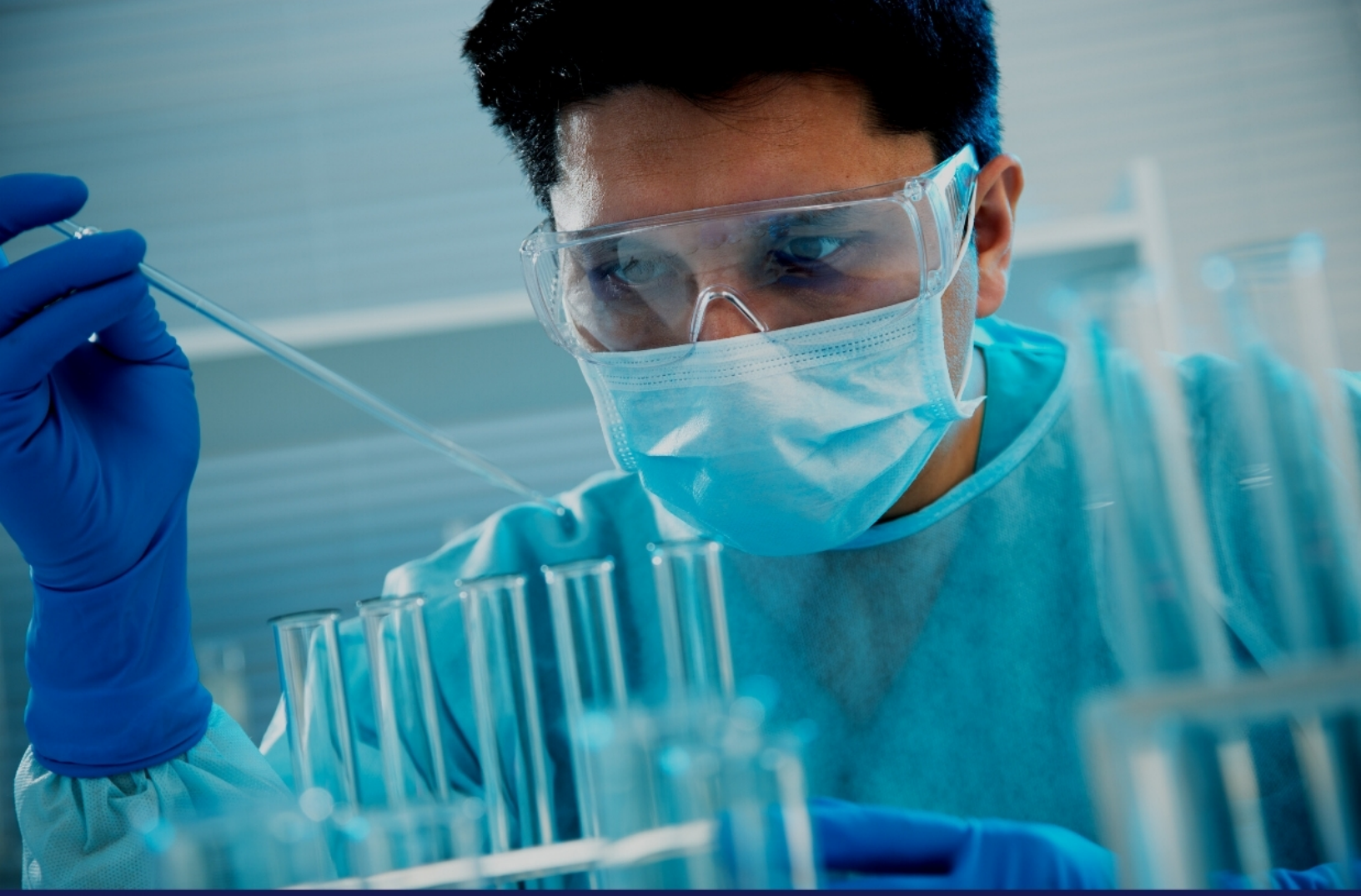

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Saliva-based testing for diagnosis of SARS-CoV-2 infection: A meta-analysis.

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To the Editor,

Diagnostic testing of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is primarily conducted from an upper respiratory specimen, like nasopharyngeal swab (NPS) or oropharyngeal swab (OPS) obtained by the health-care personnel. Recent systematic reviews concluded that non-invasive saliva might serve as an alternative specimen type to NPS, but evidence was still limited (1, 2). These systematic reviews included studies with confirmed coronavirus disease (COVID-19) patients, therefore

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addressing different population and context (i.e. utility of test during some follow-up) compared to testing patients without COVID-19.

The Food and Drug Administration has authorized at least six saliva-based tests for emergency use for SARS-CoV-2 diagnosis (3). Nonetheless, the World Health Organization does not currently recommend saliva specimen for routine diagnostic use (4).

We conducted a meta-analysis of diagnostic accuracy studies that compared saliva-based index test to NPS or OPS based reference test in patients without confirmed SARS-CoV-2 at enrollment. PubMed was used (latest search as of September 15) with a search strategy: *saliva and diagnosis and (COVID-19 or COVID 19 or SARS-COV-2 or SARS-COV 2)*. In addition, medRxiv and bioRxiv were used, and references checked from published studies on the topic. Studies with less than 50 patients, studies with patients with confirmed SARS-CoV-2 infection, and studies without relevant diagnostic data for sensitivity and specificity were excluded. Stata version 16.0 with a user-written module (5) was used for bivariate modeling to obtain average sensitivity and specificity with 95% confidence interval (CI).

Fourteen studies (16 cohorts) were included (6-19). A total number of patients for sensitivity and specificity comparison was 5863 (median 158, interquartile range 94 to 234) (Supplemental Table 1). Mean or median age of patients ranged from 33.5 to 44.9 years in six studies (seven cohorts) where information was available, and three studies included some pediatric patients. A consecutive enrollment of patients was mentioned in one study and no patients were excluded from one study's other cohort. One study estimated specificity of saliva-based test in a subsample of patients, which excluded most of the test negative patients.

Nine studies reported polymerase chain reaction (PCR) cycle threshold (Ct) for positivity, and it varied from 37 to 45. Out of 10 studies that reported specific SARS-CoV-2 target genes, four focused on single E or N target genes.

A prevalence of SARS-CoV-2 infection varied from 0.3% to 78.4% (median 20.8%, interquartile range 7.1% to 37.2%) with NPS or OPS across the 16 cohorts. Average sensitivity was 0.85 (95% CI 0.77 to 0.91) and average specificity 0.99 (95% CI 0.98 to 1.00) with saliva-based index test compared to NPS or OPS based reference test (Figure 1). Positive and negative likelihood ratio was 90 (95% CI 35 to 234) and 0.15 (95% CI 0.10 to 0.23), respectively. Between-study heterogeneity is visualized in Supplemental Figure 1.

Two studies (two cohorts) (13, 19) were outliers on model check, and exclusion of these studies did not markedly affect average sensitivity and specificity, as did not when Ct for positivity was adjusted with meta-regression.

Our meta-analysis shows that saliva-based nucleic acid amplification tests have lower sensitivity and comparable specificity in diagnostic testing of SARS-CoV-2 infection among nearly 5900 asymptomatic or symptomatic patients without confirmed COVID-19 diagnosis at study enrollment, which reflects a typical testing setting in general population.

Some reasons, like lower viral loads in saliva specimens, might explain why saliva is an inferior specimen type compared to swab specimen for the detection of SARS-COV-2. Studies included in our analyses tended to report higher Ct values (suggesting lower viral loads) for saliva specimens although not systematically evaluated.

Czumbel and coworkers highlighted conditions to be standardized for optimal saliva-based testing, such as sample collection, transportation and test methods (1). Nonetheless, saliva-based testing can offer benefits, including no need of health-care workers for sample collection. According to one study, only a small proportion of self-collected saliva samples were deemed unsuitable (20).

Our meta-analysis has limitations. First, one author conducted search and extracted data from the included studies. Second, no risk of bias assessment was done. Third, average sensitivity and specificity warrants cautious interpretation due to unclear or varying thresholds for positivity.

In conclusion, saliva-based test appears to be a less sensitive specimen type compared to upper respiratory specimens for SARS-CoV-2 nucleic acid amplification. This highlights the need for proper validation of diagnostic tests that rely on specimen types less frequently deployed. Saliva-based tests might require fewer resources, less technical expertise, and cause less discomfort to patients compared upper respiratory specimens. Thus, the inferior performance of saliva-based tests may be overcome by their better utility in specific settings.

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Figure Legends

Figure 1. Sensitivity and specificity of saliva-based index test compared to nasopharyngeal or oropharyngeal swab-based reference test for diagnostic testing of SARS-CoV-2 infection with nucleic acid amplification, based on 14 studies (16 cohorts).