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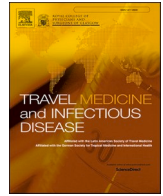
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Review

Saliva as a possible tool for the SARS-CoV-2 detection: A review

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ABSTRACT

Background: Salivary tests for the new coronavirus (SARS-CoV-2) diagnosis have been suggested as alternative methods for the nasopharyngeal and oropharyngeal tests.
Method: Two reviewers independently performed a search in the following electronic databases: PubMed, Medline, Cochrane Library, Web of Science, Embase and Scopus to identify cross-sectional and cohort studies that used saliva samples for SARS-CoV-2 detection. The search strategy was: *("saliva") and ("SARS-CoV-2" or "coronavirus" or "COVID-1").*
Results: A total of 363 studies were identified and 39 were selected for review. Salivary samples for SARS-CoV-2 detection was as consistent and sensitive as the nasopharyngeal swabs in most studies, having been effective in detecting asymptomatic infections previously tested negative in nasopharyngeal samples. Viral nucleic acids found in saliva obtained from the duct of the salivary gland may indicate infection in that gland. Live viruses could be detected in saliva by viral culture.
Conclusions: Salivary samples show great potential in SARS-CoV-2 detection and may be recommended as a simple and non-invasive alternative.

1. Introduction

In December 2019, an infection outbreak of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) emerged in Wuhan, Hubei province, China, and rapidly spread around the world [1], having been declared a pandemic by the WHO on March 11, 2020. More than 37.8 million cases were reported by October 14, 2020 around the world, resulting in 1,081,868 deaths [2]. The new 2019 coronavirus (2019-nCoV) is easily transmitted between humans through aerosol generation from infected people coughing, speaking or sneezing in close contact with others, and has an incubation period that ranges from 1 to 14 days [3,4].

The genetic sequencing done to 2019-nCoV, on January 7, 2020, allowed for fast tool-development for diagnostic tests through RT-PCR (reverse transcription polymerase chain reaction) [1]. Besides preventing transmission, its early and rapid detection is essential in controlling the virus spread [3,5]. Nasopharyngeal swabs (NPS) are widely used and

recommended as a standard sample for the respiratory virus diagnosis, including SARS-CoV-2. However, this approach requires close contact with health professionals, increasing the cross-infection risk and may cause discomfort, coughing and even bleeding in patients, not being so desirable for serial viral load monitoring [6,7].

Salivary use for viral infection diagnosis has produced interest in recent years, mainly because it is a non-invasive technique, easy to collect and has a low cost [8]. Due to the absence of a standard protocol, saliva collection can be obtained from: a) stimulated or unstimulated saliva t or through oral swabs. Several viral infections can be detectable in saliva, as Epstein Barr virus, HIV, Hepatitis C virus, Rabies virus, Human papillomavirus, Herpes simplex virus and Norovirus [9]. In addition, saliva has also been reported as a positive detection means for coronavirus nucleic acid associated with severe acute respiratory syndrome [10] and, more recently, SARS-CoV-2 [3].

The advantages of using saliva samples for SARS-CoV-2 diagnosis, such as self-collection and collection outside hospitals, are that multiple

samples can be easily obtained and there is a reduced need for health care professional handling during the sample collection, reduced nosocomial transmission risk, reduced test waiting time, and reduced PPE, transport and storage costs [7]. Another benefit for this non-invasive and economical collection method is a better perspective as community monitoring, both for asymptomatic infections and to guide end of quarantine [5,11]. Therefore, this work aims to conduct an integrative literature review reporting saliva use as a sample for the SARS-CoV-2 diagnosis.

2. Materials and methods

2.1. Research question

Can saliva be used as a diagnostic sample for SARS-CoV-2?

2.2. Search strategy

It is a current literature integrative review on saliva's use as a diagnostic tool for the new coronavirus discovered in 2019. Searches were carried out in the main national and international databases (PubMed, Medline, Cochrane Library, Web of Science, Embase and Scopus), in addition to a manual search. The search strategy used in all databases mentioned included the keywords and the terms MeSH (Medical Subject Headings): *("saliva") and ("SARS-CoV-2" or "coronavirus" or "COVID-19")*. The analyzed articles were published in English, Spanish or Portuguese.

For this integrative review, cross-sectional and cohort studies that corresponded the inclusion criteria dated from January to October 2020 were selected. Inclusion was based on two blind reviewers reading the manuscripts and confirming the eligibility criteria. The inclusion criteria referred to articles in English, Spanish or Portuguese who utilized saliva tests for detection of SARS-CoV-2. The exclusion criteria referred to articles that did not consider saliva as a possible diagnostic strategy for 2019-nCoV, besides literature reviews, letters to the editor, protocols and case reports.

Assessments were carried out by two independent reviewers in order to verify if the selected articles met the inclusion criteria. In case of disagreements, a third reviewer was consulted regarding the decision to include or not the article. Initially, studies were identified by reading title and articles abstracts. After that, the references selected were analyzed, manual searches for new studies were performed. Nineteen cross-sectional and cohort studies were considered in this research. After reading the selected articles, relevant information was collected and typed into a database according to the following criteria: authors, study design, study population, sample size, age range, test, saliva type, saliva collection method, respiratory or another sample and results (Tables A.1, A.2 and A.3).

3. Results

3.1. Study selection

Nine hundred and sixty five studies published between January and October 2020 were identified after an initial electronic search in the main databases, in addition to four identified through manual search. Three hundred and sixty-three articles were evaluated after duplicates removed. After reading the titles and abstracts, 291 articles were excluded. Of the 72 articles selected for reading in full text, 29 were excluded (literature reviews, letters to the editor and protocols). Forty-three were fully evaluated, four being excluded when the inclusion/exclusion criteria were applied once they were case reports, totaling 39 manuscripts included in the analysis (Fig. A.1). No randomized controlled clinical trial was found. All manuscripts included were cross-sectional or cohort studies [6,7,12–48] (Tables A.1, A.2 and A.3).

In samples whose posterior oropharyngeal saliva is collected, other

secretions are added besides the saliva that is secreted by larger or smaller salivary glands, which may come from the upper or lower respiratory tract and gingival fluid [7,55]. All studies that used this collection method demonstrated good performance in SARS-CoV-2 detection, including asymptomatic and pre-symptomatic infections [7, 13,21,23,27,34].

3.2. Study characteristics

According to the methodology used and the results obtained, the studies were subdivided into three sessions: studies that directly compared saliva use in SARS-CoV-2 detection with respiratory samples and that demonstrated good saliva results; those who directly compared saliva use in SARS-CoV-2 detection with respiratory samples and who demonstrated inaccurate saliva results; and those who did not directly compare saliva use in SARS-CoV-2 detection with respiratory samples.

3.2.1. Studies that directly compared saliva use in SARS-CoV-2 detection with respiratory samples and that demonstrated good results from saliva

In total, 25 articles compared saliva use in relation to the other respiratory sample for the SARS-CoV-2 detection and obtained promising results regarding the salivary samples use, both for the initial diagnosis and for monitoring the course of the disease (Table A.1). The approaches reported in these studies for the saliva collection included: spit, cough, drooling technique, oral swab and swab with absorbed saliva.

Pasomsub et al., (2020) evaluated two hundred pairs of nasopharyngeal and oropharyngeal swab samples, and saliva samples from potentially infected patients, demonstrated that saliva tests had high sensitivity (84.2%) and specificity (98.9%), with good diagnostic performance when compared to standard nasopharyngeal and oropharyngeal swab tests.

High sensitivity and specificity were also found in a mass screening study, evaluating 1924 people possibly infected, both for saliva samples (86% and 99.96%) and for NPS (92% and 99.93%) [15]. In this study, three samples negative for saliva were positive for NPS, while six samples negative for NPS were positive for saliva. Observing the median cycle threshold (Ct) values, being 40 in the qRT-PCR test for NPS and between 33.7 and 37.2 per qRT-PCR for saliva, it was demonstrated that the viral load was equivalent between the samples.

Similarly, Wyllie et al., (2020) [6], Azzi et al., (2020), Kojima et al., (2020) and Pasomsub et al., (2020) were able to detect SARS-CoV-2 in saliva samples, while negative NPS were observed in 11% (2/18), 20% (6/29) 8% (2/25) and 21% (8/38) of infected patients, respectively, the last two after treatment days. In addition, viral RNA was found in the saliva from asymptomatic patients who presented negative NPS in three studies (2/98 [6]; 1/50 [39]; 1/106 [20]). Wyllie et al., (2020) [6] also demonstrated five nasopharyngeal sample cases (22.7%) in which there was a negative test followed by a positive result during the next collection, without any occurrences being seen for the saliva samples.

In contrast, To et al., (2020) [7] demonstrated that all patients whose nasopharyngeal samples showed negative results for 2019-nCoV, obtained negative results for saliva samples. Meanwhile, Vaz et al., (2020) found four participants with the virus detected in NPS or oropharyngeal swab (OPS) but not in the saliva. However, the difference in the SARS-CoV-2 detection rate found between saliva and swabs did not reach statistical significance.

It was detected a general decline in the saliva samples viral load after hospitalization in most patients [6,7,16]. A case with viral spillage in saliva was found by To et al., (2020) [7] even after 11 days on hospitalization. In another study by To et al., (2020) [13], 2019-nCoV RNA was detected for 20 days or more in recovered and symptom-free patients, and one patient tested positive for SARS-CoV-2 in saliva even after two days of negative results. In that study, the mean viral load of salivary or other respiratory samples was 5.2 log10 copies/mL.

When comparing the viral load between nasopharyngeal and

Table A.1 Studies that directly compared saliva use in SARS-CoV-2 detection with respiratory samples and that demonstrated good saliva results. Natal/RN, 2020.

Authors	Study design	Study population	Sample size [Gender]	Age range [Mean] (Years)	Test	Saliva type	Saliva collection method	Respiratory sample	Results
Wyllie et al., 2020[6]	Cohort study	Patients who tested positive for SARS-CoV-2. Asymptomatic health professionals.	44 [23 M, 21 F] 98 [16 M, 82 F]	23-92 [61] 22-67 [36]	RT-PCR	Saliva	Self-collection by spit.	OPS or NPS	37 samples (84%) of saliva tested positive for SARS-CoV-2. SARS-CoV-2 detection in the saliva from two health professionals who tested negative by nasopharyngeal swab.
To et al., 2020[7]	Cohort study	Patients hospitalized with COVID-19 confirmed in the laboratory.	12 [7 M, 5 F]	37-75 [62,5]	RT-PCR and viral culture	POS	Saliva with cough.	NPS	2019-nCoV was detected in the initial saliva samples from 11 patients (91.7%). Live viruses were found in the saliva from 3 patients.
Azzi et al., 2020[12]	Cohort study	Patients with severe or very severe COVID-19.	25 [17 M, 8 F]	39-85 [61,5]	RT-qPCR	Saliva	Drooling technique.	NPS	All 25 initial samples showed positive results for the SARS-CoV-2 presence.
To et al., 2020[13]	Cohort study	Patients hospitalized with COVID-19 confirmed in the laboratory.	23 [13 M, 10 F]	37-75 [62]	RT-qPCR and EIA	POS	Saliva with cough.	NPS	20 cases (87%) in which 2019 RNA-nCoV was detectable in saliva.
Iwasaki et al., 2020[14]	Cohort study	Patients suspicious of COVID-19 and patients with the diagnosis of COVID-19.	76 [-]	30-97* [69]	RT-qPCR	Saliva	Self-collection by spit.	NPS	SARS-CoV-2 was detected in 8 (among 10 patients) with COVID-19 in nasopharyngeal and saliva samples. The overall agreement rate for virus detection was 97.4%.
Yokota et al., 2020[15]	Cohort study	Asymptomatic persons who have close contact with clinically confirmed COVID-19 patients. Asymptomatic travellers arriving at Tokyo and Kansai international airports	161 [44 M, 26 F, 91U] 1763 [927 M, 832 F, 4U]	29.8–66.4 [44.9] 22.6–47.4 [33.5]	qRT-PCR and RT-LAMP	Saliva	Self-collection.	NPS	The nasopharynx and saliva samples obtained high sensitivity, with 86% and 92%, respectively, and specificity (greater than 99%) to the nucleic acid amplification test.
Wyllie et al., 2020[16]	Cohort study	COVID-19 inpatients at Yale-New Haven Hospital.	70 [41 M, 29 F]	13-91 [61,4]	RT-PCR	Saliva	Self-collection by spit.	NPS	From 1 to 5 days after diagnosis, saliva samples (81%) were positive, while nasopharyngeal smear samples (71%) were positive, suggesting that both samples have at least similar sensitivity in the initial detection of SARS-CoV-2.
Han et al., 2020[17]	Cohort study	Mildly symptomatic and asymptomatic children with coronavirus disease.	12 [5 M, 7 F]	27 (days)-16 [5,6]	–	–	–	NPS	Saliva was collected from 11 children, with 8 tested positive for SARS-CoV-2. Positivity in saliva samples decreased from 80% at week 1–33% at week 2 and 11% at week 3.
Mao et al., 2020[18]	Cohort study	Patients with asymptomatic disease Patients with mild disease Patients with moderate disease	6 [4 M, 2 F] 6 [6 M, 0 F] 22 [10 M, 12 F]	28–48 [37] 21-57 [7,38] 21-64 [4,44]	RT-qPCR	–	–	OPS and sputum	Saliva sample sensitivity, efficiency and specificity were only 74.10%, 83.90% and 94.40%, respectively, whereas for saliva-expectoration they were 93.40%, 94.00% and 95.20%, respectively, being a

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(*continued*)

Author	Study type	Population	N [sex]	Age [ref]	Method	Sample 1	Sample 1 detail	Sample 2	Results
Kojima et al., 2020[19]	Cross-sectional study	Symptomatic individuals not hospitalized recently tested for SARS-CoV-2 infection.	45 [-]	31-52 [42]	RT-qPCR	Saliva	Self-collected oral swab with and without doctor's supervision.	NPS and nasal swab	more effective diagnostic method. Oral swab samples self-collected and supervised by the physician detected 26 (90%) of the 29 infected individuals. Non-monitored self-collected oral fluid swab samples detected 19 (66%).
Pasomsub et al., 2020[20]	Cross-sectional study	Patients who experience fever or acute respiratory symptoms, along with a 14-day travel history from a COVID-19 endemic area or contact with an individual who has been confirmed or COVID-19 suspected.	200 [69 M, 131 F]	28-48 [36]	RT-PCR	Saliva	Saliva without cough.	NPS and throat swab	The COVID-19 prevalence diagnosed by saliva RT-PCR was 9.0%, showing high sensitivity and performance 84.2% and 98.9%, respectively.
Chen et al., 2020[21]	Cross-sectional study	Positive patients for COVID-19.	58 [28 M, 30 F]	31-52 [38]	RT-PCR POCT	POS	Saliva with cough.	NPS	Some patients (84.5%) had a positive result in both the nasopharyngeal swab and saliva, 10.3% had a positive result only in the nasopharyngeal swab and 5.2% had a positive result only in saliva.
McCormick-Baw et al., 2020[22]	Cross-sectional study	Patients with suspected COVID-19 and hospitalized patients positive for COVID-19 without the need for mechanical ventilation.	156 [90 M, 66 F]	[8,47]	POCT	Saliva	Saliva without cough.	NPS	49 positive tests by nasopharyngeal swab (47 also had positive saliva samples). A single sample demonstrated detectable SARS CoV-2 nucleic acid levels in saliva, but the nasopharyngeal swab was negative.
Leung et al., 2020[23]	Cross-sectional study	Patients admitted to the Prince of Wales Hospital in Hong Kong.	62 [26 M, 36 F]	19-85 [42]	RT-PCR	POS	Saliva with cough.	NPS	95 sample pairs, 75 were positive for both nasopharyngeal and saliva samples; 13 positive saliva samples had corresponding negative nasopharyngeal samples and 7 positive nasopharyngeal samples had negative saliva samples.
Cheuk et al., 2020[24]	Cross-sectional study	Tested Patients for COVID-19.	95 [38 M, 57 F]	4-92 [39]	RT-PCR	Saliva	Self-collection by spit.	NPS	Saliva and nasopharyngeal samples positivity was 61.6% and 53.3%, respectively. Among the 6 discordant results, 4 presented positive saliva samples and negative nasopharyngeal samples.
Güçlü et al., 2020[25]	Cross-sectional study	Hospitalized patients with and without laboratory-confirmed Covid-19, with a finding consistent with COVID-19 in the Lung Computed Tomography (CT),	64 [37 M, 27 F]	-[51,04]	RT-PCR	Saliva	Self-collection.	OP/NP swab	Among 64 patients, 23 (35.9%) obtained positive saliva and OP-NP swab samples, 4 (6.25%) had only positive saliva sample and 4 (6.25%) only the OP/N swab. NP was positive. In general,

(*continued*)

		and patients with complaints compatible with COVID-19 but normal CT.						saliva sensitivity and specificity was 85.19% and 89.19%, respectively.
Vaz et al., 2020[26]	Cross-sectional study	Health professionals with signs/symptoms suggestive of COVID-19, and infirmary patients with confirmed infection.	155 [46 M, 109 F]	33-48,5 [40]	RT-PCR	Saliva	Saliva without cough.	NPS or OPS	RT-PCR sensitivity and specificity for saliva were 94.4% and 97.62%, respectively. In addition, there was a high general agreement (96.1%) comparing the salivary sample with the gold standard test.
Rao et al., 2020[27]	Cross-sectional study	Asymptomatic adult male participants in a COVID-19 quarantine center.	160 [160 M]	18-36 [27]	RT-PCR	POS	Saliva with cough.	NPS	A higher detection rate for SARS-CoV-2 was found in saliva compared to NPS, being 93.1% and 52.5%, respectively. E and RdRp genes Ct values from the 73 concordant samples were significantly lower in saliva than in NPS (p < 0.05).
Byrne et al., 2020[28]	Cross-sectional study	Patients with COVID-19 symptoms.	110 [49 M, 61 F]	–	RT-qPCR	Saliva	Self-collection.	Nasal and throat swab	Among 110 paired samples, 12 saliva samples tested positive for SARS-CoV-2, while 14 nasal and throat swab samples tested positive. The general viral loads were similar among all positive samples, ranging from 36 to 3.3 × 10 6 copies/mL.
Hanson et al., 2020[29]	Cross-sectional study	Adult patients with symptoms suggestive of COVID-19.	354 [195 M, 173 F]	18-75 [35]	RT-PCR	Saliva	Self-collection by spit.	NPS and anterior nasal swab	NPS and saliva samples had the highest positivity rates (22.5% and 22.9%) compared to the ANS (19.7%). The average Ct values for positive samples only for NPS was 27.0, and 28.2 for positive samples only for saliva.
Aita et al., 2020[30]	Cross-sectional study	Inpatients with COVID-19.	49 [33 M, 16 F]	28-86 [64] (M) 25-94 [60] (F)	rRT-PCR	Saliva	Swab with absorbed saliva.	NPS	Among 43 patients with NPS and saliva samples paired, 7 cases tested positive in both samples and 35 tested negative for both NPS and saliva. One patient tested positive for saliva (Ct = 26), but not for NPS.
Uwamino et al., 2020[31]	Cross-sectional study	Hospitalized patients with COVID-19. Symptomatic university staff.	32 [-] 115 [-]	–	RT-PCR	Saliva	Saliva without cough.	NPS	From 196 samples collected, 32 tested positive for SARS-CoV-2 by both NPS and saliva, 15 by NPS but negative by saliva, and 11 samples that tested positive for saliva had NPS negative. The results obtained in the first 10 days of symptom onset were 96.4%. It was possible to detect viable viruses in two saliva samples.

(*continued*)

Migueres et al., 2020[32]	Cross-sectional study	Hospitalized and ambulatory patients.	123 [49 M, 74 F]	- [43]	RT-PCR	Saliva	Self-collection by spit.	NPS	Thirty-four patients tested positive in both samples, three only for saliva and 7 only for NPS. Saliva samples sensitivity was high for asymptomatic and symptomatic patients tested early, with 88.2% and 94.7% respectively, and lowest (50%) for symptomatic patients tested late after symptoms onset.
Senok et al., 2020[33]	Cross-sectional study	Adult patients undergoing COVID-19 testing.	401 [329 M, 72 F]	[5,35]	RT-PCR	Saliva	Saliva without cough.	NPS	Saliva sensitivity and specificity were 73.1% and 97.6%, respectively. The general SARS-CoV-2 detection prevalence by NPS was 6.5%, while, by saliva, it was 7%.
Altawalah et al., 2020[34]	Cross-sectional study	COVID-19 suspected patients.	891 [-]	–	RT-PCR	POS	Saliva with cough.	NPS	The general agreement between the NPS and saliva samples was 91.25%. Saliva sensitivity and diagnostic specificity were 83.43% and 96.71%, respectively, and the detection rate was 83.43%. The median Ct values did not differ significantly between NPS and saliva.

POS: Posterior Oropharyngeal Saliva; **NPS:** Nasopharyngeal swab; **OPS:** Oropharyngeal swab; **RT-PCR:** Reverse Transcription Polymerase Chain Reaction; **rRT-PCR:** Real-time Reverse Transcription Polymerase Chain Reaction; **RT-qPCR:** Quantitative Reverse Transcription Polymerase Chain Reaction; **EIA:** Enzyme Immunoassays; **RT-LAMP:** Reverse-Transcription Loop Mediated Isothermal Amplification; **U:** unknown; **POCT:** Point-of-care testing.

*Age group (10 patients with COVID-19).

salivary samples, Iwasaki et al., (2020) did not identify significant differences in viral loads between samples, with a mean of 5.4 ± 2.4 and 4.1 ± 1.4 log10 copies of the gene/ml in nasopharynx and saliva samples, respectively (p = 0.184), while Wyllie et al., (2020) [6], using a SARS-CoV-2 detection limit of 5610 virus copies/mL, found significantly higher SARS-CoV-2 titers in saliva than nasopharyngeal smears for the corresponding samples (p = 0.0001).

Kojima et al. (2020) evaluated the performance of the saliva swab samples self-collected by the individuals recruited, who had been tested positive for SARS-CoV-2 and compared to nasopharyngeal swabs, The four testing groups were as follows: a) with and b) without a doctor's supervision, c) self-collected nasal swab samples and d) nasopharyngeal swab collected by the doctor. For both saliva tests, all participants received the same instructions. The unsupervised group performed the collection only following these instructions, while the supervised group had instant feedback. The supervised saliva swab collection group was able to detect 90% of the infected individuals, being the highest rate when compared to the saliva swab group performed without supervision (66%), which was also the worst performance in the study sample. Meanwhile, posterior nasopharyngeal swab samples detected 79% of those infected.

3.2.2. Studies that directly compared saliva use in SARS-CoV-2 detection with respiratory samples and that demonstrated inaccurate saliva results

Nine studies demonstrated less saliva sensitivity as a diagnostic sample or that there was less time of viral shedding compared to respiratory samples when comparing the saliva use in relation to the other respiratory sample for the SARS-CoV-2 detection (Table A.2). The saliva collection approaches were by spitting, using a syringe, oral swab and clearing the throat and gargling the saliva itself.

Kam et al., (2020) and Chong et al., (2020) demonstrated low sensitivity in saliva samples use for SARS-CoV-2 detection in infected children, varying from 25 to 71.4% on different collection days in the first week after diagnosis [40] and reaching a sensitivity peak of 52.9% in the period of 4–7 days [38]. Kam et al., (2020) still found statistically significant differences (p < 0.001) between the median Ct values of the oral and nasopharyngeal samples of infected patients, with an average difference of 10.7 (range 6.1–16, 1).

Likewise, Williams et al., (2020) showed lower Ct values in nasopharyngeal samples than in saliva samples, suggesting lower viral loads in saliva. In addition, Jamal et al., (2020) observed greater sensitivity in nasopharyngeal swab samples compared to saliva samples in SARS-CoV-2 detection, especially in disease with advanced stages. Both samples showed greater sensitivity in the first week, with less difference in sensitivity between them.

Meanwhile, Kim et al., (2020) observed a greater difference in sensitivity between naso/oropharyngeal and saliva samples in the initial stage of symptoms (93% and 53%, respectively), and saliva sensitivity was especially lower in patients who had no sputum (55%). Despite this, the median Ct value of saliva did not differ significantly from the naso/oropharyngeal samples (p = 0.7531), being 32 (IQR 28–38) and 33 (27–35), respectively.

3.2.3. Studies that did not directly compare saliva use in SARS-CoV-2 detection with respiratory samples

A total of 5 non-comparative studies between saliva and respiratory

Table A.2 Studies that directly compared saliva use in SARS-CoV-2 detection with respiratory samples and that demonstrated inaccurate saliva results. Natal/RN, 2020.

Authors	Study design	Study population	Sample size [Gender]	Age range [Mean] (Years)	Test	Saliva type	Saliva collection method	Respiratory sample	Results
Jamal et al., 2020[35]	Cohort study	Positive patients for COVID-19 with nasopharyngeal, midturbinate or nasal swab.	91 [52 M, 39 F]	23-106 [66]	RT-PCR	Saliva	Self-collection by spit.	NPS	72 patients had at least one positive specimen (nasopharyngeal swab or saliva). 61% of these 72 patients, both were positive, 28% only the nasopharyngeal swab was positive, and in 11% only saliva was positive. Nasopharyngeal swabs were 17% more sensitive than saliva overall.
Fang et al., 2020[36]	Cohort study	COVID-19 patients admitted to Central Hospital of Xiangtan.	32 [16 M, 16 F]	34-54 [41]	RT-PCR	–	–	Nasal swab.	Nasal swab samples showed 100.0% positivity, while the positive rate for saliva was 78.1%. The viral shedding time of SARS-CoV-2 of nasal swab was significantly longer than that of blood and saliva.
Kim et al., 2020[37]	Cohort study	Patients with SARS-CoV-2 infection.	15 [5 M, 10 F]	17-91 [59]	rRT-PCR	Saliva	Self-collection by spit.	NPS/OPS and sputum.	General rRT-PCR sensitivity for saliva compared to the sensitivity for naso/oropharyngeal samples was lower, being 64% and 77% respectively.
Chong et al., 2020[38]	Cohort study	COVID-19-infected children.	18 [10 M, 8 F]	1,8–11,1 [6,6]	rRT-PCR	Saliva	Self-collection by spit or through syringe.	NPS	The Ct values had statistically significant differences between saliva and NPS samples (1–3, 4–7 and 8–10 days after onset symptoms), and did not differ significantly in the period of 11–15 days. In five children, saliva samples tested negative on day 1–3 and became positive on day 4–7.
Williams et al., 2020[39]	Cross-sectional study	Outpatients who come to a COVID-19 screening clinic.	622 [-]	–	RT-PCR	Saliva	Self-collection by spit.	NPS	39 positive tests for SARS-CoV-2 by nasopharyngeal swab (33 tested positive for saliva). Nucleic acid was detected in the saliva from 1 out of 50 patients with negative test for nasopharyngeal swab.
Kam et al., 2020[40]	Cross-sectional study	Pediatric hospitalized patients confirmed for COVID-19.	11 [-]	Symptomatic 2,1–12,5 [4,8] Asymptomatic 0,3–11,8 [3,8]	RT-qPCR	Saliva	Oral swab.	NPS	SARS-CoV-2 was detected in at least 1 oral swab sample in 9 of the 11 children (81.8%). Two children with positive nasopharyngeal tests had negative results in the saliva samples in two collection days. In general, oral samples produced lower viral loads and had low sensitivity (25–71.4%) compared to nasopharyngeal samples.
				30-51 [39]		Saliva		NPS/OPS	

(continued)

Skolimowska et al., 2020[41]	Cross-sectional study	Symptomatic healthcare workers and household contacts presenting to a COVID-19 outpatient clinic.	132 [43 M, 89 F]		RT-PCR		Saliva without cough.		Among the paired samples, 18 NP/OP swab samples tested positive, with 15 tested positive also for saliva. Saliva obtained sensitivity and specificity of 83.3% and 99.1%, respectively. Saliva Ct values were significantly higher than for swabs.
Lai et al., 2020[42]	Cross-sectional study	Patients with SARS-CoV-2 infection confirmed.	50 [23 M, 27 F]	16-72 [-]	RT-PCR	Saliva	Clearing the throat gargling saliva.	NPS and throat swab and sputum.	Saliva samples obtained RT-PCR positivity lower rates (68.7%) and lower viral RNA concentrations (mean log copy/mL 3.54) compared to sputum (89.4%, 5.03) and swabs (80.4%, 4.63).
Landry et al., 2020[43]	Cross-sectional study	COVID-19 suspected symptomatic outpatients.	–	–	RT-PCR	Saliva	Saliva without cough.	NPS	Among the 35 positive samples, 33 were positive for NPS, while 30 were positive for saliva. The general sensitivity for saliva was 85.7% (95% CI 70.6%–93.7%). The median Ct value was significantly lower for NPS than for saliva (p = 0.0331).

NPS: Nasopharyngeal swab; **OPS:** Oropharyngeal swab; **RT-PCR:** Reverse Transcription Polymerase Chain Reaction; **rRT-PCR:** Real-time Reverse Transcription Polymerase Chain Reaction; **RT-qPCR:** Quantitative Reverse Transcription Polymerase Chain Reaction.

samples were evaluated (Table A.3). These included saliva samples analyzed at different times of the day, in different tests, investigating the specific antibodies responses to salivary SARS-CoV-2, evaluating the saliva collected directly from the salivary duct and comparing it with samples and blood and anal swabs.

Evaluating saliva samples at different times during the day, Hung et al., (2020) suggested a trend for higher viral loads in the morning (median Ct value = 34,5) compared to the other four times: before lunch (38,2), before tea time (36,3), before dinner (41) and before bed (41), occurring in 8 out of 13 patients who had detectable viral loads [45].

When analyzing saliva samples in different tests, Nagura-Ikeda et al. (2020) showed sufficient sensitivity in clinical use to detect SARS-CoV-2 from tests such as LDT RT-qPCR, cobas SARS-CoV-2 high-throughput system and RT-LAMP. However, it was observed that rapid antigen tests using saliva are not recommended for the early disease diagnosis due to their low sensitivity [47].

However, when it comes to serological testing using saliva collected 10 days or more after the onset of symptoms, Randad et al. (2020) demonstrated that the *anti*-SARS-CoV-2 IgG assay detects SARS infection -CoV-2 with high sensitivity and specificity, reaching 100% and 99%, respectively, for the GenScript N antigen, and 89% and 100% for Mt. Sinai RBD [48].

2019-nCoV nucleic acid was detected in pure saliva [46]. The samples were collected from the salivary gland canal opening after cleaning the oral cavity, avoiding contamination by other respiratory tract secretions. Among the 13 patients positive for oropharyngeal swab, four tested positive also for saliva, being three critical cases with ventilatory support. In addition, the authors assessed the oral symptoms reported by patients with COVID-19, and reported that main symptoms were dry mouth (46.3%) and dysgeusia (47.2%).

Zhang et al., (2020) [44] collected blood samples, oral and anal swabs from patients at the Wuhan Lung Hospital who had nCoV 2019

positive oral swabs on admission. For the virus molecular detection, it was demonstrated that, of the positive tests in the initial phase of the disease, the majority were oral swabs (50%), while the minority were anal swabs (25%). In the later phase, this relationship was reversed, with more positive tests of anal swabs (37.5%) than of oral swabs (25%).

4. Discussion

Diagnostic techniques based on nasopharyngeal and oropharyngeal samples were recommended for the COVID-19 detection in outpatients by WHO on January 9, 2020 [49]. These tests for the virus detection have strong evidence, with studies indicating they are more sensitive than other respiratory samples. This is because it has been proven that there is active viral replication in the tissues of the upper respiratory tract, with higher viral loads being seen in the first week of symptoms in the pharynx samples [50]. However, its performance can cause pain and discomfort in patients, in addition to bleeding in patients with thrombocytopenia, making them uninteresting for serial monitoring about the viral load [7,51].

Saliva is a hypotonic liquid secreted by the parotid, submandibular, sublingual and minor salivary glands that are distributed throughout the oral cavity. These glands are very permeable and surrounded by blood capillaries, allowing the molecules and biomarkers exchange, which can be secreted together with saliva. Thus, these biomarkers in saliva have been analyzed and used to detect local and systemic diseases, such as caries, periodontitis, oral and lung cancer, diabetes, cardiovascular diseases and viral infections [11]. Oral fluid samples can indicate the virus infection presence by screening for viral nucleic acids, antigens and antibodies [9].

Thus, saliva samples have been suggested as tools for the respiratory viruses' detection, such as influenza A virus, influenza B virus, parainfluenza virus and respiratory syncytial virus (RSV), in order to reduce

Table A.3 Studies that did not directly compare saliva use in SARS-CoV-2 detection with respiratory samples. Natal/RN, 2020.

Authors	Study design	Study population	Sample size [Gender]	Age range [Mean] (Years)	Test	Saliva type	Saliva collection method	Another samples	Results
Zhang et al., 2020[44]	Cohort study	Patients at Wuhan Pulmonar Hospital.	15 [-]	–	RT-qPCR	Saliva	Oral swab.	Anal swab and blood.	8 patients (53.3%) were positive for 2019-nCoV in oral swab on day 0, while there were only 4 (25%) positive oral swab on day 5.
Hung et al., 2020[45]	Cohort study	Patients confirmed with SARS-CoV-2 infection.	18 [8 M, 10 M]	18-61 [53]	RT-PCR	POS	Saliva with cough.	–	Higher viral loads were found in saliva samples collected in the morning, showing statistically significant differences when compared to the samples collected at night.
Chen et al., 2020[46]	Cross-sectional study	Patients whose 2019-nCoV nucleic acid detection remained positive before or on the sample collection day.	31 [15 M, 16 F]	18-86 [60,6]	RT-PCR	Saliva	Swab at the salivary gland canal opening.	OPS	13 positive cases for 2019-nCoV nucleic acid detection by oropharyngeal swab (4 cases with positive saliva detection and 3 in serious condition).
Nagura-Ikeda et al., 2020[47]	Cross-sectional study	Patients with laboratory-confirmed COVID-19.	103 [66 M, 37 F]	18-87 [46]	LDT RT-qPCR, cobas SARS-CoV-2 test, direct RT-qPCR, RT-LAMP, RAT.	Saliva	Self-collection.	–	The viral RNA detection was significantly higher in saliva samples collected from symptomatic patients within 9 days after the symptoms onset than in samples collected 10 days after symptoms onset or in the saliva from asymptomatic patients.
Randad et al., 2020[48]	Cross-sectional study	Patients with RT-PCR confirmed prior SARS-CoV-2 infection	28* [−]	[−]	RT-PCR, IgG, IgA, IgM	Saliva	Brushing the gum line.	Serum sample.	22 amostras combinadas obtiveram resultado positivo para detecção de SARS-CoV-2 pela saliva e pelo soro, e 6 resultados foram negativos para ambas amostras. A detecção salivar específica de IgG para SARS-CoV-2 obteve alta sensibilidade e especificidade.

POS: Posterior Oropharyngeal Saliva; **OPS:** Oropharyngeal swab; **RT-PCR:** Reverse Transcription Polymerase Chain Reaction; **RT-qPCR:** Quantitative Reverse Transcription Polymerase Chain Reaction; **LDT:** Laboratory developed tests; **RT-LAMP:** Reverse-Transcription Loop Mediated Isothermal Amplification; **RAT:** Rapid Antigen Test.
*Participants with matched saliva-serum samples.

costs and time associated with collections [52,53]. A cohort study demonstrated that the detection of respiratory viruses in salivary samples, by an automated multiplex Clinical Laboratory Improvement Amendments-waived point-of-care molecular assay, has high sensitivity and specificity [53].

In 2003, the coronavirus from severe acute respiratory syndrome (SARS-CoV) spread rapidly from China to more than 30 countries, being a highly contagious disease [10]. It is known that both SARS-CoV and 2019-nCoV, a coronavirus similar to SARS-CoV, can be transmitted efficiently between humans through the droplets generation when speaking, coughing or sneezing [11]. In addition, they interact with the angiotensin II-converting enzyme receptor (ACE2) in host cells, found expressed in the lungs, esophagus, ileum, colon, liver, bladder and in the salivary gland and tongue [3,54].

The results found by Chen et al., (2020) [46] may suggest that epithelial cells that line the minor salivary glands ducts, which express ACE2, were infected, generating infected saliva. In addition, viable viruses could be identified in saliva samples in two studies, using collecting saliva method with and without cough [7,31]. Thus, the oral cavity can be a host for 2019-nCoV.

Viral nucleic acid's presence after treatment days seen in some studies [7,13] may indicate low excretion levels in saliva, even after resolution symptoms. Thus, reliable tests are necessary, including different tests combinations, at the time of hospital discharge for

patients admitted with SARS-CoV-2, avoiding the possibility that these recovered patients continue to transmit the virus through direct or indirect contact through the generation of droplets from infected saliva.

Although most studies in this review have shown good results utilizing saliva as a diagnostic sample, compared to the gold standard of nasopharyngeal samples, some limitations have been reported. Among them, the faster decrease in viral load than NPS in hospitalized patients [14,17], less sensitivity compared to nasopharyngeal samples during the one week collection period in children [38,40] and the saliva characteristics that could making sample processing difficult [43].

Given that saliva collection is a simpler technique, it is strongly suggested as an alternative screening procedure in places with limited resources. In addition, the ease in salivary sample collection for the SARS-CoV-2 diagnosis allows for self-sample collection by the patients themselves, not necessarily in a hospital environment or with the health professional presence. This system would make it possible, in addition to epidemiological control and self-surveillance, to reduce the exposure risk for health professionals and to reduce the need for personal protective equipment.

On May 7, 2020, the U.S. Food and Drug Administration (FDA) approved the first in home saliva collection test for the SARS-CoV-2 diagnosis [56]. Thus, saliva's self-collection may allow for more specific results due to the possibility of performing it when symptoms arise, especially in the first week, and in the morning, when the saliva has
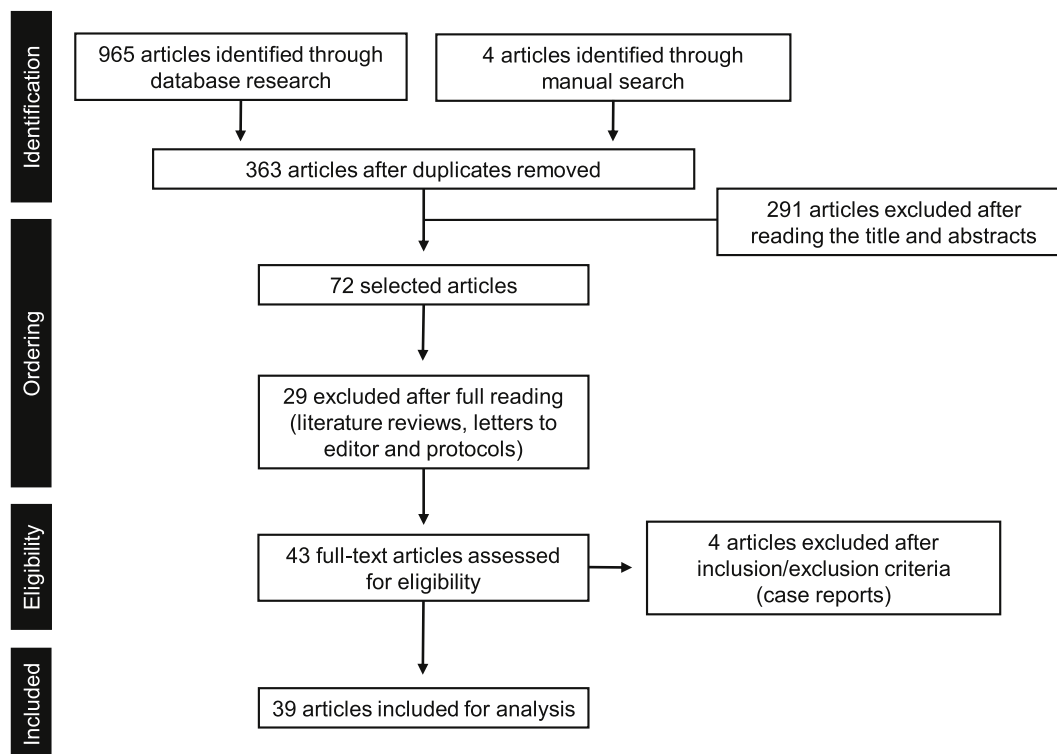
Fig. A.1. Article selection flowchart.
Nine hundred and sixty five studies identified through electronic search and 4 through manual search, totaling 363 articles after duplicates removed, published between January and October 2020 were evaluated. After reading the titles and abstracts, 291 articles were excluded. Of the 72 articles selected for reading in full text, 29 were excluded. Forty three were fully evaluated, four being excluded when the inclusion / exclusion criteria were applied, totaling thirty nine articles included for the current review .

higher viral loads [6,19,45].

A study evaluated the general acceptability of North American adults in relation to the collecting process, packaging and sending self-collected saliva samples, oropharyngeal swab and dried blood card [57]. It was possible to observe high acceptability and confidence in relation to the self-collection of both saliva and other samples by patients, which reinforces the possibility of facilitating mass screening processes, reducing the costs associated with collections.

The possibility of utilizing this simple technique, with lower cost and more comfort in detecting 2019-nCoV in non-hospital environments would bring advantages to dental care, reducing the waiting period or even allowing immediate intervention based on positive results.

5. Conclusions

Saliva seems to be a promising resource in the SARS-CoV-2 detection, having demonstrated similar performance to nasopharyngeal swabs, plus advantages such as low cost, disease course monitoring, not being invasive and avoiding close contact with health professionals. In addition, salivary samples are a good alternative for epidemiological studies and asymptomatic or pre-symptomatic infections detection and can be useful in screening systems and dental care.

Conflicts of interest

A conflicting interest exists when professional judgement concerning a primary interest (such as patient's welfare or the validity of research) may be influenced by a secondary interest (such as financial gain or personal rivalry). It may arise for the authors when they have financial interest that may influence their interpretation of their results or those of others. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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