EDITORIAL

Symptomatic and Asymptomatic Viral Shedding in Pediatric Patients Infected With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Under the Surface

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Related article

Since the global emergence and spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initial attention appropriately focused on severely affected adults, who represent the highest proportion of symptomatic infections.[1] However, as the pandemic has evolved, a significant effect on children has also become evident.[2] Data from multiple affected countries have corroborated that children are clearly susceptible to infection and may develop severe primary and unique secondary inflammatory complications of infection, including multisystem inflammatory syndrome of children.[3-5] However, the vast majority of infected children have mild or unrecognized disease, and this population may play important epidemiologic roles by potentiating spread of infection through communities[6] and/or boosting herd immunity. Only small numbers of children have been included in prior studies focused on kinetics of viral shedding in the setting of symptomatic or asymptomatic SARS-CoV-2 infection.[7-12] To our knowledge, no prior studies have systematically focused on the frequency of asymptomatic infection in children or the duration of symptoms and viral shedding in both asymptomatic and symptomatic children.

Han and colleagues[13] provide data accumulated from 22 centers throughout South Korea that address this important knowledge gap. The unique structure of the South Korean public health system facilitated large-scale testing, aggressive contact tracing and testing, and isolation/direct observation of asymptomatic or mildly symptomatic children in designated health care facilities (rather than home quarantine). This structure allowed for the sequential observation, testing (median testing interval of every 3 days), and comparison of 91 asymptomatic, presymptomatic, and symptomatic children with mild to moderate upper and lower respiratory tract infection, identified primarily by contact tracing from laboratory-proven cases.

The first important take-home point from this study is that not all infected children have symptoms, and even those with symptoms are not necessarily recognized in a timely fashion. A major strength of this study is the inclusion of asymptomatic children (20 of 91 [22%]), presymptomatic children (18 of 91 [20%]), and symptomatic children (53 of 91 [58%]).[13] Most symptomatic infected children had experienced symptoms a median (range) of 3 (1-28) days prior to being diagnosed by testing, despite the fact that they were presumably under closer scrutiny by nature of being identified as a known contact. Presymptomatic children remained symptom free for a median (range) of 2.5 (1-25) days before exhibiting any symptoms, despite detectable virus. Only a minority of children (6 [7%]) were identified as infected by testing performed concurrent with onset of their symptoms. This highlights the concept that infected children may be more likely to go unnoticed either with or without symptoms and continue on with their usual activities, which may contribute to viral circulation within their community.

The authors' inclusion of asymptomatic patients in the study is particularly important and has rarely been addressed in the pediatric population. Interestingly, this study aligns with adult data in which up to 40% of adults may remain asymptomatic in the face of infection.[14] The true burden of unrecognized asymptomatic disease is still not known but is emerging as both viral molecular testing as well as antibody testing to establish seroprevalence have become more broadly available and applied. Application of these methodologies to specifically characterize the pediatric population is sorely needed. In the absence of test-based strategies for social reentry or the ability to aggressively perform contact tracing, asymptomatic infected individuals remain undetected and not isolated. The study by Han et al[13] corroborates that children are no exception. In this study, the authors estimate that 85 infected children (93%) would have been missed using a testing strategy focused on testing of symptomatic patients alone. A surveillance strategy that tests only symptomatic children will fail to identify children who are silently shedding virus while moving about their community and schools. In regions where use of face masks is not widely accepted or used by the general public, asymptomatic carriers may serve as an important reservoir that may facilitate silent spread through a community.

The second important take-home point from this study is that the duration of symptoms in symptomatic infected pediatric patients varies widely. The median (range) duration of symptoms for the full cohort was 11 (1-36) days.[13] However, the group of children who were presymptomatic at the time of laboratory diagnosis had the shortest median (range) duration of symptoms (3.5 [1-21] days), which was significantly shorter than the median (range) duration of symptoms in children who had symptoms develop concomitant with diagnosis (6.5 [1-12] days) and those who were symptomatic preceding their diagnosis

(13 [3-36] days). Although the majority of symptomatic children (41 of 71 [58%]) had upper respiratory tract disease, there was no difference in the duration of symptoms between those with upper vs mild or moderate lower respiratory tract infection. This suggests that even mild and moderately affected children remain symptomatic for long periods of time.

The third and most important take-home point from this study relates to the duration of viral shedding in infected pediatric patients. Virus was detectable for a mean (SD) of 17.6 (6.7) days overall and was detectable for a prolonged period of time in all cohorts of children, whether symptoms were present or not.[13] Asymptomatic children had detectable virus for a mean (SD) of 14.1 (7.7) days after their initial positive test result, and 4 asymptomatic children (20%) continued to have detectable virus 21 days after initial detection. The authors appropriately note that the duration of viral shedding in asymptomatic patients could have been even longer because the date of initial infection cannot be known with clarity. There was no difference in the mean (SD) duration of detectable virus in children with upper respiratory tract infection (18.7 [5.8] days) compared with those with lower respiratory tract infection (19.9 [5.6] days). Fully half of symptomatic children with both upper and lower tract disease were still shedding virus at 21 days. These are striking data, particularly since 86 of 88 diagnosed children (98%) either had no symptoms or mild or moderate disease.

Despite the value of the study by Han et al,[13] there are limitations that leave important remaining knowledge gaps that are ripe for investigation. The first limitation is due to qualitative molecular detection methods, which are the standard clinical approach for testing of nasopharyngeal swab specimens. Qualitative positive or negative findings for molecular detection of virus may not necessarily correlate with infectivity. Sensitive molecular detection methods may detect viable, infective virus but also nonviable or fragments of RNA with no capability for transmission. Additionally, even if viable virus is present, transmissibility is related to the quantity of virus present in the respiratory tract. In the absence of quantitative methods, many centers have attempted to correlate semiquantitative methods (eg, cycle time to positivity) as a surrogate for this measure, where higher cycle times are assumed to reflect lower viral loads, but the validity of this technique has not been established.[15,16] A focused study of semiquantitative cycle time and/or quantitative viral load in the pediatric population to clarify the dynamics and duration of shedding at different time points preceding and following symptoms and correlation with infectivity would be valuable to shed light on the clinical and public health significance of prolonged viral detection weeks after symptoms.

Another important consideration is the inherent variability in sensitivity of qualitative molecular detection platforms. It is clear that negative or positive cutoffs oversimplify the classification of the infection. For example, at our institution, we have implemented 4 different molecular platforms to meet the demand for SARS CoV-2 virus testing, which now encompasses general hospital entry screening, preoperative and preprocedural screening, occupational health testing, symptomatic patient testing and retesting, and ongoing testing for reentry into clinical care. Sampling of different locations within the respiratory tract and even by different staff can lead to different laboratory results. Further, because of different gene targets and limits of detection of each gene target within platforms, samples that have negative test findings on one platform may have positive findings on another. Until quantitative molecular techniques are used to study and compare different pediatric populations, including immunocompromised hosts (who were not included in the study by Han et al[13]), using a stable sample type, it remains unknown if asymptomatically infected children shed similar, higher, or lower amounts of virus than symptomatic individuals. This has major public health implications and should be a priority for future research.

Finally, this study only addresses duration of viral shedding from the respiratory tract assessed from sampling of nasopharyngeal and oropharyngeal (and, in some cases, sputum) samples. Multiple studies have now demonstrated that virus is detectable from additional body fluids, including stool, for prolonged periods.[17,18] The duration and kinetics of shedding are likely to be different in each of these, and there are also likely differences between shedding in adults and children. While most studies and public health interventions focus primarily on the respiratory route (face masks), the spread of virus within communities may be affected by these alternative routes of transmission, particularly in day care and preschools where children are not continent.

Additional questions remain regarding viral load and its relationship to severity of disease and duration of shedding in children. Does higher peak viral load correlate with disease severity and/or longer periods of shedding?[19] Do other sources of viral shedding, such as stool or saliva, contribute significantly to transmission? Do viral loads correlate directly or inversely with appropriate and/or aberrant immune and inflammatory responses to viral infection, as seen in the setting of multisystem inflammatory syndrome of children? For instance, could prolonged shedding result in continued low-level activation of the immune system and/or hyperinflammatory states?

Although this study sheds important light on testing in a controlled situation, real-life scenarios where molecular testing of children is applied are more varied. Children may present for testing to ambulatory clinics when mildly symptomatic, emergency departments when moderate or severely ill, or when hospitalized. Testing of asymptomatic children is now increasingly common after contact with known positive household contacts or as preprocedural, prechemotherapy, preimmunomodulation, pretransplant, or prehospitalization screening. There are likely to be expanding scenarios for testing children as schools reopen and sports and other activities resume. A qualitative molecular test at a single point in time in each of these scenarios cannot be assumed to be equal; the degree of viral load or kinetics of shedding is very likely to be different in each of these, and formal studies to dissect this are needed to fill this knowledge gap. Even larger knowledge gaps exist with respect to serologic responses to coronavirus disease 2019 infection. There is a paucity of seroprevalence data in the population at large and a near-complete deficit in pediatric populations. Estimates of herd immunity must take into account the possibility that the general seroprevalence of dis-

ease in the pediatric population could be the same or higher or lower than that in adults. Until these studies are performed, we are shooting in the dark.

In summary, the study by Han et al[13] highlights that a large percentage of infected children may be asymptomatic or presymptomatic despite infection with SARS CoV-2 and that both asymptomatic and symptomatic individuals may shed virus for prolonged periods of time (2 to 3 weeks) regardless of symptoms. These findings are highly relevant to the development of public health strategies to mitigate and contain spread within communities, particularly as affected communities begin their recovery phases.

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