Performance of RT-PCR on Saliva Specimens Compared With Nasopharyngeal Swabs for the Detection of SARS-CoV-2 in Children

A Prospective Comparative Clinical Trial

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Background: Saliva reverse transcriptase-Polymerase chain reaction (RT-PCR) is an attractive alternative for the detection of severe acute respiratory syndrome coronavirus 2 in adults with less known in children.

Methods: Children with coronavirus disease 2019 symptoms were prospectively enrolled in a 1-month comparative clinical trial of saliva and nasopharyngeal (NP) RT-PCR. Detection rates and sensitivities of saliva and NP RT-PCR were compared as well as discordant NP and saliva RT-PCR findings including viral loads (VLs).

Results: Of 405 patients enrolled, 397 patients had 2 tests performed. Mean age was 12.7 years (range, 1.2–17.9). Sensitivity of saliva was 85.2% (95% confidence interval: 78.2%–92.1%) when using NP as the standard; sensitivity of NP was 94.5% (89.8%–99.2%) when saliva was considered as the standard. For a NP RT-PCR VL threshold of $\geq 10^3$ and $\geq 10^4$ copies/mL, sensitivity of saliva increases to 88.7% and 95.2%, respectively. Sensitivity of saliva and NP swabs was, respectively, 89.5% and 95.3% in patient with symptoms less than 4 days ($P = 0.249$) and 70.0% and 95.0% in those with symptoms ≥4–7 days ($P = 0.096$). The 15 patients who had an isolated positive NP RT-PCR were younger ($P = 0.034$), had lower NP VL (median 5.6×10^3 vs. 3.9×10^7, $P < 0.001$), and could not drool saliva at the end of the sampling ($P = 0.002$). VLs were lower with saliva than with NP RT-PCR (median 8.7 cp/mL $\times 10^4$; interquartile range 1.2×10^4–5.2×10^5; vs. median 4.0×10^7 cp/mL; interquartile range, 8.6×10^5–1×10^8; $P < 0.001$).

Conclusions: While RT-PCR testing on saliva performed more poorly in younger children and likely after longer duration of symptoms, saliva remains an attractive alternative to NP swabs in children.

Key Words: SARS-CoV-2, saliva, viral loads, children, sensitivity

(*Pediatr Infect Dis J* 2021;40:e300–e304)

Accepted for publication April 24, 2021

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The saliva PCR were paid for by the cantonal health authorities.

The authors have no conflicts of interest to disclose.

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ISSN: 0891-3668/21/4008-e300

DOI: 10.1097/INF.0000000000003198

Diagnosis for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is pivotal in the management of coronavirus disease 2019 (COVID-19). Accurate and prompt testing of symptomatic children is a foundation for public health decision-making and implementation of appropriate measures including isolation and quarantine.[1]

The Infectious Diseases Society of America guidelines recommend testing for SARS-CoV-2 by reverse transcriptase-Polymerase chain reaction (RT-PCR) on various respiratory specimens, nasopharyngeal (NP) swabs being referenced as the standard.[2,3] However, NP swab collection is an unpleasant procedure, which requires trained staff for collection and can be hampered by shortages in swabs.[4] Saliva is as an attractive alternative for the detection of SARS-CoV-2 with a reported sensitivity of 83.2% compared with 84.8% for NP samples, respectively.[3,5,6]

Given the overlap of symptoms caused by SARS-CoV-2 and other respiratory viruses, children qualify for SARS-CoV-2 testing very often. A simple specimen collection such as saliva is thus particularly attractive in children.[7]

Pediatric evidence for the use of saliva specimens for detection of SARS-CoV-2 is weak with sensitivities ranging from 52.9% up to 85.0% compared with NP reported from small sample sizes.[8,9] This ancillary study of the adult PCR and Rapid Diagnostic Test on Saliva and Nasopharyngeal Swabs for the Detection of SARS-CoV-2 (RADICO) project[10] aims to prospectively compare the paired saliva and NP samples collected from symptomatic children consulting in outpatient settings for the detection of SARS-CoV-2. The secondary objectives were to compare discordant NP and saliva RT-PCR findings as well as their viral loads (VLs).

METHODS

Study Design, Setting and Populations

This study is an observational prospective multicenter comparative study. Children 1 month to 18 years of age were recruited from 2 different outpatient clinics in Lausanne (Montétan screening site, Department Mother-Woman-Child; Lausanne University Hospital and Vidy-Med Pediatric Emergency Center; when presenting with symptoms compatible with COVID-19 according to national guidelines; check.bag-coronavirus.ch/screening).[11] Children 12 years of age and over who reported at least one of the following symptom including fever, respiratory symptoms such as cough, throat pain, dyspnea or thoracic pain, anosmia, dysgeusia or a least 1 minor symptom and close contact with a documented COVID-19 case were invited to be tested for SARS-CoV-2 (check.bag-coronavirus.ch/screening). Testing

criteria were more restrictive for children <12 years of age[11] (www.coronabambini.ch).

Informed consent from the legal guardians or adolescents ≥14 years were mandatory for inclusion. Exclusion criteria included hospitalized children, those requiring anticoagulation and children with a documented past SARS-CoV-2 infection.

This study was approved by the ethics committee of Canton de Vaud (CER-VD 2020-02269) and conducted in accordance with the principles of the Declaration of Helsinki, the standards of Good Clinical Practice and Swiss regulatory requirements.

Study Procedures

Saliva specimens for RT-PCR analyses were collected either by a healthcare professional, the patient, or its caregiver under supervision, following a standard procedure that included the collection of a significant amount of saliva and the drooling of at least 10 µL of saliva in a tube when possible.[10,12] The healthcare professional collected concomitantly 1 NP swab for RT-PCR. Saliva and NP samples collected in standard viral transport media of 3 mL and were sent the same day or the next morning to the molecular diagnostics laboratory for RT-PCR analyses.

General information including age, gender, type and duration of symptoms and information on the quality of the saliva sample were collected by the healthcare worker on an electronic case report form (REDCap: v10.3.3, Vanderbilt University, Nashville, TN). The results of both NP swabs and saliva samples were next reported in REDCap (Vanderbilt University) by the study investigators.

SARS-CoV-2 RT-PCR, Cycle Thresholds and VL Quantification

SARS-CoV-2 RT-PCR were performed using an in-house RT-PCR on the automated molecular diagnostic platform targeting the E gene[13–15] or using the SARS-CoV-2 test of the Cobas 6800 instrument (Roche, Basel, Switzerland).[16] The cycle threshold (cycle when the RT-PCR was positive, ie, above the threshold of fluorescence) was provided automatically by the instruments by using the default parameters. VL was then obtained by converting (cycle threshold) of the RT-PCR instruments, using the formula $\log VL = -0.27Ct + 13.04$, as previously reported.[17,18]

Outcomes

The primary outcome was the proportion of SARS-CoV-2–positive children detected from saliva samples and NP swabs by RT-PCR assays. The secondary outcome was the VLs of SARS-CoV-2 measured by RT-PCR assays on saliva and NP samples.

Statistical Analysis

The estimated sample size was 50 positives among 500 cases tested to have a precision of ±2% on the detection rate if the latter was 20%. The χ^2 test was used to compare categorical variables between groups. We derived medians, used the Mann-Whitney nonparametric method for comparisons of non-normally distributed continuous data and a Student *t* test for normally distributed continuous data. The sensitivity of saliva and NP samples was first calculated by using each other as the standard. Next, a composite standard combining any positive RT-PCR result reported from saliva and/or NP swabs was used to determine the sensitivity of both samples. Stratified subgroup analyses for different age groups divided into 3 age groups: 0–6, ≥6–12 and ≥12 years of age and 3 symptom duration groups: 0–3, ≥4–7 and >7 days were conducted. Posthoc analyses using the Bonferroni correction were performed between age groups [age group effect: $P < 0.017$ (0.05/3)] that presented statistically significant different detection rates and sensitivities. Statistical analyses were computed using R software, v 3.6.1, and the 2019 R Studio interface (R Studio Team, Boston, MA).

RESULTS

Patient Characteristics

Eight hundred and seventy-eight children and adolescents were screened between November 4 and December 12, 2020, for SARS-CoV-2. Among them, 405 children were included in this study, of whom the 397 who had both NP and saliva samples collected were included in the analyses. The characteristics of the patient population stratified by SARS-CoV-2 positive and negative results are summarized in Table 1.

A vast majority of children of ≥12 years of age presented at least 1 major symptom (89.9%), mostly sore throat (68.6%) and cough (49.5%). From children <12 years of age, 81.5% (97/117) presented with fever (47.9%) and/or a severe cough (52.1%) associated at least with a bad general condition, other manifestations suggestive of COVID-19 or symptoms lasting more than 3 days.

Detection Rates of NP RT-PCR and Saliva RT-PCR

Of the 397 participants included in the analyses, 91 (22.9%) tested positive by saliva samples, 101 (25.4%) by NP swabs, and 106 (26.7%; 22.4%–31.1%) by any of the 2 samples. Detection rates were equivalent for both NP and saliva specimens (−8.7% to 3.7%; $P = 0.457$). Respectively 15 and 5 children were detected positive only on NP swabs or saliva specimens. The detection rates significantly differed between the age groups of 0–6 and ≥6–12 years (3.2% vs. 30.7%; $P = 0.004$).

Diagnostic Test Performance (Sensitivity, Specificity) of NP RT-PCR and Saliva RT-PCR

Using NP as the standard, the sensitivity of saliva was 85.2% [95% confidence interval (CI): 78.2%–92.1%]. When saliva was considered as the standard, the sensitivity of NP was 94.5% (95% CI: 89.8%–99.2%; $P = 0.058$). When using the composite reference as the standard, the respective sensitivity of saliva and NP swabs was 85.9% (95% CI: 79.2%–92.5%) and 95.3% (95% CI: 91.3%–99.3%; $P = 0.034$). The sensitivity of saliva RT-PCR was dependent on NP VLs and was maximal with a VL of 10^6 cp/mL (Fig. 1). When stratified by age groups, the respective sensitivity of saliva and NP swabs was 89.9% and 97.1% in children ≥12 years of age and 84.4%, 90.6% in children ≥ 6–12 years of age. Only 4 children <6 years of age were detected positive from NP swabs, with only 1 child being documented positive from saliva. The reported sensitivity was significantly different between the 0- to 6-year subgroup and the ≥12 years of age subgroup (25% vs. 89.9%; $P = 0.003$). When stratified by the duration of symptoms, the respective sensitivity of saliva and NP swabs was 89.5% and 95.3% in patient with symptom duration <4 days (95% CI: −14.8% to 3.2%; $P = 0.249$) and 70.0% and 95.0% in those with symptom duration (95% CI: −52.2% to 2.2%; $P = 0.096$) ≥4–7 days. Only 3 patients had symptoms above 7 days and all were tested negative from both samples.

Viral Loads

VLs documented from saliva were significantly lower compared with those reported from paired NP swabs (median 8.7 cp/mL × 10^4; interquartile range, 1.2 × 10^4–5.2 × 10^5; vs. median 4.0 × 10^7 cp/mL; interquartile range, 8.6 × 10^5–1 × 10^8; $P < 0.001$, 95% CI: −4.5 × 10^2 to −7.7 × 10^1).

TABLE 1. Patient Characteristics Stratified by SARS-CoV-2 Positive or Negative Results

Characteristics	All, n = 397	SARS-CoV-2 Positive, n = 106	SARS-CoV-2 Negative, n = 291	*P* Value	95% Confidence Interval
Demographics					
Female, n (%)	192 (48.3%)	47 (44.3%)	145 (49.8%)	0.393	−17.2% to 6.2%
Age, mean years (SD)	12.7 (3.8)	12.7 (3.7)	12.6 (3.8)	0.904	−0.8 to 0.9
Age categories (y)					
0–6, n (%)	31 (7.8%)	4 (3.8%)	27 (9.3%)	0.110	−11.1% to 0.7%
≥6–12, n (%)	88 (22.2%)	32 (30.2%)	56 (19.2%)	0.029	4.6% to 21.4%
≥12, n (%)	278 (70.0%)	70 (66.0%)	208 (71.5%)	0.356	−16.5% to 5.6%
Duration of symptoms, mean days (SD)	2.4 (1.8)	2.3 (1.6)	2.5 (1.8)	0.428	−0.5 to 0.2
Duration of symptoms < 4 d, n (%)	316 (79.6%)	86 (81.1%)	230 (79.0%)	0.751	−7.3% to 11.5%
Saliva sampling					
Able to drool saliva, n (%)	368 (92.7%)	100 (94.3%)	268 (92.1%)	0.588	−3.8% to 83%
Able to drool saliva by age (y)					
0–6, n (%)	15 (3.8%)	1 (0.9%)	14 (4.8%)	0.126	−7.6% to −0.2%
≥6–12, n (%)	81 (20.2%)	29 (27.4%)	51 (17.5%)	0.043	0.4% to −20.0%
≥12, n (%)	273 (68.8%)	70 (66.0%)	203 (69.8%)	0.558	−14.8% to 7.4%
Tested by the:					
Patient, n (%)	202 (50.9%)	59 (55.7%)	143 (49.1%)	0.300	−5.2% to 18.2%
Adult (parent or caregiver), n (%)	187 (47.1%)	46(43.4%)	141 (48.5%)	0.436	−16.7% to 6.6%
Patient + adult n (%)	8 (4.5%)	1 (0.9%)	7 (2.4%)	0.608	−4.7% to 1.7%

SD indicates standard deviation.

Comparison of Discordant NP and Saliva RT-PCR Results

Table 2 displays the characteristics of the 15 children with NP swabs only positive compared with the 86 documented positive from both NP swabs and saliva samples. The 5 patients with saliva swabs detected only positive were all males, had a median age of 11.1 years (10.3–14.6), and presented with median saliva VLs of 4.0×10^3 cp/mL (1.1×10^3–8.8×10^3).

DISCUSSION

This study is by far, the largest cohort reporting on the performance of saliva specimens in children. As observed in

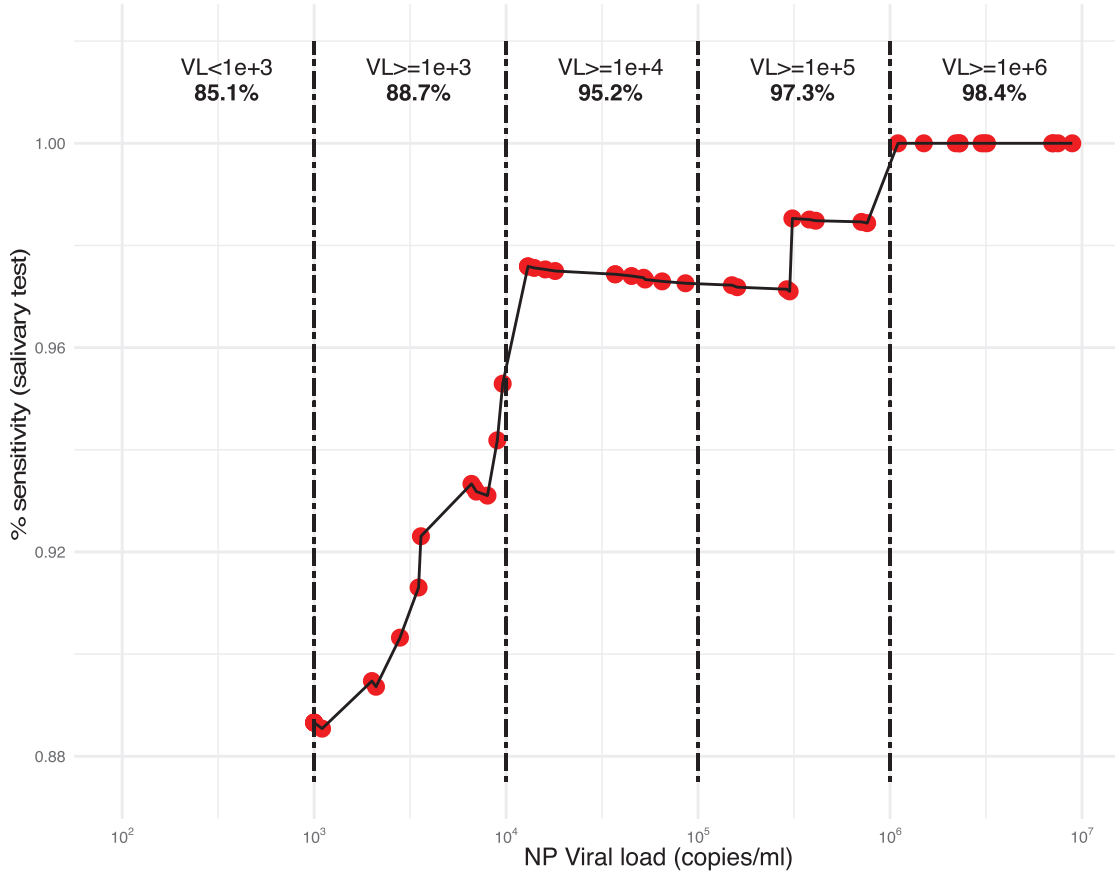

FIGURE 1. Sensitivity of saliva PCR in relation to NP viral loads.

TABLE 2. Characteristics Stratified by the Concordance of Positive NP and Saliva RT-PCR Findings

Characteristics	Negative Saliva PCR, NP PCR +, n = 15	NP and Saliva PCR +, n = 86	*P* Value	95% Confidence Interval
Age, median (IQR)	11.2 (7.3–14.0)	14.1 (11.8–15.4)	0.034	−4.7 to −0.2
Female, n (%)	9 (60.0%)	45 (52.3%)	0.788	−23.2% to 38.5%
Age categories (y)				
0–6, n (%)	3 (20.0%)	1 (1.2%)	0.006	5.4%–43.1%
≥6–12, n (%)	5 (33.3%)	24 (27.9%)	0.905	−24.2% to 35.0%
≥12, n (%)	7 (46.7%)	61 (70.9%)	0.121	−55.2% to 6.7%
Duration of symptoms, median, (IQR)	3 (1.5–4.5)	2 (1–3)	0.094	0–2
Duration of symptoms < 4 d, n (%)	9 (60.0%)	73 (84.9%)	0.055	−54.7% to 5.0%
NP viral load, median (IQR)	5.6×10^3 (1.5×10^3–1.0×10^4)	3.9×10^7 (8.6×10^5–1.0×10^8)	<0.001	-1.5×10^4 to -4.6×10^2
Tested by the:				
Participant, n (%)	7 (46.7)	50 (58.1%)	0.586	−42.7% to 19.8%
Adult (parent or caregiver), n (%)	8 (53.3)	35 (40.7%)	0.529	−18.6% to 43.8%
Patient + adult, n (%)	0 (0.0%)	1 (1.1%)	1.000	−4.6% to 2.3%
Able to drool saliva, n (%)	11(73.3%)	84 (97.7%)	0.002	−50.9% to 2.2%
Able to drool saliva by age (y):				
0–6, n (%)	0 (0.0%)	1 (1.2%)	>0.999	−4.6% to 2.3%
≥6–12, n (%)	4 (26.7%)	22 (25.6%)	>0.999	−24.2% to 26.4%
≥12, n (%)	7 (46.7%)	61 (70.9%)	0.121	−55.2% to 6.7%

IQR indicates interquartile range.

another study including children[8] and the RADICO study that used the same saliva collection approach,[10,19] somewhat lower detection rates of SARS-CoV-2 were reported from saliva as compared with NP specimens. This difference in sensitivity is likely explained by a 2 log lower VL detection in saliva compared with NP samples.[9,10,20] SARS-CoV-2 detection in saliva is dependent on VLs and reaches an equivalent sensitivity to NP swabs for NP VL thresholds of 10^4 copies/mL. However, as no cultivable viable virus is detected under the threshold of 10^4 copies/mL, children detected SARS-CoV-2 negative from saliva samples but positive from NP swabs might potentially be less contagious or reflect past infections.[21–23]

Lower VLs documented in younger children may have impacted the detection rates and the sensitivity of SARS-CoV-2 in saliva in this age group as supported.[24] However, children <6 years of age only represented 8% of our cohort, thereby limiting our ability to make conclusions in this age group. In addition, the absence of drooling observed in most of the younger children might have impacted the sensitivity. Yet, data from the RADICO study[10] and elsewhere[25] reported no impact of drooling on the sensitivity of saliva nor the VL count.[10] Sensitivity of saliva was also influenced by the duration of symptoms which correlated with VLs. A higher sensitivity was reported from children with symptoms less than 4 days likely because of higher VLs detected during the acute phase.[22]

Strengths of the current study include the large pediatric sample size in addition to the detailed prospectively collected information. Limitations are predominantly related to the inclusion of outpatients but not hospitalized nor asymptomatic children, which might affect the generalizability of our findings. Furthermore, children <6 years were under-represented, thus limiting our ability to draw conclusions in this age group. Since inability to drool into tube and age <6 years were likely highly correlated, the impact of these 2 factors cannot be separately evaluated in this study. Likewise, the power of this study was limited to detect differences in performance by age and duration of symptoms. Our study was also conducted during a high prevalence of SARS-CoV-2 (up to 30%), thereby affecting our positive predicted values. Saliva collection is currently not a standardized procedure with various procedures including or not drooling or coughing thus resulting in different sensitivities.[3]

CONCLUSIONS

The sensitivity of SARS-CoV-2 RT-PCR assays in saliva was lower compared with NP swabs in children. An equivalent sensitivity was reached between both samples when using a VL threshold of $\geq 10^4$ copies/mL that indicates cultivable viable virus. In this regard, this noninvasive procedure might facilitate large-scale screening in children and potentially limit quarantine measures to most contagious children. Lower VLs documented from saliva in younger children and those with longer duration of symptoms, likely limited the diagnostic performance of saliva in children <6 years of age and those with duration of symptoms ≥4 days.

ACKNOWLEDGMENTS

The authors thank Marion de Vallière and Maria Daniela Garrido for help in patient recruitment, the patients for participation in this study, and the health authorities of the Canton de Vaud for their support. The authors thank the Vidy-Med team and the Montétan screening site teams for the recruitment of participants. The authors thank all the team of the Laboratory of Molecular Diagnostics of the Institute of Microbiology and Anne Tabard-Fougère for her help in the statistical analyses and figure elaboration.

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