Systematic Severe Acute Respiratory Syndrome Coronavirus 2 Screening at Hospital Admission in Children: A French Prospective Multicenter Study

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Systematic Severe Acute Respiratory Syndrome Coronavirus 2 Screening at Hospital Admission in Children: A French Prospective Multicenter Study

Julie Poline,[1,2] Jean Gaschignard,[1,3,4,5,6] Claire Leblanc,[7] Fouad Madhi,[5] Elsa Foucaud,[7] Elodie Nattes,[5] Albert Faye,[1,4,8] Stéphane Bonacorsi,[3,4,6] Patricia Mariani,[6] Emmanuelle Varon,[9,10] Mounira Smati-Lafarge,[9] Marion Caseris,[1] Romain Basmaci,[3,11] Noémie Lachaume,[11] and Naïm Ouldali[1,4,6,12][AU: Please note that inclusion or deletion of names to the author group, on the title page, cannot be made directly in the manuscript at the proof stage, as certain formalities have to be completed for doing the same. Hence, kindly confirm whether you require any changes to be made in the author group, and the Editorial office will follow up.]

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Intercommunal de Créteil, Créteil, France, [10]National Reference Center for Pneumococci, Créteil, France, [11]Service de Pédiatrie-Urgences, Assistance Publique-Hôpitaux de Paris, Hôpital Louis-Mourier, Colombes, France, and [12]Association Clinique et Thérapeutique Infantile du Val-de-Marne, Créteil, France
Correspondence: N. Ouldali, Department of General Pediatrics, Pediatric Infectious Disease and Internal Medicine, Robert Debré University Hospital, Assistance Publique-Hôpitaux de Paris, F-75019 Paris, France (naim.ouldali@aphp.fr).
To[AU: Your article has been edited for spelling, grammar, clarity, consistency, and adherence to journal style and the American Medical Association Manual of Style (10th edition). Please read the article and author queries carefully to make sure your meaning has been retained. If changes are required, please enter the changes directly into the text. Please note that we may be unable to make changes that conflict with journal style, obscure meaning, or create grammatical or other problems.] assess the relevance of systematic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) screening of all children admitted to hospital, we conducted a prospective multicenter study including 438 consecutive hospitalized children. A symptom-based SARS-CoV-2 testing strategy failed to identify 45% (95% confidence interval, 24%–68%) of hospitalized children infected by SARS-CoV-2. To limit intrahospital transmission, a systematic screening of children admitted to hospital should be considered.
Keywords.[AU: Please provide up to 5 keywords.] xxx; xxx; xxx.

Since the first cases of pneumonia in Wuhan, China in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been responsible for a global pandemic, leading to >300 000 deaths [1][AU: Please consider updating the first 2 sentences of the main text and reference [1] to reflect the current numbers of deaths.]. France is among the main affected countries, with >27 000 deaths to date [1]. The reproduction number (R_0), initially underestimated due to the large proportion of paucisymptomatic or asymptomatic individuals, has since been estimated between 3 and 6, explaining the rapid worldwide spread of the virus [2, 3]. A recent analysis has highlighted that >40% of transmissions could occur before the onset of symptoms [4], challenging the detection of contagious patients and the implementation of appropriate prevention measures [4].

Healthcare workers have the potential for frequent contact with infected patients [5], and several intrahospital clusters have been reported [6, 7], including in pediatric settings [8], threatening both healthcare workers and vulnerable inpatients [6, 8, 9]. In Italy, up to 20% of healthcare workers may have been infected by SARS-CoV-2 [10]. In the context of maximal pressure applied on healthcare systems in many countries, protecting healthcare workers and fighting against nosocomial coronavirus disease 2019 (COVID-19) are major issues [5, 9]. To limit the risk of intrahospital transmission, optimal SARS-CoV-2 screening strategies and prevention measures are required [6, 8].

In pediatrics, given the low prevalence of severe COVID-19 forms described to date, the diagnostic strategy in hospital settings is often limited to performing a real-time reverse-transcription polymerase chain reaction (rRT-PCR) assay of nasopharyngeal swabs in patients presenting symptoms of suspected COVID-19 [8]. However, given the broad spectrum of SARS-CoV-2 manifestations in children [11], which are often similar to other highly prevalent viral infections in children, detecting all COVID-19 patients with this testing strategy may be highly challenging.

In this context, we hypothesized that a substantial proportion of children admitted to hospital could escape current SARS-CoV-2 screening strategies, potentially leading to avoidable intrahospital transmission. To test this hypothesis, we set up a systematic SARS-CoV-2 screening strategy in several tertiary pediatric hospitals, for all children admitted for surgical or medical reasons, whether scheduled or after a consultation in pediatric emergencies. Our aim was to assess, in children, the proportion of patients with confirmed SARS-CoV-2 infection that would not have been detected by screening strategy based on clinical presentation alone.

MATERIALS AND METHODS

We conducted a prospective multicenter study in 4 tertiary pediatric hospitals located in the region of Paris, one of the epicenters of the COVID-19 epidemic in France [12]. A national lockdown was implemented in France on 17 March 2020. We conducted our study between 15 April and 30 April 2020 (ie, 4 weeks after the lockdown), in a situation of reduced circulation of SARS-CoV-2 due to major social contact restrictions [12]. We assumed that over this short study period, the incidence of COVID-19 did not change substantially [12].

We included all pediatric patients hospitalized in one of the participating centers during the study period. Before admission, each patient had a nasopharyngeal-specific SARS-CoV-2 rRT-PCR test using the Xpert Xpress SARS-CoV-2 assay (Cepheid), according to local hospital guidelines. We recorded demographic data, symptoms, and clinical findings. The cycle threshold value, which is inversely proportional to the viral load, was used as an indicator of the copy number of SARS-CoV-2 RNA [13].

The main outcome was the proportion of patients without any symptoms of suspected COVID-19 among children with confirmed SARS-CoV-2 infection confirmed by rRT-PCR. To define children suspected to have COVID-19, we conducted a review of the literature to identify any symptoms or clinical signs reported in children during SARS-CoV-2 infection (details are shown in Supplementary Appendix 1). The following characteristics were considered: fever; upper respiratory tract symptoms (cough, rhinitis, tonsillitis, odynophagia, otalgia, otitis, conjunctivitis); influenza-like illness (including asthenia, headache, and myalgia); anosmia; dysgeusia; dyspnea; chest pain; vomiting or diarrhea; abdominal pain; skin involvement; arthritis or arthralgia; mucosal hemorrhage;

Kawasaki syndrome; and myocarditis. Patients were suspected to have COVID-19 if any of these symptoms or signs were identified.

We hypothesized that the rate of positive SARS-CoV-2 nasopharyngeal rRT-PCR would be 5%, and the proportion of positive patients without any symptom of suspected COVID-19 would be 35%. Under these assumptions, we calculated that to estimate the proportion of patients with SARS-CoV-2 infection without any symptom of suspected COVID-19 with a 95% confidence interval (CI) of ±20%, 400 patients would be required. We described patient characteristics as numbers and percentages for categorical variables, and median with interquartile range (IQR) for quantitative variables. We then assessed the association between these characteristics and results of SARS-CoV-2 PCR using the Fisher exact test for categorical variables and the Mann-Whitney *U* test for quantitative variables. The likelihood ratios (LRs), sensitivity, and specificity were calculated with their 95% CIs. A 2-sided *P* value < .05 was considered statistically significant. All statistical analyses were performed using R version 3.6.1 software (http://www.R-project.org).

This study received approval from the Robert Debré Hospital institutional review board.

RESULTS

Among the 446 consecutive pediatric patients admitted in the 4 hospitals during the study period, 438 (98.2%) with available clinical data were included. Median age was 6.5 years (IQR, 2.1–13.0 years). Two hundred nine (47.7%) patients presented an underlying condition, and 33 had an immunosuppressive treatment. Overall, 182 (41.6%) had suspected symptoms of COVID-19. Most frequent suspected symptoms were fever

(126/182 [69.8%]), diarrhea or vomiting (83/182 [45.6%]), abdominal pain (60/182 [33.0%]), upper respiratory tract infection symptoms (52/182 [28.6%]), dyspnea (27/182 [14.8%]), and skin involvement (20/182 [11.0%]) (Supplementary Appendix 2).

SARS-CoV-2 PCR was positive for 22 of 438 children (5.0%). Patients with underlying conditions were not more frequently infected by SARS-CoV-2 than other children (9/209 [4.3%] vs 13/229 [5.7%], respectively; *P* = .63), nor were patients with chronic immunosuppressive treatment (2/33 [6.1%] vs 20/405 [4.9%]; *P* = 1.0). Symptoms that most increased the likelihood to have a positive SARS-CoV-2 PCR were dyspnea (positive LR, 6.6 [95% CI, 3.1–14.0]), skin involvement (positive LR, 6.3 [95% CI, 2.5–15.7]), upper respiratory tract symptoms (positive LR, 2.9 [95% CI, 1.5–5.8]), and diarrhea or vomiting (positive LR, 2.3 [95% CI, 1.3–4.0]). Kawasaki syndrome and myocarditis were also strongly associated with COVID-19 (Supplementary Appendix 2). However, none of these parameters had sensitivity above 41% (Table 1). Combining all symptoms or signs of suspected COVID-19, the sensitivity remained largely suboptimal (55% [95% CI, 32%–76%]). Hence, 10 of 22 patients (45% [95% CI, 24%–68%]) with positive SARS-CoV-2 PCR did not exhibit any symptom or sign of suspected COVID-19. Among these 10 children, 5 had a familial history of proven (n = 1) or suspected (n = 4) COVID-19. Of note, the median cycle threshold value was similar between patients with or without symptoms of COVID-19 (37 vs 32.3; *P* = 1.0).

DISCUSSION

To our knowledge, this is the first prospective multicenter study including all consecutive hospitalized children to assess the performance of a symptom-based testing strategy for COVID-19. We observed that this strategy failed to detect 45% (95% CI, 24%–68%) of

infected children, despite an extensive definition of suspected symptoms and signs of COVID-19. These patients, however, exhibited a similar viral load to patients with classical symptoms of COVID-19, suggesting a comparable potential for contamination [8]. This finding is in line with He et al, who reported that 44% of contaminations occurred before onset of symptoms [4]. Altogether, these findings raise major concerns regarding a symptom-based COVID-19 screening strategy, which could lead to a substantial increased risk of intrahospital transmission.

In our study, respiratory and digestive symptoms were highly associated with an increased likelihood of positive PCR, in line with the literature [14]. However, the lockdown may have reduced the circulation of other common viruses associated with similar symptoms, leading to an overestimation of these LRs.

Interestingly, Kawasaki-like syndrome[AU: Please check "Kawasaki-like syndrome"; elsewhere in the text and table, this was described as "Kawasaki syndrome." Please ensure that this term is reported consistently throughout the manuscript.] and myocarditis were also highly associated with SARS-CoV-2 infection, confirming the specificity of these novel clinical forms to suspect COVID-19 [15]. In contrast, immunosuppressive treatment, including corticosteroids, and underlying medical conditions were not associated with a higher risk of COVID-19. This suggests that these conditions may not be a major risk factor for COVID-19, an important consideration at the time of reopening schools. Further studies are required to confirm these findings.

Recent studies suggested that despite the magnitude of the outbreak, only a small proportion of the population may have been infected [16]. Thus, with the end of lockdown in process, this rate of immunized population may not be sufficient to exclude

the possibility of a second wave, as suggested by recent simulation studies [16, 17]. These observations make optimal screening strategies all the more important.

The strength of our study is the prospective inclusion of consecutive admitted patients over a short period (14 days) during which the incidence of SARS-CoV-2 was relatively stable [12]. Our study still has limitations. A potential infection with SARS-CoV-2 was assessed by PCR of nasopharyngeal swab alone, which may be associated with a substantial proportion of false negatives. However, this proportion seems lower during the contagious period, which begins before the onset of symptoms, and during which the PCR is currently considered the most sensitive [13, 18].

In summary, a symptom-based SARS-CoV-2 testing strategy would fail to identify up to 45% of hospitalized children infected by SARS-CoV-2. To limit further intrahospital transmission to both healthcare workers and vulnerable inpatients, a systematic screening of all children admitted to hospital should be considered, especially in the postlockdown era.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Note

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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Table 1. Performance of Signs and Symptoms in Identifying Children With Coronavirus Disease 2019 (N = 438) <?double?>

Symptom/Clinical Sign	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
Fever	36 (17–59)	72 (67–76)	1.3 (.7–2.3)	0.9 (.6–1.2)
Diarrhea or vomiting	41 (21–64)	82 (78–86)	2.3 (1.3–4.0)	0.7 (.5–1.0)
Abdominal pain	14 (03–35 [AU: Table 1: Please clarify the range 03–35; should the first value be 3, or 0.3?])	86 (83–89)	1.0 (.3–2.9)	1.0 (.8–1.2)
URTI symptoms	32 (14–55)	89 (86–92)	2.9 (1.5–5.8)	0.8 (.6–1.0)
Dyspnea	32 (14–55)	95 (93–97)	6.6 (3.1–14.0)	0.7 (.5–1.0)
Skin involvement	23 (08 [AU: Table 1: Please clarify the range 08–45; should the first value be 8, or 0.8?]–45)	96 (94–98)	6.3 (2.5–15.7)	0.8 (.6–1.0)
Any symptom of	55 (32–76)	59 (54–64)	1.3 (.9–	0.8 (.5–

suspected COVID-19[a]			2.0)	1.2)

Likelihood ratio was not computed for symptoms present in <20 patients.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; LR, likelihood ratio; URTI, upper respiratory tract infection.

[a]The following symptoms/clinical signs of suspected COVID-19 were considered: fever; URTI symptoms (cough, rhinitis, tonsillitis, odynophagia, otalgia, otitis, and conjunctivitis); influenza-like illness (including asthenia, headache, and myalgia); anosmia; dysgeusia; dyspnea; chest pain; vomiting or diarrhea; abdominal pain; skin involvement; arthritis or arthralgia; mucosal hemorrhage; Kawasaki syndrome; and myocarditis.

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