020, China [Journal article]	ND/ 58	**Setting:** Archived specimens collected from COVID-19 positive inpatients **Age:** Median 38 years, range 31-52 **Sex:** 48.3% male	**Index:** Saliva, self-collection morning spit, 1ml in a sterile bottle. 2 ml viral transport media was immediately added. **Reference:** NPS -HCW collected with flocked swab, immersed in 2 mL of viral transport medium	**Index:** ND **Reference:** ND	**Index:** SARS-CoV-2 RNA dependent RNA polymerase/Helicase (RdRp/Hel) real-time RT–PCR assay or Xpert Xpress SARS-CoV-2 assay (Cepheid, Sunnyvale, CA). GeneXpert XVI system (Cepheid, Sunnyvale, CA). **Reference:** As for index test	Diagnostic performance index compared to reference Ct values in paired samples
Cheuk 2020, Hong Kong, China [Online publication]	95/ 229 three time points after symptom onset:	**Setting:** Hospitalised COVID-19 patients **Age:** Median 36 years, range 4-	**Index:** Saliva, self-collection morning saliva into a sterile container, instructed by text and video	**Index:** Total nucleic acid extraction was performed using MagNA Pure LC	**Index:** r RT-PCR LightMix® Modular SARS and Wuhan CoV E-gene kit (TIB-MOLBIOL, Berlin, Germany)	Positivity rates within 7 days of symptom onset and more than 7

Study ID [Type of publication]	No patients included/ No paired samples*	Population	Sampling	Sample preparation	Analytical assay	Outcome reported relevant for this review
	161 from 44 patients at day 1; 63 from 34 patients within 7 days; 98 from 29 patients after one week	92 (> 18 =88) **Sex:** 60% male	(Posterior oropharyngeal saliva (POPS)). In-house patients, Iml viral transport medium /VTM) added, outpatients transported neat and VTM added if needed. Processed within 24 hours of collection. **Reference:** NPS -HCW	2.0 (Roche, Switzerland) or MagNA Pure 96 (Roche, Switzerland). **Reference:** As for index test	on a Cobas z480 real-time PCR analyzer (Roche Diagnostics, Mannheim, Germany). **Reference:** As for index test	days of symptom onset. Ct values in paired samples
Fernández-Pittol 2020, Spain [Preprint]	ND/51	**Setting:** Hospital emergency, patients with confirmed Covid-19 **Age:** ND **Sex:** ND	**Index:** Saliva self-collection under HCW instruction. Only samples of 0.5ml or more were included. Stored at -80 °C. **Reference:** NPS or OPS, HCW collected collected in tube with 2ml lysis buffer.	**Index:** 1. RNA extraction with MagNA Pure Compact RNA Isolation Kit, on MagNA Pure Compact Instrument (Roche, Basel, Switzerland) 2. Heat inactivation 15 min at 95 °C. **Reference:** Extraction as for Index 1.	**Index:** One step real time RT-PCR was performed using the RNA Process Control Kit (Roche, Basel, Switzerland) **Reference:** As for index	Diagnostic performance
Griesemer 2020, USA [Preprint]	Total of 463 individuals: Low frequency	**Setting:** Screening of symptomatic. **Age:** LF, range 3-105 years	**Index:** Saliva self-collection in 50 ml conical tubes. Specimens were held	**Index:** Total nucleic acid extraction bioMerieux easyMAG® or	**Index:** rRT-PCR, CDC 2019 nCoV Diagnostic Panel. **Reference:** Same as index	Diagnostic accuracy

Study ID [Type of publication]	No patients included/ No paired samples*	Population	Sampling	Sample preparation	Analytical assay	Outcome reported relevant for this review
	cohort (LF) 236; High frequency cohort (HF) 227 / LF 236; HF 227	(< 18 =17, > 65= 16, Unknown 2) HF, range 14-77 years (<18 =2, >65 = 6, Unknown=11); **Sex:** LF, 47% males; HF, 60% males	at 4°C from collection to processing. Testing was performed within 24-72 hours. Excessive mucus was digested Snap n' Digest 124 (Scientific Device Laboratory, Des Plaines, IL) **Reference:** NPS containing 1 ml Molecular Transport media Specimens were held at 4°C processing. All testing performed within 24-72 hours.	EMAG® 128 (bioMerieux Inc, Durham, NC). **Reference:** Same as index		
Hanson 2020, USA [Preprint]	368/ 354	**Setting:** Screening of symptomatic adults **Age:** Mean 35 years, range 18-75 **Sex:** 53% males	**Index:** Saliva self-collection under instruction; 1ml spit collected in a 50 ml Falcon tube. Neat transported at 4 °C. Stored refrigerated and analysed within 5 days. Samples were diluted 1:1 with ARUP Laboratories universal transport media.	**Index:** No details on extraction, possibly no extraction. **Reference:** Same as index	**Index:** rRT-PCR Hologic Aptima SARS -CoV -2 transcription mediated amplification (TMA) assay (Hologic Inc.) using the Hologic Panther Fusion (Hologic Inc.) platform. **Reference:** Same as index	Test performance Ct values in paired samples

Study ID [Type of publication]	No patients included/ No paired samples*	Population	Sampling	Sample preparation	Analytical assay	Outcome reported relevant for this review
			Reference: NPS HCW collected with flocked mini-tip or foam swabs (Puritan Medical Products) placed in 3 mL of sterile 1x phosphate-buffered saline (ARUP Laboratories)			
Iwasaki 2020, USA	76/ 66	**Setting:** Hospital admitted patients, 10 patients with confirmed COVID-19 and 66 with suspected COVID-19 **Age:** Median 69 years, range 30-97 **Sex:** ND	**Index:** Saliva self-collection under instruction. Spit was sampled into a sterile PP Screw cup 50 (ASIAKIZAI Co., Tokyo, Japan). **Reference**: NPS, HCW collected using FLOQSwabs (COPAN, Murrieta, CA, USA). The swabs were placed in saline.	**Index:** Total RNA extraction by QIAamp Viral RNA Mini Kit (QIAGEN, Hilden, Germany). **Reference:** Same as index	**Index:** rRT-PCR Detection of Pathogen 2019-nCoV Ver.2.9.1. one-Step Real-Time RT-PCR Master Mixes (Thermo Fisher Scientific, Waltham, USA), analysed on StepOnePlus Real Time PCR System (Thermo Fisher Scientific). **Reference:** Same as index	Agreement between NPS and saliva samples Ct values in paired samples
Jamal 2020, Canada [Preprint]	53/ 53	**Setting:** Hospitalised patients with confirmed Covid-19 **Age:** median age 63 years, range 27-106 **Sex:** 60% male	**Index:** Saliva sampling by HCW collecting spit into a saliva contianer. 2.5ml. **Reference:** NPS, No further data	**Index:** ND **Reference:** ND	**Index:** rRT-PCR with Allplex™ 2019-nCoV Assay(100T). **Reference:** Same as index	Test performance Ct values in paired samples

Study ID [Type of publication]	No patients included/ No paired samples*	Population	Sampling	Sample preparation	Analytical assay	Outcome reported relevant for this review
Landry 2020, USA [Journal article]	ND (only NPS positive samples)/ 124	**Setting:** Screening of symptomatic outpatients, (re -) testing of NPS positive samples **Age:** ND **Sex:** ND	**Index:** Saliva self-collection of spit into a sterile container. Samples were kept in a cooler and delivered within 2 h to laboratory and frozen at -70 degrees C. Samples positive for the first NPS were thawed and tested within 2 weeks. **Reference:** NPS, HCW collected	**Index:** Viscous saliva specimens were treated with sputasol (Thermo Scientific). Nucleic acid was extracted using EasyMag (bioMerieux, Durham, NC). **Reference:** Same as index	**Index:** rRT-PCR a EUA developed assay. Cycle threshold (Ct) values were recorded for N1, N2 andRNAse P for each sample. **Reference:** Same as index	Test concordance Ct values in paired samples
Leung 2020, Hong Kong, China [Journal article]	62/ 95	**Setting:** Hospitalised (29 confirmed Covid-19 cases, 33 negative cases with airway symptoms) **Age:** Mean: 42.0 ± 17.1 years **Sex:** 42% male	**Index:** Saliva self-collection under instruction (Deep throat saliva) into a sterile sputum container, sent immediately to the laboratory. In house viral transport medium added in laboratory. **Reference:** NPS, HCW collected using flocked swabs placed in a container with 3ml	**Index:** Total nucleic acid extraction with MagMAX (Applied Biosystems, Foster city) or a viral RNA isolation kit (Applied Biosystems). **Reference:** As for index	**Index:** rRT-PCR lightMix Modular SARS-CoV (COVID19) E-gene detection kit (TIB Molbiol, Berlin, Germany). **Reference:** As for index	Test concordance Ct values in paired samples

Study ID [Type of publication]	No patients included/ No paired samples*	Population	Sampling	Sample preparation	Analytical assay	Outcome reported relevant for this review
			viral transport medium.			
McCormick-Baw 2020, USA [Letter to editor]	ND/156	**Setting:** Symptomatic suspected cases and hospitalized COVID-19 confirmed patients **Age:** Mean 47.8 years **Sex:** 90 Males (58%)	**Index:** Saliva, self-collection under instruction. Held at 2°C to 8°C for up to 12 h prior to testing. **Reference:** NPS HCW collected	**Index:** No extraction- **Reference:** As for index	**Index** rRT-PCR (Cepheid Xpert Xpress SARS-CoV-2 (Sunnyvale, CA) Xpert Xpress SARS-CoV-2 PCR test) **Reference:** As for index	Test performance Ct values in paired samples
Miller 2020, USA [Preprint]	ND/91	**Setting:** Mixed symptomatic and asymptomic confirmed or tested with NPC. **Age:** >18 **Sex:** ND	**Index:** Saliva self-collected. **Reference:** NPS, HCW collected	**Index:** Three RNA extraction methods were evaluated: MagMAX™ Viral/Pathogen Nucleic Acid Isolation Kit (ThermoFisher Scientific); Maxwell® HT Viral TNA Kit (Promega Corporation); Maxwell RSC TNA Viral Kit (Promega Corporation). **Reference:** As for index	**Index:** rRT-PCR targeting SARS-CoV-2 nucleocapsid (N) gene (N1 and N2), CFX384 Touch Real-Time PCR Detection System with CFX Manager software version 3.1 (Bio-Rad Laboratories). **Reference:** As for index	Test performace Ct values in paired samples (Clincal validation for FDA, EUA)
Pasomsub 2020, Thailand [Preprint]	**200/200**	**Setting:** Screening of symptomatic adults, with a travel history from an endemic area or those with a history of contact	**Index:** Saliva self-collection, void of coughing in a sputum collection container containing Universal Transport Medium™	**Index:** Automated Viral RNA extraction using using MagDEA® Dx reagents (Precision System Science, Chiba, Japan).	**Index:** rRT-PCR using a SARS-CoV-2 Nucleic Acid Diagnostic Kit (Sansure Changsha, China), approved by the China Food and	Diagnostic accuracy

Study ID [Type of publication]	No patients included/ No paired samples*	Population	Sampling	Sample preparation	Analytical assay	Outcome reported relevant for this review
		with a Covid-19 confirmed or suspected person **Age:** 36 (28-48) years **Sex:** 69 (34.5%) male	(UTM®; COPAN, Brescia, Italy). **Reference:** NPS and OS**,** HCW collected with Copan FLOQSwabs® inserted in a sterile tube containing UTM®	**Reference:** As for index test.	Drug Administration **Reference:** As for index test	
Rao 2020, Malaysia [Accepted Preprint]	217/217	**Setting:** Confirmed SARS-CoV-2 positives in quarantine sampled at day 8-10 **Age:** 27(18-36) **Sex:** All male	**Index:** Saliva self-collection deep throat morning saliva under instruction. Stored at room temperature until laboratory processing within 5 hours **Reference:** NPS collected by HCW using sterile flocked swab placed in a sterile tube containing Viral transport medium (VTM).	**Index:** Total nucleic acid extraction, MagNA Pure 96 system with the MagNA Pure 96 DNA and Viral NA Small Volume extraction kit (Roche Diagnositc GmBH, Germany) **Reference:** As for index	**Index:** One-step RT-PCR of Real-Q 2019 nCoV detection kit (Biosewoom, Inc, South Korea) **Reference:** As for index	Test concordance Ct values in paired samples
Skolimowska 2020, UK [Letter to editor]	132/ 131	**Setting:** Screening of symptomatic HCWs **Age:** 39 years (interquartile range 30-51 years **Sex:** 89/132 (67.4%) female	**Index:** Saliva self-collection, spit into a container, without preceding coughing **Reference:** NPS and OPS com-	**Index:** 4.3ml Roche cobas® PCR medium added in laboratory **Reference:** ND	**Index:** Roche, AusDiagnostics, ThermoFisher and Abbott (no further details) **Reference:** As for index test	Diagnostic accuracy

Study ID [Type of publication]	No patients included/ No paired samples*	Population	Sampling	Sample preparation	Analytical assay	Outcome reported relevant for this review
			bined, HCW collected in 4.3ml Roche cobas® PCR medium			
Vogels 2020, USA [Preprint]	70/ 67	**Setting:** Re-testing samples from hospitalised patients and HCWs, mixed symptomatic and asymptomatic. **Age:** ND **Sex:** ND	**Index:** Saliva sampling, (SalivaDirect protocol) -further details not provided. **Reference:** NPS further details not provided.	**Index:** No extraction (SalivaDirect protocol) **Reference:** Total nucleic extraction (MagMax, ThemoFisher combo kit)	**Index:** ThermoFisher Scientific proteinase K, ThermoFisher Scientific TaqPath RT-PCR kit, a multiplex RT-PCR diagnostic assay targeting 3 regions of the SARS-CoV-2 genome and Bio-Rad CFX96 instrument. **Reference:** The ThermoFisher Scientific TaqPath COVID-19 combo kit, multiplex RT-PCR targeting 3 regions of the SARS-CoV-2 genome on the ABI 7500 Fast Dx instrument.	Test performance Ct values in paired samples (Clinical validation of a kit)

Study ID [Type of publication]	No patients included/ No paired samples*	Population	Sampling	Sample preparation	Analytical assay	Outcome reported relevant for this review
Williams 2020, Australia [Letter to editor]	622/ 522 paired samples collected, 39 NPS positive samples and 50 NPS negative samples retested as paired samples	**Setting:** Ambulatory patients presenting to a dedicated COVID-19 screening clinic (mixed symtomatic/asymptomatic) **Age:** ND **Sex:** ND	**Index:** Saliva self-collection under instruction, spit 1 to 2 ml of into a 25- ml collection pot. In the laboratory, 1:1 ratio of liquid Amies medium was added. Median time from sample collection to addition of medium was 180 min (range, 55 to 537 min). **Reference:** NPS HCW collected	**Index:** Nucleic acid extraction on the Qiagen EZ1 platform (Qiagen, Hilden, Germany). **Reference:** As for index test	**Index:** rRT-PCR using a multiplex RT-PCR test for SARS-CoV-2 and other seasonal coronaviruses (coronavirus typing [8-well] assay; AusDiagnostics, Mascot, Australia). **Reference:** As for index	Diagnostic accuracy (?)
Wyllie 2020 b [Letter to the Editor]	202/ 70	**Setting**: Hospitalized confirmed Covid-19 patients, retested **Age:** Range: 13-91 (mean =61.4) **Sex:** 56% male	**Index:** Saliva self-collection under instruction, spit into a sterile urine cup. Samples were stored at room temperature and tested within 12 hours of sample collection. A stabilizing solution was not added to the saliva. **Reference:** NPS HCW collected added to BD universal vital transport medium	**Index:** Proteinase K was added to viscous saliva samples. Total nucleic acid extraction using MagMAX Viral/Pathogen Nucleic Acid Isolation kit (ThermoFisher Scientific). **Reference:** As for index test	**Index:** US CDC real-time RT-qPCR primer/probe sets for 2019-nCoV_N1 and 2019-nCoV_N2 and the human RNase P (RP) as an extraction control. (Positives: CT <38). **Reference:** As for index test	Test poitivity (sensitivity)

Study ID [Type of publication]	No patients included/ No paired samples*	Population	Sampling	Sample preparation	Analytical assay	Outcome reported relevant for this review
Yokota 2020, AQ [Preprint]	1,924 included / Two Cohorts: Asymptomatic travellers (AT), 1763 paired samples; Asymptomatic contacts (AC), 161 paired samples;	**Setting:** AT: Screening of asymtomatic travellers; CT: Contact screening **Age:** AT, Median [IQR] 33.5 [22.6, 47.4]; AC, Median [IQR]44.9 [29.8, 66.4]; HCW, average 37.6, range 22-44 **Sex:** AT:832 (47.2 %) female; AC: 26 (16.1 %) female;	**Index:** Self collectedc saliva. **Reference:** NPS or OPS HCW collected	**Index:** RNA extraction using QIAsymphony DSP Virus/Pathogen kit and QIAamp Viral RNA Mini Kit (QIAGEN, Hilden, Germany). **Reference:** As for index test	**Index:** rRT-PCR One step qRT-PCR according to The Japanese National Insitute of Infecious Disease protocol, THUNDERBIRD® Probe One-step qRT-PCR Kit (TOYOBO, Osaka, Japan) and 7500 Real-time PCR Systems (Thermo Fisher Scientific, Waltham, USA). (+RT-LAMP, extracted for this review) **Reference:** CT Cohort: As index AT Cohort: Either RT-PCR or reverse transcriptase loop-mediated isothermal amplification (RT-LAMP) using Loopamp® 2019-SARS-CoV-2 Detection Reagent Kit (Eiken Chemical, Tokyo, Japan).	Diagnostic accuracy Ct values in paired samples

Appendix 2 Risk of Bias assessment and GRADE evaluations

Risk of Bias assessment (adapted from QUADA2 tool, https://www.acpjournals.org/doi/pdf/10.7326/0003-4819-155-8-201110180-00009)

	Risk of Bias (RoB)				Applicability with regard to review question and context			Overall RoB/Applicability
Study ID	**Patient selection**	**Index Performance/ Blinding**	**Reference Performance/ Blinding**	**Flow and timing**	**Patient Selection**	**Index**	**Reference**	
Akgun 2020	Unclear	Unclear	Unclear	A) Low B) Low	Low	Low	Low	Unclear[1]/Low
Azzi 2020	Low	Low	Low	A) Low B) Low	Low	Low	Low	Low/Low
Becker 2020	Unclear	Unclear	Unclear	A) Low B) Low	Low	Low	Low	Unclear[1]/Low
Byrne 2020	Unclear	Unclear	Unclear	A) Low B) Low	Low	Low	Low	Unclear[2]/Low
Caulley 2020	Low	Unclear	Unclear	A) High B) Low	Low	Low	Low	Unclear[3]/Low
Chen 2020	Unclear	Unclear	Unclear	A)Low B) Low	Low	Low	Low	Unclear[2]/Low
Cheuk 2020	High	Unclear	Unclear	A) Low B) Unclear	Low	Low	Low	High[4]/Low
Fernandez-Pittol 2020	Unclear	Unclear	Unclear	A)Low B) Low	Low	Low	Low	Unclear[1]/Low
Griesemer 2020	Unclear	Unclear	Unclear	A) Low B) Low	Low	Low	Low	Unclear[1]/Low
Hanson 2020	Low	Unclear	Unclear	A) Low B) Low	Low	Low	Low	Unclear[5]/Low
Iwasaki 2020	Unclear	Unclear	Unclear	A) Low B) Low	Low	Low	Low	Unclear[6]/Low
Jamal 2020	Unclear	Unclear	Unclear	A) Low B) Low	Low	Low	Low	Unclear[1]/Low
Landry 2020	Unclear	Unclear	Unclear	A) Low B) Low	Low	Low	Low	Unclear[6]/Low
Leung 2020	Unclear	Unclear	Unclear	A) Low B) Low	Low	Low	Low	Unclear[1]/Low
McCormick-Baw 2020	High	Unclear	Unclear	A) Low B) Low	Low	Low	Low	High[1]/Low
Miller 2020	High	Low	Low	A) Low B) Low	Unclear	Unclear	Low	High[7]/Unclear
Pasomsub 2020	Unclear	Unclear	Unclear	A) Low B) Low	Low	Low	Low	Unclear[1]/Low
Rao 2020	Unclear	Unclear	Unclear	A) Low B) Low	Low	Low	Low	Unclear[6]/Low
Skolimowska 2020	Unclear	Unclear	Unclear	A) Low B) Low	Low	Low	Low	Unclear[6]/Low
Vogels 2020	Low	Unclear	Unclear	A) Low B)High	Low	Unclear	Low	Unclear[8]/Low
Williams 2020	Unclear	Unclear	Unclear	A) Low B) Low	Low	Low	Low	Unclear[1]/Low
Wyllie 2020	Unclear	Unclear	Unclear	A) Low B) Low	Low	Low	Low	Unclear[1]/Low
Yokota 2020	Low	Low	Low	A) High for AT cohort, Low for CT Cohort B) Low	Low	Low	High for AT cohort, Low for CT cohort	Low/High

[1] Exclusion of patients/samples, indeterminate samples and blinding not reported

[2] Saliva sampled freeze thawed may have influenced the results (noted by the authors); Blinding-not reported

[3] Different analytical assays used in index and reference makes it possible that the results could be related to analytical assay; Blinding not reported

[4] Retrospective. Binding not reported

[5] Blinding not reported

[6] Exclusion of indeterminate samples and blinding not reported

[7] Exclusion of patients/samples, indeterminate samples and blinding not reported. Index test applicability unclear as we don't know the availability of the kit in Norway

[8] Blinding not reported; Paired samples were collected a maximum 4 days apart; Index test applicability Unclear as we don't know if the kit is available in Norway

Summary of findings and GRADE evaluations

Question 1: Should rRT PCR on saliva samples be used to screen for SARS-CoV-2 in mainly asymptomatic persons?

Sensitivity	0.61 to 1.00
Specificity	0.95 to 0.99

Prevalences	0.5%	3%	10%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1 000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 0.5%	pre-test probability of 3%	pre-test probability of 10%	
True positives	5 studies 4299 patients	cohort & case-control type studies	not serious	not serious	not serious	serious [a]	none	3 to 5	18 to 30	61 to 100	⨁⨁⨁◯ MODERATE
False negatives								0 to 2	0 to 12	0 to 39	
True negatives	5 studies 4299 patients	cohort & case-control type studies	not serious	not serious	not serious	not serious	none	945 to 985	922 to 960	855 to 891	⨁⨁⨁⨁ HIGH
False positives								10 to 50	10 to 48	9 to 45	

Explanations

a. Variation and large confidence intervals for sensitivity

Question 2: Should rRT PCR on saliva samples be used to screen for SARS-CoV-2 in mainly symptomatic persons?

Sensitivity	0.55 to 0.97
Specificity	0.44 to 1.00

Prevalences	0.5%	3%	10%

Out-come	№ of studies (№ of pa-tients)	Study design	Factors that may decrease certainty of evidence					Effect per 1 000 patients tested			Test accu-racy CoE
			Risk of bias	Indi-rect-ness	Incon-sistency	Im-pre-ci-sion	Publica-tion bias	pre-test proba-bility of 0.5%	pre-test proba-bility of 3%	pre-test proba-bility of 10%	
True posi-tives	12 stud-ies 1612 patients	cohort & case-control type studies	seri-ous [a]	not seri-ous	serious [b]	not seri-ous	publica-tion bias sus-pected	3 to 5	17 to 29	55 to 97	⨁⨁◯◯ LOW
False nega-tives CoV-2)								0 to 2	1 to 13	3 to 45	
True nega-tives	12 stud-ies 1612 patients	cohort & case-control type studies	seri-ous [a]	not seri-ous	serious [b]	not seri-ous	publica-tion bias sus-pected	438 to 995	427 to 970	396 to 900	⨁⨁◯◯ LOW
False posi-tives								0 to 557	0 to 543	0 to 504	

Explanations

a. Unclear blinding in most studies and publication bias suspected

b. Cause of variation is not clear

Question 3: Should rRT PCR on saliva samples be used to diagnose Covid 19 in symptomatic patients?

Sensitivity	0.49 to 1.00
Specificity	0.74 to 0.96

Prev-a-lences	10%	50%	90%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1 000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 10%	pre-test probability of 50%	pre-test probability of 90%	
True positives	10 studies 1154 patients	cohort & case-control type studies	serious [a]	not serious	serious [b]	not serious	publication bias strongly suspected [c]	49 to 100	245 to 500	441 to 900	⨁◯◯◯ VERY LOW
False negatives								0 to 51	0 to 255	0 to 459	
True negatives	10 studies 1154 patients	cohort & case-control type studies	serious [a]	not serious	serious [b]	serious [d]	publication bias strongly suspected [c]	666 to 864	370 to 480	74 to 96	⨁◯◯◯ VERY LOW
False positives								36 to 234	20 to 130	4 to 26	

Explanations

a. Unclear risk of blinding in most studies

b. Cause of variation not clear

c. Mainly small studies with high diagnostic accuracy (positive results)

d. Mainly positives tested in the studies

Appendix 3 Excluded records assessed in full-text

Systematic reviews and HTA reports

Full Reference	Reason for exclusion, comment on use
1. Boger, B., Fachi, M. M., Vilhena, R. O., Cobre, A. F., Tonin, F. S., & Pontarolo, R. (2020). Systematic review with meta-analysis of the accuracy of diagnostic tests for COVID-19. American Journal of infection control, 10, 10.	Outdated, Search, last updated April 2020.
2. Bwire, G. M., Majigo, M. V., Njiro, B. J., & Mawazo, A. (2020). Detection profile of SARS-CoV-2 using RT-PCR in different types of clinical specimens: a systematic review and meta-analysis. Journal of Medical Virology.	Only positivity rate, published July 2020, no information on search date.
3. Czumbel, L. M., Kiss, S., Farkas, N., Mandel, I., Hegyi, A. E., Nagy, A. K., . . . Varga, G. (2020). Saliva as a Candidate for COVID-19 Diagnostic Testing: A Meta-Analysis (preprint). medRxiv, 2020.2005.2026.20112565.	Outdated, published preprint 28.05.2020, Search updated 25th of April 2020.
4. Fakheran, O., Dehghannejad, M., & Khademi, A. (2020). Saliva as a diagnostic specimen for detection of SARS-CoV-2 in suspected patients: a scoping review. Infectious diseases of poverty, 9(1), 100.	Outdated Search date May 3rd.
5. Khurshid, Z., Zohaib, S., Joshi, C., Moin, S. F., Zafar, M. S., & Speicher, D. J. (2020). Saliva as a non-invasive sample for the detection of SARS-CoV-2: a systematic review (preprint). medRxiv, 2020.2005.2009.20096354.	Outdated, Search date April 25th
6. Mohammadi, A., Esmaeilzadeh, E., Li, Y., Bosch, R. J., & Li, J. (2020). SARS-CoV-2 Detection in Different Respiratory Sites: A Systematic Review and Meta-Analysis (preprint). medRxiv, 2020.2005.2014.20102038.	Outdated, Search date April 20th
7. Peeters, E., Kaur Dhillon Ajit Singh, S., Vandesompele, J., Mestdagh, P., Hutse, V., & Arbyn, M. (2020). Rapid systematic review of the sensitivity of SARS-CoV-2 molecular testing on saliva compared to nasopharyngeal swabs (preprint). medRxiv, 2020.2008.2005.20168716.	Search date June 6th, inspected for references of primary studies
8. Tu, Y. P., & O'Leary, T. J. (2020). Testing for Severe Acute Respiratory Syndrome-Coronavirus 2: Challenges in Getting Good Specimens, Choosing the Right Test, and Interpreting the Results. Critical care medicine.	Not an SR, included as a reference in the discussion
9. Jones, S. (2020). Saliva-Based Tests to Detect Active Severe Acute Respiratory Syndrome Coronavirus 2 Infection (Health Technology Update 27). Ottawa, ON: C. A. f. D. a. T. i. Health. Canadian Agency for Drugs and Technologies in Health. Retrieved from https://cadth.ca/saliva-based-tests-detect-active-severe-acute-respiratory-syndrome-coronavirus-2-infection	Rapid HTA, Not a systematic review,
10. https://eunethta.eu/wp-content/uploads/2020/07/Project_Plan_RCROT02_Molecular_Methods_31.07.2020_final.pdf	Ongoing HTA including a systematic review on Diagnostic accuracy of (CE IVD labelled) molecular

Full Reference	Reason for exclusion, comment on use
	SARS-CoV-2 tests, revised planned publication date November 7th 2020
11. https://www.hiqa.ie/sites/default/files/2020-06/Evidence-summary-for-salivary-detection-of-SARS-CoV-2.pdf	Rapid HTA, with a systematic review. Search date 27th of May 2020, Inspected for references

Primary studies

Full Reference	Reason for Exclusion
1. Azzi L, Carcano G, Gianfagna F, Grossi P, Gasperina DD, Genoni A, et al. Saliva is a reliable tool to detect SARS-CoV-2. J Infect. 2020.	No paired samples (Patient had tested positive at another time point)
2. Ben-Assa, N., Naddaf, R., Gefen, T., Capucha, T., Hajjo, H., Mandelbaum, N., . . . Geva-Zatorsky, N. (2020). Direct on-the-spot detection of SARS-CoV-2 in patients. *Experimental biology and medicine (Maywood, NJ)*, 1535370220941819.	Wrong index and reference (Saliva POC RT-Lamp compared to Saliva rRT-PCR
3. Bosworth, A., Whalley, C., Poxon, C., Wanigasooriya, K., Pickles, O., Aldera, E. L., . . . Beggs, A. D. (2020). Rapid implementation and validation of a cold-chain free SARS-CoV-2 diagnostic testing workflow to support surge capacity. Journal of Clinical Virology.	<20 paired samples, comparision of two rRT-PCR assays. DA not calcuable
4. Cassinari, K., Alessandri, E., Chambon, P., Charbonnier, F., Gracias, S., Beaussire, L., . . . Frebourg, T. (2020). Assessment of multiplex digital droplet RT-PCR as an accurate diagnosis tool for SARS-CoV-2 detection in nasopharyngeal swabs and saliva samples (preprint). medRxiv, 2020.2008.2002.20166694.	< 20 paired samples This study is a validation study of RT-ddPCR in NPS and Saliva, DA not calcuable
5. Chau, N. V. V., Thanh Lam, V., Thanh Dung, N., Yen, L. M., Minh, N. N. Q., Hung, L. M., . . . group, O. C.-r. (2020). The natural history and transmission potential of asymptomatic SARS-CoV-2 infection. *Clinical Infectious Diseases, 04*, 04.	DA not calcuable (only sensitivity)
6. Chen L et al. Detection of 2019-nCoV in Saliva and Characterization of Oral Symptoms in COVID-19 Patients. 2020 [Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3557140.	< 20 paired samples, DA not calcuable
7. Chen, J. H., Yip, C. C., Poon, R. W., Chan, K. H., Cheng, V. C., Hung, I. F., . . . To, K. K. (2020). Evaluating the use of posterior oropharyngeal saliva in a point-of-care assay for the detection of SARS-CoV-2. *Emerging microbes & infections*, 1-14.	Paired samples, but DA not calcuable (only sensitivity)
8. Fang Z, Zhang Y, Hang C, Ai J, Li S, Zhang W. Comparisons of viral shedding time of SARS-CoV-2 of different samples in ICU and non-ICU patients. J Infect. 2020.	DA not calcuable (only positive rate)
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10. Genetics, A., & Hospital, T. S. (2020). COVID-19 and SARS-CoV-2 Detection in Saliva *ClinicalTrials*: https://ClinicalTrials.gov/show/NCT04517682.	Ongoing
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12. Ikeda, M., Imai, K., Tabata, S., Miyoshi, K., Mizuno, T., Murahara, N., . . . Kato, Y. (2020). Clinical evaluation of self-collected saliva by RT-qPCR, direct RT-qPCR, RT-LAMP, and a rapid antigen test to diagnose COVID-19 (preprint). *medRxiv*, 2020.2006.2006.20124123.	DA not calcuable (Only sensitivity)
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18. Lu, J., Becker, D., Sandoval, E., Amin, A., De Hoff, P., Diets, A., . . . Grzymski, J. (2020). Saliva is less sensitive than nasopharyngeal swabs for COVID-19 detection in the community setting (preprint). *medRxiv*, 2020.2005.2011.20092338.	Duplicate Becker 2020 (included), - wrong author listing
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23. Neurognos. (2020). Evaluation of an Alternative Method of Obtaining Viral RNA for the Detection of SARS-CoV-2 Virus Using PCR *ClinicalTrials*: https://ClinicalTrials.gov/show/NCT04468217.	Ongoing
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30. To KK, Tsang OT, Yip CC, et al. Consistent Detection of 2019 Novel Coronavirus in Saliva. Clin Infect Dis. 2020;71(15):841-843. doi:10.1093/cid/ciaa149	No paired samples (Patient had tested positive at another time point)
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33. Wang, K., Zhang, X., Sun, J., Ye, J., Wang, F., Hua, J., . . . Wu, X. (2020). Differences of SARS-CoV-2 Shedding Duration in Sputum and Nasopharyngeal Swab Specimens among Adult Inpatients with COVID-19. *Chest*.	<20 paired samples
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35. Wyllie AL, Fournier J, Casanovas-Massana A, Campbell M, Tokuyama M, Vijayakumar P, et al. Saliva is more sensitive for SARS-CoV-2 detection in COVID-19 patients than nasopharyngeal swabs. medRxiv. 2020:2020.04.16.20067835.	DA not calcuable, A continuation of this study (Wyllie 2020) was included.

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Published by the Norwegian Institute of Public Health
November 2020
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