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REVIEW

The Sensitivity and Costs of Testing for SARS-CoV-2 Infection With Saliva Versus Nasopharyngeal Swabs

A Systematic Review and Meta-analysis

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Background: Nasopharyngeal swabs are the primary sampling method used for detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), but they require a trained health care professional and extensive personal protective equipment.

Purpose: To determine the difference in sensitivity for SARS-CoV-2 detection between nasopharyngeal swabs and saliva and estimate the incremental cost per additional SARS-CoV-2 infection detected with nasopharyngeal swabs.

Data Sources: Embase, Medline, medRxiv, and bioRxiv were searched from 1 January to 1 November 2020. Cost inputs were from nationally representative sources in Canada and were converted to 2020 U.S. dollars.

Study Selection: Studies including at least 5 paired nasopharyngeal swab and saliva samples and reporting diagnostic accuracy for SARS-CoV-2 detection.

Data Extraction: Data were independently extracted using standardized forms, and study quality was assessed using QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2).

Data Synthesis: Thirty-seven studies with 7332 paired samples were included. Against a reference standard of a positive result on either sample, the sensitivity of saliva was 3.4 percentage points lower (95% CI, 9.9 percentage points lower to 3.1 percentage points higher) than that of nasopharyngeal swabs. Among persons with previously confirmed SARS-CoV-2 infection, saliva's sensitivity was 1.5 percentage points higher (CI, 7.3 percentage points lower to 10.3 percentage points higher) than that of nasopharyngeal swabs. Among persons without a previous SARS-CoV-2 diagnosis, saliva was 7.9 percentage points less (CI, 14.7 percentage points less to 0.8 percentage point more) sensitive. In this subgroup, if testing 100 000 persons with a SARS-CoV-2 prevalence of 1%, nasopharyngeal swabs would detect 79 more (95% uncertainty interval, 5 fewer to 166 more) persons with SARS-CoV-2 than saliva, but with an incremental cost per additional infection detected of $8093.

Limitation: The reference standard was imperfect, and saliva collection procedures varied.

Conclusion: Saliva sampling seems to be a similarly sensitive and less costly alternative that could replace nasopharyngeal swabs for collection of clinical samples for SARS-CoV-2 testing.

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As of 16 December 2020, more than 74 million cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been diagnosed and more than 1.6 million persons have died of it (1). One of the most important components of public health strategies to contain SARS-CoV-2 is maintaining a high level of testing. Testing is prioritized for persons with symptoms of coronavirus disease 2019 (COVID-19) and contacts of those with confirmed SARS-CoV-2 infection (2), but it is often offered to persons at increased risk for exposure (such as health care workers). However, as economies and schools reopen, the pool of persons who may be at increased risk for SARS-CoV-2 exposure will grow (3), placing strain on testing systems.

Reverse transcriptase polymerase chain reaction (RT-PCR) on nasopharyngeal swabs is the reference method to detect SARS-CoV-2 (4). Yet, nasopharyngeal swabs present several barriers to reaching the level of testing required to meet demand and optimally control SARS-CoV-2. Their collection requires a trained health care professional (for example, a nurse), who must be in extensive personal protective equipment (5). Further, although more prominent early in the COVID-19 pandemic, supply chain issues (6) for nasopharyngeal swabs—and the transport media used during their transportation—still exist (7).

Saliva-based sampling for SARS-CoV-2 detection via RT-PCR has the potential to address many of the barriers associated with nasopharyngeal swab sampling (8). Saliva samples can be collected by the persons being tested themselves, with instruction from lower-cadre health care professionals or other personnel. This reduces exposure to health care workers and the need for personal protective equipment during collection. Saliva can be collected in sterile containers, removing the need for swabs. These practical advantages reduce human resource needs and could expand the number of persons who can be tested. However, the comparative sensitivity of saliva and nasopharyngeal swabs for SARS-CoV-2 detection is uncertain, which has impeded saliva's adoption.

We conducted a systematic review and meta-analysis to estimate the comparative sensitivity of saliva versus nasopharyngeal swabs for detection of SARS-CoV-2 and an economic evaluation to estimate the incremental cost

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per additional SARS-CoV-2 infection detected with nasopharyngeal swabs.

METHODS

Systematic Review and Meta-analysis

This systematic review follows PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) (9) and MOOSE (Meta-analysis of Observational Studies in Epidemiology) (10) guidelines, and its protocol is registered on PROSPERO (CRD42020203415).

Data Sources and Searches

We searched Medline and Embase from 1 January to 1 November 2020. We used a comprehensive search strategy (Table 1 of Supplement 1, available at Annals.org) with a combination of medical subject headings and free text containing concepts related to SARS-CoV-2, molecular diagnosis (such as RT-PCR), and respiratory specimens (such as nasopharyngeal swabs and saliva). No language restrictions were used. We additionally searched medRxiv and bioRxiv until 1 November 2020 for preprint literature; we used analytic code to screen for preprint manuscripts containing the words "COVID-19" or "SARS-CoV-2" and "saliva" in titles and abstracts before reviewer screening.

Study Selection

Eligible studies were randomized clinical trials, case series, cohort studies, case–control studies, and cross-sectional studies that reported accuracy of saliva-based sampling compared with nasopharyngeal swabs for SARS-CoV-2, reported at least 5 paired samples (that is, nasopharyngeal and saliva samples collected at the same time), and used the same method for detecting SARS-CoV-2 in nasopharyngeal and saliva samples. We excluded studies that did not assess diagnostic accuracy, as well as reviews, commentaries, editorials, case reports, mathematical modeling studies, economic analyses, and conference abstracts.

Three reviewers (M.L.B., S.P., and J.R.C.) independently screened all titles, abstracts, and full texts. At the full-text stage, reference lists were reviewed for relevant additional studies. Discordance on which studies to include was resolved by consensus.

Data Extraction and Quality Assessment

Two reviewers (M.L.B. and S.P.) independently extracted 25% of the data using a standardized form (fields are shown in Table 2 of Supplement 1); findings were checked for agreement. Concordance was high; thus, a single reviewer extracted the remaining data, and the other reviewer verified extractions. Extracted information included study design, location, enrollment dates, included population (persons presenting for SARS-CoV-2 testing or persons with confirmed SARS-CoV-2 infection), study setting (inpatient or outpatient), presence of symptoms when sampling was done, demographic information (age and sex), laboratory methods (analytic method used, primer, transport media, and cycle threshold values), and sampling method for saliva collection. We extracted the number of persons testing positive via nasopharyngeal swabs, saliva sampling, or on either sample. To complete missing data, we contacted 25 authors, of whom 18 (72%) replied.

Risk of bias and applicability concerns among included studies were assessed using an adapted QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) (11) tool. The tool assessed the following domains: patient selection, performance of the index test, performance of the reference test, and flow and timing (Table 3 of Supplement 1). Two reviewers (M.L.B. and S.P.) independently assessed studies, and disagreement was resolved through consensus.

Data Synthesis and Analysis

The primary outcome of interest was the difference between saliva samples and nasopharyngeal swabs in sensitivity for SARS-CoV-2 detection; a positive result with either sample was considered the reference standard. The secondary outcome of interest was the sensitivity of saliva for SARS-CoV-2 detection, with a positive result with either saliva or nasopharyngeal swabs as the reference standard. Because we assumed that any positive result was a true positive, we could not estimate specificity.

In our primary analysis, we estimated the pooled difference in sensitivity between saliva samples and nasopharyngeal swabs for all included studies. To assess possible sources of heterogeneity, we did numerous stratified analyses. The a priori–specified analyses were on population sampled (persons presenting for SARS-CoV-2 testing or those with confirmed SARS-CoV-2 infection), age (adult or pediatric) and symptoms present at sampling (asymptomatic or symptomatic). The post hoc analyses were on study setting (outpatient or inpatient), method of saliva collection (general spitting technique, early-morning posterior oropharyngeal spitting technique, drooling technique, posterior pharyngeal spitting technique, or saliva collection device), use of transport media with the saliva sample (yes or no), analytic platform (laboratory-based RT-PCR or other), and number of risk of bias domains at low risk of bias (≥4 or <4). We pooled results only when at least 3 studies were included in stratified analyses; otherwise, we report only individual study estimates.

Meta-analyses were done with package meta, version 4.14 (12), and package metafor, version 2.4-0 (13), in R (R Foundation) (see Supplement 2, available at Annals.org, for additional methods and code). We estimated the difference and SE in sensitivity between saliva and nasopharyngeal swabs for each study, accounting for the paired nature of sample collection using the Wilson method (14), and calculated 95% CIs. We pooled estimates with random-effects meta-analysis using the inverse variance method and Sidik–Jonkman estimator with a Knapp–Hartung adjustment for heterogeneity (15–17). For the secondary analysis estimating the sensitivity of saliva sampling, we used random-effects meta-analysis with generalized linear mixed models (18); individual study estimates were logit-transformed for pooling, and

pooled estimates were back-transformed. For all analyses, heterogeneity was reported using the I^2 statistic (19).

Economic Evaluation

Data Inputs

We collected costs associated with both nasopharyngeal swabs and saliva sampling using a microcosting approach. To arrive at costs per person sampled, we considered costs associated with materials (swabs, transport media, containers, and personal protective equipment) and personnel to collect the samples. On the basis of previous experience in Canada (3), we estimated that a nurse would take 6 minutes to conduct sampling with a nasopharyngeal swab (including changing of gloves and gown), whereas saliva-based sampling would be task-shifted to a lower-cadre health care professional or administrative personnel and would take 4 minutes (including changing of gloves). Transportation and laboratory costs for sample analysis were assumed to be identical. Cost estimates for materials and nurse salary (20) were from nationally representative sources in Canada in 2020 Canadian dollars. To enhance generalizability, we estimated the salary difference between a nurse and lower-cadre health care professional using data from an econometric analysis (21) for high-income countries; we assumed that administrative personnel would have the same salary. We converted cost estimates to U.S. dollars using exchange rates for materials costs (22) and purchasing power parity for personnel costs (23). Cost inputs are reported in Table 4 of Supplement 1.

Data Analysis

All analyses were conducted in R (see Supplement 2 for additional methods and code). The population of interest for the economic evaluation was persons presenting for SARS-CoV-2 testing (that is, without confirmed SARS-CoV-2 infection). We selected this group a priori because they were the most probable target population where saliva testing would be implemented. Using sensitivity difference estimates from our meta-analysis, we estimated the additional number of infections detected with nasopharyngeal swabs versus saliva sampling per 100 000 persons tested at population prevalence levels of 0.01%, 0.1%, 1%, and 10%. We fitted our estimate for the difference in sensitivity between nasopharyngeal swabs and saliva to a normal distribution and cost parameters to γ distributions (Table 5 of Supplement 1). We sampled from these distributions 1000 times and estimated the difference and 95% uncertainty interval (UI) in cost and number of persons correctly diagnosed with SARS-CoV-2 infection with nasopharyngeal swabs or saliva. Using these outputs, we calculated the proportion of samples where saliva was dominant to nasopharyngeal sampling (that is, lower cost and better sensitivity). We report point estimates of the incremental cost-effectiveness ratio and visualize uncertainty using a cost-effectiveness plane.

To cover a range of possible scenarios, we did post hoc secondary analyses to evaluate implications of sensitivity differences. We evaluated several scenarios where nasopharyngeal swabs were more sensitive than saliva (1, 2, 5, 10, and 20 percentage points more) at different SARS-CoV-2 prevalence estimates (0.01%, 0.1%, 1%, and 10%). For each analysis, we calculated the incremental cost per additional person with SARS-CoV-2 identified with nasopharyngeal swabs versus saliva.

Role of the Funding Source

This study was funded by the McGill Interdisciplinary Initiative in Infection and Immunity. The funders had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

RESULTS

Systematic Review and Meta-analysis

Characteristics of Included Studies

We identified 22 795 records for screening. After title and abstract screening, 127 studies entered full-text assessment. Overall, 37 studies (24–55-56–60) were included (Appendix Figure, available at Annals.org), comprising 7169 participants with 7332 paired saliva samples and nasopharyngeal swabs. Summary characteristics of included studies are reported in Table 1 and individual study characteristics in Tables 6 and 7 of Supplement 1. Of the 37 studies, 6 (16%) were at high or unclear risk of bias or applicability in 4 or more domains, 25 (68%) were at high or unclear risk of selection bias, and 32 (87%) were at high or unclear risk of bias due to blinding during sample analysis (Figure 1 of Supplement 1).

Of the 37 included studies, 34 (92%) used laboratory-based RT-PCR for SARS-CoV-2 detection and 3 (8%) used other methods (Table 8 of Supplement 1). Saliva was collected from participants using a general spitting technique in 20 studies (54%), drooling technique in 4 studies (11%), early-morning posterior oropharyngeal spitting technique in 4 studies (11%), posterior pharyngeal spitting technique in 4 studies (11%), and saliva collection device in 3 studies (8%) (Table 9 of Supplement 1 gives detailed collection descriptions). Transport media was used for saliva specimens in 18 studies (49%) (Table 10 of Supplement 1). Eighteen studies (49%) reported results for only symptomatic participants and 2 (5%) for only asymptomatic participants. The population of interest was only persons presenting for SARS-CoV-2 testing (that is, undiagnosed SARS-CoV-2 infection) in 17 studies (46%), whereas in 11 (30%) it was only persons with previously confirmed SARS-CoV-2 (by pharyngeal swab).

Primary Analysis

Among 7332 paired samples included, 2327 (32%) were positive on either nasopharyngeal swab or saliva. For our primary outcome, we estimated that saliva's sensitivity was 3.4 percentage points lower (95% CI, 9.9 percentage points lower to 3.1 percentage points higher) than that of nasopharyngeal swabs (Figure). Heterogeneity based on the I^2 statistic was 89%. For our secondary outcome, among the 2327 samples positive on either saliva or nasopharyngeal swabs, 1927 were positive with saliva, for a pooled sensitivity of 86.9% (CI, 82.3% to 90.4%).

Table 1. Summary Characteristics of Included Studies

Factor/Parameter	Studies (*n* = 37), *n* (%)	Participants Included (*n* = 7169), *n* (%)	Paired Samples (*n* = 7332), *n* (%)
Analysis method			
Laboratory-based RT-PCR	34 (91.9)	6587 (91.9)	6765 (92.3)
Other molecular method*	3 (8.1)	582 (8.1)	567 (7.7)
Population			
Only persons presenting for SARS-CoV-2 testing	17 (45.9)	5058 (70.6)	5045 (68.8)
Only persons with confirmed SARS-CoV-2	11 (29.7)	786 (11.0)	840 (11.5)
Both populations†	9 (24.4)	1325 (18.4)	1447 (19.7)
Setting			
Only outpatient	17 (46.0)	4031 (56.2)	4150 (56.6)
Only inpatient	11 (29.7)	1735 (24.2)	1788 (24.4)
Both outpatient and inpatient‡	9 (24.3)	1403 (19.6)	1394 (19.0)
Symptoms at sampling			
Only asymptomatic	2 (5.4)	378 (5.3)	378 (5.2)
Only symptomatic	18 (48.6)	3059 (42.7)	3093 (42.2)
Both symptomatic and asymptomatic§	17 (46.0)	3732 (52.0)	3861 (52.6)
Population age group			
≥18 y	23 (62.2)	3647 (50.9)	3789 (51.7)
Mixed or not reported‖	14 (37.8)	3522 (49.1)	3543 (48.3)
Country			
Brazil	1 (2.8)	13 (0.2)	13 (0.2)
Canada	3 (8.1)	401 (5.6)	401 (5.5)
China	2 (5.4)	120 (1.7)	153 (2.1)
Dubai	1 (2.8)	401 (5.6)	401 (5.5)
France	1 (2.7)	123 (1.7)	123 (1.7)
French Guiana	1 (2.7)	776 (10.8)	776 (10.6)
India	1 (2.7)	74 (1.0)	74 (1.0)
Italy	2 (5.4)	171 (2.4)	156 (2.1)
Japan	4 (10.8)	475 (6.6)	475 (6.5)
Kuwait	1 (2.8)	891 (12.4)	891 (12.2)
Malaysia	1 (2.8)	217 (3.0)	217 (3.0)
Singapore	2 (5.4)	242 (3.4)	379 (5.2)
Thailand	1 (2.7)	200 (2.8)	200 (2.7)
Turkey	1 (2.7)	200 (2.8)	200 (2.7)
United Kingdom	1 (2.7)	110 (1.5)	110 (1.5)
United States	14 (37.8)	2755 (38.2)	2763 (37.7)
Saliva collection method			
Drooling technique	5 (13.5)	890 (12.4)	882 (12.0)
Early-morning posterior oropharyngeal spitting technique	3 (8.1)	337 (4.7)	370 (5.0)
General spitting technique	20 (54.1)	4216 (58.8)	4223 (57.6)
Saliva collection device	3 (8.1)	107 (1.5)	101 (1.4)
Posterior pharyngeal spitting technique	4 (10.8)	1349 (18.8)	1486 (20.3)
Not reported	2 (5.4)	270 (3.8)	270 (3.7)
Used transport media with saliva			
Yes	18 (48.6)	3230 (45.1)	3380 (46.1)
No	18 (48.6)	3865 (53.9)	3878 (52.9)
Not reported	1 (2.8)	74 (1.0)	74 (1.0)

RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
* Includes point-of-care polymerase chain reaction system (Xpert Xpress [Cepheid]) and transcription-mediated amplification.
† Five studies reported information stratified by persons presenting for testing and patients with confirmed SARS-CoV-2 infection. One study reported information stratified by confirmed SARS-CoV-2, but persons presenting for testing were excluded from analyses because they had no positive results in saliva or nasopharyngeal swabs.
‡ Three studies provided information stratified by setting.
§ Six studies provided information stratified by symptoms.
‖ One study provided results stratified by adults vs. the pediatric population. However, in the stratified results, the authors reported any positive sample (*n* = 43, in the pediatric group) but did not report the stratified results by age for the dual negatives (*n* = 203).

Stratified Analysis

Table 2 shows results stratified by population characteristics, in which we observed no significant differences. Among 22 studies with data on persons presenting for SARS-CoV-2 testing consisting of 5599 paired samples, saliva was 7.9 percentage points less (CI, 16.7 percentage points less to 0.8 percentage point more) sensitive than nasopharyngeal swabs. Conversely, among 17 studies with data on

persons with previously confirmed SARS-CoV-2 infection, saliva's sensitivity was 1.5 percentage points higher (CI, 7.3 percentage points lower to 10.3 percentage points higher) among 1158 paired samples (**Table 11** of **Supplement 1**). Saliva was 4.9 percentage points less (CI, 10.2 percentage points less to 0.4 percentage point more) sensitive than nasopharyngeal swabs among symptomatic persons and 1.6 percentage points less (CI, 37.4 percentage points less to 34.1 percentage points more) sensitive than nasopharyngeal swabs among asymptomatic persons (**Table 12** of **Supplement 1**). Differences in sensitivity did not differ between inpatients and outpatients (**Table 13** of **Supplement 1**). In the only study with stratified data on pediatric participants, saliva was 9.3 percentage points less (CI, 26.1 percentage points less to 7.5 percentage points more) sensitive than nasopharyngeal swabs among 43 samples positive on either specimen (**Table 14** of **Supplement 1**). Heterogeneity remained high ($I^2 \geq 75\%$) in stratified analyses.

Results stratified by study-level characteristics are reported in **Table 3**; we found no significant differences in sensitivity except when considering the saliva collection method (**Table 15** of **Supplement 1**). The sensitivity of saliva versus nasopharyngeal swabs was 15.4 percentage points higher (CI, 42.9 percentage points lower to 73.8 percentage points higher) with early-morning posterior oropharyngeal spitting technique ($n = 370$ paired samples), 1.6 percentage points higher (CI, 44.5 percentage points lower to 47.6 percentage points higher) with a saliva collection device ($n = 101$ paired samples), 0.6 percentage point higher (CI, 38.4 percentage points lower to 39.6 percentage points higher) with drooling technique ($n = 882$ paired samples), 1.8 percentage points lower (CI, 38.8 percentage points lower to 35.1 percentage points higher) with posterior pharyngeal spitting technique ($n = 1486$ paired samples), and 8.1 percentage points lower (CI, 15.3 to 0.9 percentage points lower) with a general spitting technique ($n = 4223$ paired samples). Transport media, analytic method, study design, and study quality (Tables 16 to 19, respectively, of **Supplement 1**) did not seem to affect sensitivity differences. Heterogeneity remained high ($I^2 \geq 75\%$) in most stratified analyses.

Economic Evaluation

We estimated that the collection of specimens by saliva compared with nasopharyngeal swab would save $636 105 (95% UI, $467 427 to $831 770) per 100 000 persons sampled (**Table 4**). If the prevalence of SARS-

Figure. Forest plot of all included studies in the primary analysis estimating the difference in sensitivity between saliva and nasopharyngeal swabs.

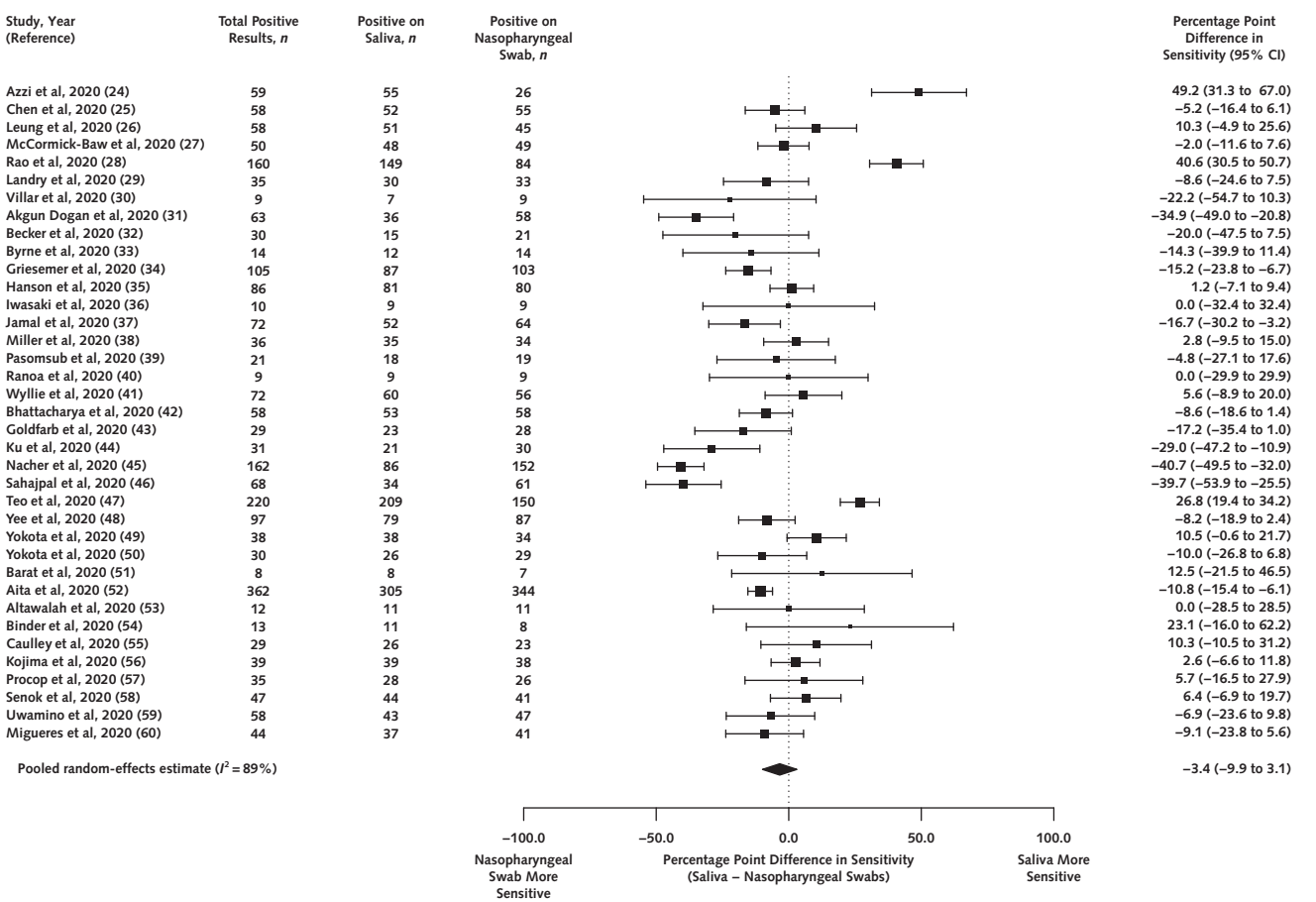

Table 2. Summary Table of Pooled Estimates on Difference in Sensitivity for SARS-CoV-2 Between Nasopharyngeal Swabs and Saliva, Stratified by Population Characteristics

Population Characteristic	Studies, *n*	Paired Samples Tested, *n*	Positive Results on Nasopharyngeal Swab, *n*	Positive Results on Saliva, *n*	Positive Results on Any Sample (Reference), *n*	Saliva Sensitivity		Difference in Sensitivity (Saliva – Nasopharyngeal)	
						Estimate (95% CI), %	I^2, %	Estimate (95% CI), *percentage points*	I^2, %
Population sampled*									
Persons with confirmed SARS-CoV-2 infection	17	1158	637	701	808	87.3 (81.3 to 91.6)	74	1.5 (−7.3 to 10.3)	78
Persons presenting for SARS-CoV-2 testing	22	5599	1243	1100	1381	85.4 (78.1 to 90.6)	89	−7.9 (−16.7 to 0.8)	89
Symptoms at the time of sampling†									
Symptomatic	24	3605	1292	1221	1437	87.0 (81.6 to 90.9)	82	−4.9 (−10.2 to 0.4)	75
Asymptomatic	8	800	226	317	357	85.8 (69.6 to 94.1)	83	−1.6 (−37.4 to 34.1)	96
Setting‡									
Outpatient	20	4429	899	862	1039	87.9 (81.5 to 92.2)	82	−4.3 (−11.8 to 3.2)	79
Inpatient	14	1917	865	784	950	85.3 (77.3 to 90.9)	85	−6.6 (−14.7 to 1.4)	79
Age group§									
Adults (≥18 y)	24	3843	983	1104	1243	90.4 (86.1 to 93.5)	76	3.1 (−5.1 to 11.3)	86
Pediatric (<18 y): only 1 study, not pooled									
Yee et al, 2020 (48)	1	43	38	34	43‖	79.1 (64.4 to 88.7)	–	−9.3 (−26.1 to 7.5)	–

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
* Three studies did not report information stratified by population being sampled.
† Ten studies did not report information stratified by symptoms.
‡ Six studies did not report information stratified by setting.
§ Thirteen studies did not report information by age group.
‖ This study did not report information on dual negatives stratified by age.

CoV-2 is 1% among persons presenting for SARS-CoV-2 testing, then, on the basis of our estimates of the pooled difference in sensitivity in this population, we estimated that use of nasopharyngeal swabs would identify 79 more (95% UI, 5 fewer to 166 more) persons with SARS-CoV-2 infection per 100 000 persons sampled. This equated to a cost of $8093 per additional infection identified when using a nasopharyngeal swab. We estimated a 3.9% probability that saliva would both be cheaper and identify more persons with SARS-CoV-2 infection than nasopharyngeal swabs (**Figure 2** of **Supplement 1**). In secondary analyses, the cost per additional person with SARS-CoV-2 identified varied proportionally with changes in prevalence and differences in sensitivity (**Table 20** of **Supplement 1**).

Discussion

In this meta-analysis of 37 studies comprising 7169 participants providing 7332 paired saliva samples and nasopharyngeal swabs, we found no statistically significant difference in sensitivity between these specimens for SARS-CoV-2 detection. In the economic evaluation of the subgroup of undiagnosed persons presenting for SARS-CoV-2 testing, in whom nasopharyngeal swabs were nonsignificantly more sensitive, the incremental cost per additional SARS-CoV-2 infection detected with nasopharyngeal swabs versus saliva was $8093 if the prevalence was 1%, although UIs were wide. These data suggest that saliva sampling could be an important alternative to nasopharyngeal swabs.

We found indications that the method of saliva collection might affect sensitivity. Studies using a general spitting technique for saliva collection showed a significantly lower sensitivity for saliva than for nasopharyngeal swabs. These data suggest use of other saliva collection techniques (such as early-morning posterior oropharyngeal spitting or drooling) when possible. Saliva sensitivity was not significantly different from nasopharyngeal swab sensitivity among asymptomatic persons and outpatients (suggesting milder disease). These results suggest that saliva may be a particularly useful method of sample collection in community settings.

Previous systematic reviews and meta-analyses have compared nasopharyngeal swabs with saliva sampling (61, 62). These reviews were done earlier in the pandemic and were limited by few studies (≤8) and the participant populations (majority symptomatic) examined at the time. Our meta-analysis builds on this literature with more diverse participant populations, settings, and saliva collection methods. An important additional advantage is our paired economic evaluation, making explicit the potential tradeoffs with moving to saliva sampling. At a prevalence of 1%, our analysis suggests that the added cost ($8093) of detecting an additional SARS-CoV-2 infection with nasopharyngeal swabs could be used to collect more than 3900 saliva samples.

Saliva sampling is an immediate way to expand testing access, while freeing up much-needed health care resources. Saliva sampling has already launched in some jurisdictions (63–65), and a laboratory protocol has received emergency use authorization from the U.S. Food and Drug Administration (66, 67). Although laboratories analyzing saliva will need to validate analytic methods, this can be done and implemented much more quickly than approving, producing, and distributing new tests, such as those intended to be used daily or at the point of care (68).

Maintaining a high level of testing has been repeatedly shown to be an important part of public health strategies to contain SARS-CoV-2 (2, 69, 70). Although laboratory reagents (such as primers and extraction reagents) are an ongoing bottleneck, so too is access to nasopharyngeal swabs (and viral transport media) and trained health care professionals to administer them (71–73). Such methods as pooling samples may overcome some reagent shortages when SARS-CoV-2 prevalence is low (74), but no such methods are available for swabs. Even if a minority of persons may not be able to produce adequate amounts of saliva—and thus would require a nasopharyngeal swab—nasopharyngeal swabs are an uncomfortable method of specimen collection (75) that also carries risk for occupational exposure to the health care workers collecting the samples. We expect that a less invasive and cheaper approach with similar sensitivity may allow a rapid increase in testing, while freeing up much-needed health care professionals for forthcoming vaccinations.

The most important strength of this study is the large number of studies included in the meta-analysis, with participants from many settings with diverse clinical characteristics. These qualities permitted extensive stratified analyses to examine potentially important sources of variability, such as saliva collection method, study setting, testing purpose, and presence of symptoms. We found consistent results in nearly all stratified analyses, enhancing generalizability. In addition, pairing the meta-analysis with an economic evaluation provides data to policymakers about cost and feasibility should they consider adopting saliva sampling. The probabilistic nature of the analysis makes explicit the uncertainty in our estimates,

Table 3. Summary Table of Pooled Estimates on Difference in Sensitivity for SARS-CoV-2 Between Nasopharyngeal Swabs and Saliva, Stratified by Study Characteristics

Study Characteristic	Studies, *n*	Paired Samples Tested, *n*	Positive Results on Nasopharyngeal Swab, *n*	Positive Results on Saliva, *n*	Positive Results on Any Sample (Reference), *n*	Saliva Sensitivity		Difference in Sensitivity (Saliva – Nasopharyngeal)	
						Estimate (95% CI), %	I^2, %	Estimate (95% CI), %	I^2, %
Used transport media*									
Yes	18	3380	1066	1036	1232	88.0 (80.2 to 93)	89	−2.8 (−11.6 to 6.1)	86
No	18	3878	859	838	1037	85.4 (79.3 to 89.9)	80	−3.7 (−14.8 to 7.3)	90
Saliva collection method†									
Drooling technique	5	882	133	137	173	87.9 (69.9 to 95.8)	77	0.6 (−38.4 to 39.6)	90
Early-morning posterior oropharyngeal spitting technique	3	370	184	252	276	91.3 (87.4 to 94.1)	0	15.4 (−42.9 to 73.8)	93
General spitting technique	20	4223	960	827	1064	84.7 (77.4 to 90)	87	−8.1 (−15.3 to −0.9)	80
Saliva collection device	3	101	39	41	46	89.1 (76.4 to 95.4)	0	1.6 (−44.5 to 47.6)	47
Posterior pharyngeal spitting technique	4	1486	562	574	652	91.5 (72.7 to 97.7)	94	−1.8 (−38.8 to 35.1)	97
Laboratory method‡									
RT-PCR	34	6765	1799	1746	2133	85.9 (80.9 to 89.8)	87	−3.6 (−10.7 to 3.6)	89
Other molecular method‡	3	567	184	181	194	93.3 (88.8 to 96.1)	0	−1.4 (−9.1 to 6.3)	8
Study design									
Cohort	34	7192	1915	1850	2240	86.8 (81.9 to 90.5)	87	−4.2 (−11 to 2.6)	89
Case–control: only 2 studies, not pooled									
Leung et al, 2020 (26)	1	95	45	51	58	87.9 (76.7 to 95)	–	10.3 (−4.9 to 25.1)	–
Kojima et al, 2020 (56)	1	45	23	26	29	89.7 (72.6 to 97.8)	–	10.3 (−10.5 to 30.4)	–
Quality assessment									
Scored ≥4 points across 7 domains	31	6902	1783	1724	2093	86.5 (81.1 to 90.5)	89	−4.1 (−11.7 to 3.5)	91
Scored <4 points across 7 domains	6	430	200	203	234	86.8 (81.8 to 90.5)	0	−0.1 (−11.4 to 11.2)	44

RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
* One study did not report whether transport medium was used.
† Two studies did not report method of saliva collection.
‡ Two studies used point-of-care polymerase chain reaction system (Xpert Xpress [Cepheid]), and 1 used transcription-mediated amplification.

Table 4. The Incremental Cost per Additional SARS-CoV-2 Infection Identified via Nasopharyngeal Versus Saliva Sampling at Varying Levels of SARS-CoV-2 Prevalence in Persons Presenting for Testing*

Prevalence of SARS-CoV-2 in Sampled Population, %	Additional SARS-CoV-2 Infections Identified (Nasopharyngeal − Saliva) per 100 000 Persons Sampled (95% UI), *n*	Incremental Cost per Additional SARS-CoV-2 Infection Identified (Nasopharyngeal − Saliva), *$*
0.01	0.8 (−0.1 to 1.7)	809 277
0.1	7.9 (−0.5 to 16.6)	80 928
1	78.6 (−5.2 to 166.0)	8093
10	786.0 (−51.8 to 1659.9)	809

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; UI = uncertainty interval.

* The difference in cost per 100 000 persons sampled (nasopharyngeal – saliva) is $636 105 (95% UI, $467 427 to $831 770). The probability that saliva is dominant (i.e., cheaper and more sensitive) is 3.9%. Estimates and uncertainty ranges are derived from sampling 1000 times from probabilistic distributions of cost and sensitivity parameters. The difference in sensitivity between nasopharyngeal swabs and saliva sampling was derived from meta-analysis of persons with undiagnosed SARS-CoV-2 infection presenting for testing (saliva sensitivity is 7.9 percentage points lower [95% CI, 14.7 percentage points lower to 0.8 percentage point higher] than nasopharyngeal swab sensitivity)—i.e., the point estimate indicates that saliva is *less* sensitive.

allowing informed decision making in various realistic prevalence scenarios.

These analyses also have limitations. We used an imperfect reference standard assuming that tests would not result in false positives. This precludes estimation of specificity and results in the sampling method with the most positive results being the most sensitive method. Contamination is the most likely source of false positives (76). However, we did not observe systematic trends across included studies, which may suggest that contamination with 1 sampling method was driving results. Different methods of saliva collection and transport media were used, although in most cases these did not seem to affect results. In the subgroup of participants with paired samples who already had confirmed SARS-CoV-2 infection, the method of initial diagnosis was by pharyngeal swab in all studies. This might be expected to bias estimates in favor of nasopharyngeal swabs, but sensitivity differences were nonsignificant. Many studies had risk of bias due to lack of blinding during analysis. Although samples are unlikely to be easily identified after processing in the laboratory, it is uncertain what effect this might have had on outcomes. We assumed that laboratory costs for saliva and nasopharyngeal samples were identical; some samples may require additional processing, but this is unlikely to significantly affect our findings. Further, we did not consider potential downstream costs and impacts. However, we judge it unlikely that these would be affected by method of sampling. The economic and public health implications of missing SARS-CoV-2 infections are important, but no sample collection method, including nasopharyngeal swabs, is 100% sensitive. Missed infections already occur, particularly if persons at risk are not tested at all. Finally, we identified only 1 study that stratified pediatric results. Caution is required in generalizing findings to pediatrics, although saliva sample collection in children may be preferable given the difficulties of nasopharyngeal swabbing in this population (63).

In this study, saliva sampling had similar yield to and lower costs than nasopharyngeal swabs for detecting SARS-CoV-2. Given these findings, plus the advantages of reduced invasiveness, reduced need for trained health care professionals, lower risk for occupational exposure, and reduced need for specialized supplies, we suggest that saliva sampling should replace nasopharyngeal swabs in most populations being tested for SARS-CoV-2.

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Note: Drs. Campbell and Menzies affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix Figure. Evidence search and selection.