Systematic SARS-CoV-2 screening at hospital admission in children:

a French prospective multicenter study

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Abstract: To assess the relevance of systematic 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%CI [24; 68]) of hospitalized children infected by SARS-CoV-2. To limit intra-hospital transmission, a systematic screening of children admitted to hospital should be considered.

Introduction.

Since the first cases of pneumonia in Wuhan in December 2019, SARS-CoV-2 is responsible for a global pandemic, leading to more than 300,000 deaths.[1] France is among the main affected countries, with more than 27,000 deaths to date.[1] The reproduction number (R_0) initially underestimated due to the large proportion of pauci 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 more than 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 intra-hospital 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 COVID-19 are major issues.[5,9] To limit the risk of intra-hospital 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 transcriptase–polymerase chain reaction (rRT-PCR) of nasopharyngeal swabs in patients presenting symptoms suspect of 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 part of children admitted to hospital could escape current SARS-CoV-2 screening strategies, potentially leading to avoidable intra-hospital 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 reason, 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.

Methods.

We conducted a prospective multicenter study in four tertiary pediatric hospitals located in the region of Paris, one of the epicenters of COVID-19 epidemic in France.[12] A national lockdown was implemented in France on March 17th, 2020. We conducted our study between April 15th and April 30th, 2020, i.e. four 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 using the Xpert® Xpress SARS-CoV-2 (Cepheid), according to local hospital guidelines. We recorded demographic data, symptoms and clinical findings. The cycle threshold value (CT value), which is inversely proportional to the viral load, was used as indicator of the copy number of SARS-CoV-2 RNA.[13]

The main outcome was the proportion of patients without any symptom suspect of COVID-19 among children with confirmed SARS-CoV-2 infection confirmed by rRT-PCR. To define children suspected of COVID-19, we conducted a review of the literature to identify any symptom or clinical sign reported in children during SARS-CoV-2 infection (details in 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, myocarditis. Patients were considered suspect of COVID-19 if any of these symptoms or signs was identified.

We hypothesized that the rate of positive SARS-COV-2 nasopharyngeal rt-PCR would be 5%, and the proportion of positive patients without any symptom suspect of 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 suspect of COVID-19 with a 95% confidence interval of +/- 20%, 400

patients would be required. We described patient characteristics as numbers and percentages for categorical variables, and median with interquartile range for quantitative ones. We then assessed the association between these characteristics and results of SARS-CoV-2 PCR using the Fisher's exact test for categorical variables and the Mann-Whitney U test for quantitative ones. The likelihood ratios (LRs), sensitivity, and specificity were calculated with their 95%CIs. A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed using R v3.6.1 (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 four 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]. Two hundred and nine (47.7%) patients presented an underlying condition, and 33 had an immunosuppressive treatment. Overall, 182 (41.6%) had symptoms suspect of COVID-19. Most frequent suspect 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%) (Appendix 2).

SARS-CoV-2 PCR was positive for 22/438 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=0.63), nor were patients with chronic immunosuppressive treatment (2/33, 6.1% vs 20/405, 4.9%, p=1.0). Symptoms which most increased likelihood to have a positive SARS-CoV-2 PCR were dyspnea (LR+ 6.6, 95%CI [3.1; 14.0]), skin involvement (LR+ 6.3, [2.5; 15.7]), upper respiratory tract symptoms (LR+ 2.9, [1.5; 5.8]), and diarrhea or vomiting (LR+ 2.3, [1.3; 4.0]). Kawasaki syndrome and myocarditis were also strongly associated with COVID-19 (Appendix 2). However, none of these parameters had a sensitivity above 41% (Table 1). Combining all symptoms or signs suspect of COVID-19, the sensitivity remained largely suboptimal (55%, 95%CI [32; 76]). Hence 10/22 patients (45%, 95%CI [24; 68]) with positive SARS-CoV-2 PCR did not exhibit any symptom or sign suspect of 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 CT 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 multicentre 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% [24; 68] of infected children, despite an extensive definition of symptoms and signs suspect of COVID-19. These unsuspected 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 Xi He et al. who underlined 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 intra-hospital 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 likelihood ratios.

Interestingly, Kawasaki-like and myocarditis were also highly associated with SARS-CoV-2 infection, confirming the specificity of these novel clinical forms to suspect COVID-19.[15] On the opposite, immunosuppressive treatment, including corticosteroids, or 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 re-opening 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 all the more important optimal screening strategies.

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 negative. 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]

Conclusion.

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 intra-hospital transmission to both healthcare workers and vulnerable inpatients, a systematic screening of all children admitted to hospital should be considered, especially in the post lockdown era.

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Table 1. Performance of Signs and Symptoms in identifying children with COVID-19

Symptom/clinical sign	Sensitivity (95% CI), %	Specificity (95% CI), %	LR+ (95% CI)	LR- (95% CI)
Fever	36 (17; 59)	72 (67; 76)	1.3 (0.7; 2.3)	0.9 (0.6; 1.2)
Diarrhea or vomiting	41 (21; 64)	82 (78; 86)	2.3 (1.3; 4.0)	0.7 (0.5; 1.0)
Abdominal pain	14 (03; 35)	86 (83; 89)	1.0 (0.3; 2.9)	1.0 (0.8; 1.2)
URTI symptoms	32 (14; 55)	89 (86; 92)	2.9 (1.5; 5.8)	0.8 (0.6; 1.0)
Dyspnea	32 (14; 55)	95 (93; 97)	6.6 (3.1; 14.0)	0.7 (0.5; 1.0)
Skin involvement	23 (08; 45)	96 (94; 98)	6.3 (2.5; 15.7)	0.8 (0.6; 1.0)
Any symptom suspect of COVID*	55 (32; 76)	59 (54; 64)	1.3 (0.9; 2.0)	0.8 (0.5; 1.2)

N=438 patients. *Following the definition detailed in the method section. The following symptoms/clinical signs suspect of COVID-19 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, myocarditis.

Abbreviations: URTI symptoms: upper respiratory tract infection symptoms: cough, rhinitis, tonsillitis, odynophagia, otalgia, otitis, conjunctivitis. LR: likelihood ratio. LR was not computed for symptoms present in fewer than 20 patients.