Concordance of Upper and Lower Respiratory Tract Samples for SARS-CoV-2 in Pediatric Patients: Research Letter

To the Editor:

Nasopharyngeal reverse-transcriptase polymerase chain reaction assay for SARS-CoV-2 is considered the gold standard for diagnosing COVID-19 infections. However, multiple reports in adults with acute COVID-19 have shown positive tracheobronchial reverse-transcriptase polymerase chain reaction for SARS-CoV-2 despite initial negative nasopharyngeal testing.[1–5] Furthermore, viral nucleic acid appears to persist longer in the lower respiratory tract than in the upper respiratory tract in adults, suggesting that the lower respiratory tract may be a more accurate sampling site later in the course of infection.[6]

Children with COVID-19 generally have less severe symptoms than adults, including significantly fewer cases of respiratory compromise and an increased likelihood of asymptomatic infection.[7–9] Lack of symptoms is insufficient to rule out lower respiratory tract disease, and characteristic ground glass opacities have been observed on chest computed tomography in asymptomatic children.[10] However, it is unclear whether children can harbor virus in their lower respiratory tract with a negative nasopharyngeal test. Understanding the SARS-CoV-2 viral reservoir in children is important for diagnostic and infection prevention control reasons and has hospital and public health implications. The aim of this study is to determine the concordance of upper and lower respiratory samples for SARS-CoV-2 in asymptomatic children presenting for surgery.

The institutional review board at The Children's Hospital of Philadelphia (Philadelphia, Pennsylvania) approved the study, and consent was obtained from guardians. A convenience sample of asymptomatic pediatric patients less than or equal to 18 yr old, undergoing procedures for which endotracheal intubation or diagnostic bronchoalveolar lavage were planned, were enrolled between July 10 and November 24, 2020. The study was conducted at a tertiary care children's hospital.

After general anesthesia was induced and subjects were unconscious, tracheal aspirate or bronchoalveolar lavage samples were collected by clinicians (anesthesiologist or pulmonologist). At the time of lower respiratory tract sample collection, nasopharyngeal swabs were also obtained. All samples were tested with an in-house–developed reverse-transcriptase polymerase chain reaction laboratory assay, which, like most commercially available reverse-transcriptase polymerase chain reaction assays, uses the same N2 primer and probe as the assay developed by the Centers for Disease Control and Prevention (Atlanta, Georgia). The cycle threshold (number of cycles needed to amplify viral RNA to a detectable level) was 40. Electronic medical records were reviewed for demographics and clinical symptoms.

Statistical analyses were performed using STATA 14.2 (StataCorp LP, USA). Concordance was determined between nasopharyngeal and lower respiratory tract samples with the Fisher exact test. A data analysis and statistical plan was written and filed with the institutional review board before data were accessed.

Three hundred sixty subjects were enrolled. Two subjects had insufficient lower respiratory tract samples, leaving 358 subjects with evaluable upper and lower respiratory sample pairs. Three hundred twenty-two tracheal aspirates and 36 bronchoalveolar lavage samples were collected. The median age was 6 yr old (range, 6 days to 18 yr). Sex, race, ethnicity, and procedure types are described in table 1. Among the 358 lower respiratory tract samples, all were negative for SARS-CoV-2. Of 358 nasopharyngeal samples, 2 of 358 (0.6%) were positive for SARS-CoV-2, with 99.4% concordance between upper and lower respiratory tract samples ($P = 0.008$; table 2). The SARS-CoV-2–positive nasopharyngeal samples had cycle thresholds of 39.86 and 39.11. Neither of the SARS-CoV-2–positive subjects reported symptoms of COVID-19.

In our cohort, the two cases of discordance were in subjects with positive nasopharyngeal swab and negative tracheal aspirate. Both nasopharyngeal-positive subjects had cycle thresholds that were very close to the limit for detection, indicating low viral loads. Our data suggest that in asymptomatic pediatric patients, nasopharyngeal samples are more sensitive for detecting SARS-CoV-2 than tracheal aspirate or bronchoalveolar lavage samples, and that false negative results are extremely rare.

There are several limitations to our study. Our cohort included few SARS-CoV-2 polymerase chain reaction–positive patients because all patients at our hospital are tested before surgery, and if positive, surgery was postponed unless emergent. Similarly, all subjects were asymptomatic with respect to SARS-CoV-2 infection. These data should also be interpreted in the setting of community prevalence. During the study period, our pediatric healthcare network-wide SARS-CoV-2 reverse-transcriptase polymerase chain reaction test positivity rate for pediatric patients was 1.1 to 8.7%.

Table 1. Demographics

Characteristic	No. (%)
Age, median (range)	6 yr (6 days–18 yr)
Male	214 (58.8%)
Race	
White/Caucasian	220 (61.5%)
Black/African American	59 (16.5%)
Asian	15 (4.2%)
Other/unknown	64 (17.9%)
Ethnicity	
Hispanic	45 (12.6%)
Non-Hispanic	309 (86.3%)
Unknown	4 (1.1%)
Procedure type*	
Otolaryngology	121 (33.8%)
General Surgery	49 (13.7%)
Plastics	33 (9.2%)
Urology	33 (9.2%)
Neurosurgery	25 (7.0%)
Dental	23 (6.4%)
Pulmonary	22 (6.1%)
Gastrointestinal endoscopy	19 (5.3%)
Orthopedics	16 (4.5%)
Oral and maxillofacial	9 (2.5%)
Oncology	2 (0.6%)
Transplant	1 (0.3%)

*May have more than one procedure per surgical case, with sum greater than 100%.

Table 2. Paired Upper Respiratory Tract and Lower Respiratory Tract Samples

	Upper Respiratory Tract		
Lower Respiratory Tract	Negative	Positive	Total
No. Negative	356	2	358
No. Positive	0	0	0

As pediatric specialists determine how to safely care for patients in the setting of COVID-19, understanding viral reservoirs and the accuracy of test sampling sites in children is vital. The results of this systematic study are reassuring to providers who perform aerosol-generating procedures in children. The results support the preprocedure use of upper respiratory sample testing as a safe and accurate screening test. Further studies in symptomatic children, in children known to be SARS-CoV-2–positive, and in special populations (*e.g.*, immunocompromised patients) are required to determine if these findings are generalizable to these populations.

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Competing Interests

Dr. Odom John reports funding from the National Institutes of Health (Bethesda, Maryland) and the Burroughs Wellcome Fund (Durham, North Carolina). Dr. John is on the scientific advisory board of Pluton Biosciences (St. Louis, Missouri). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The remaining authors declare no competing interests.

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Hypotension Prediction Index Guidance: Comment

To the Editor:

The recent article titled "Hypotension Prediction Index for Prevention of Hypotension during Moderate- to High-risk Noncardiac Surgery" explored whether a "hypotension prediction index algorithm" based on an arterial blood pressure waveform analysis can reduce the duration and severity of intraoperative hypotension.[1] The authors suggested that the hypotension prediction index failed to prevent hypotension because of the following: inadequate warning time, a complex treatment algorithm, a set blood pressure threshold, and clinicians ignoring the algorithm recommendation. We agree with the authors' above reasoning; however, we have some commentary and questions for the authors on their conclusions and plans for subsequent trials.

First, the authors conclude that the main reason the hypotension prediction index did not prevent hypotension is the inadequate warning time and that lowering the intervention alert threshold in the subsequent trial would increase the time the anesthesia clinician has to act. To proceed with such a trial design, there would need to be evidence to show that the sensitivity and specificity of a lower alert threshold to predict hypotension is similar to those with the index threshold of 85.[2,3] We are wondering whether the authors could share these data with readers.

Second, because the warning time needs to be increased, would it be possible to eliminate the manual interpretation of the algorithm altogether and use an automatic treatment recommendation algorithm incorporating the advanced hemodynamic parameters?

Third, we would like to see the authors expand on why the anesthesia team declined to intervene in many cases. Was it distrust in the in-operating room researcher interpreting the algorithm and giving the suggestion? Or was it because of a belief that vasoactive substances can cause harm?

We look forward to reading the authors' future trials because it is a subject of great interest and importance. Given that approximately 40% of patients in both groups had periods of hypotension of mean arterial pressure less than 65 mmHg, effective predictors of hypotension and timely algorithmic interventions could result in massive changes in standard intraoperative anesthetic management.

Competing Interests

The authors declare no competing interests.

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