UJEMI PERSPECTIVES

The role of children and adolescents in SARS-CoV-2 transmission and susceptibility to infection warrants further investigation

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SUMMARY Early investigations of severe acute respiratory syndrome coronavirus 2 infection revealed relatively low rates of infection and mild clinical outcomes among children and adolescents. The burden of disease on the pediatric population was thus determined to be relatively low, and their role in viral transmission likely insubstantial. However, our current understanding may be limited by the emphasis on identifying symptomatic cases and lack of widespread diagnostic testing. As such, children and adolescents, who are reportedly less likely to be symptomatic during infection may be under-represented. This paper aims to provide an updated summary of the manifestation of SARS-CoV-2 infection in children and adolescents, and their role in viral transmission as documented by previous studies. A comprehensive review of the existing literature will provide insight on the current status of our understanding of SARS-CoV-2 infection and post-infection outcomes within this subpopulation, identify limitations of early reports, and highlight the necessity for either further investigation or re-assessment of initial conclusions. Ultimately, recognizing and addressing the current gaps in our knowledge will better inform the development of public health policies to mitigate the spread of SARS-CoV-2 infection, assist clinical management of disease, and reduce the burden on our healthcare systems.

INTRODUCTION

Initial reports of an unknown pneumonia-causing pathogen emerged from the city of Wuhan, in the Hubei province of central China in late 2019. The causative agent has been identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel member of the betacoronavirus family that has since been responsible for the coronavirus disease 2019 (COVID-19) pandemic that was officially declared by the World Health Organization (WHO) as of March 11, 2020 (1). Nearly a year after the declaration of this global health emergency, SARS-CoV-2 has infected over 110 million individuals and resulted in greater than 2.6 million deaths worldwide (2).

At the onset of the pandemic, countries across the globe prioritized identification of symptomatic cases of infection in an effort to guide public health interventions and ultimately mitigate the rapid rate of viral transmission (3). Individuals presenting with symptoms suggestive of SARS-CoV-2 infection were administered diagnostic tests, which upon returning positive, informed subsequent self-isolation and quarantine strategies, and/or resulted in potential for hospitalization. A large portion of the existing literature consequently characterizes SARS-CoV-2 infection among adults, and particularly in older adults who have been observed to more commonly present with symptomatic cases of infection and more severe cases of COVID-19 (4). In contrast, children and adolescents, who have typically been defined as persons less than 20 years of age, accounted for a significantly smaller proportion of confirmed cases. Early investigations indicated that pediatric cases of SARS-CoV-2 infection generally constituted less than 2% of total cases (4, 5). The lack of symptom severity among the pediatric population resulted in the tentative conclusion that children and adolescents may be less susceptible to SARS-CoV-2 infection, and thus less likely to play a

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prominent role in viral transmission (6, 7). Therefore, cases of SARS-CoV-2 infection among children and adolescents garnered less attention in the majority of studies rapidly undertaken at the outset of the pandemic.

There are some groups, however, who have contended the necessity in elucidating the prevalence of SARS-CoV-2 infection among the pediatric population in order to gain a comprehensive understanding of the degree to which children and adolescents may be contributing to viral circulation within their communities. The concerns of these clinicians and researchers arise primarily from the initial emphasis on symptom-based testing for case detection. As a result, there is a possibility that the pediatric population may currently function as undetected, silent spreaders of SARS-CoV-2 due to their experience of a generally mild clinical course during infection, and often, their lack of symptom presentation (8, 9). The recent emergence of studies that have implemented methods of large-scale diagnostic testing and effectively discovered relatively high numbers of asymptomatic cases of infection among pediatric patients has further substantiated these concerns (10). Additionally, increasing reports of what has been classified as multisystem inflammatory syndrome in children (MIS-C) that appears to have a delayed temporal association with SARS-CoV-2 infection has triggered a revived interest in further investigating pediatric cases of COVID-19 (8).

PROPOSED RESEARCH QUESTIONS

The lack of comprehensive literature on SARS-CoV-2 infection in children and adolescents has led some scholars to refer to this subpopulation as under-represented (11). Indeed, the burden of disease among youth and the potential burden of viral spread attributed to youth remains uncertain even after a year since the declaration of the COVID-19 pandemic. This article strives to summarize the clinical manifestations and course of SARS-CoV-2 infection among children and adolescents. In effect, current understandings regarding the clinical and laboratory features, and prognosis of MIS-C will also be discussed. However, this paper aims to specifically emphasize the prevalence of subclinical or asymptomatic pediatric cases of SARS-COV-2 infection to highlight the necessity in reassessing early conclusions on the role of the pediatric population in viral transmission. To address the current gaps in our knowledge, this paper will finally explore strategies to tackle the challenge in identifying silent cases of SARS-CoV-2 infection among youth.

PROPOSED PROJECT NARRATIVE

What are the clinical manifestations of SARS-CoV-2 infection in children and adolescents? Confirmation of acute SARS-CoV-2 infection has predominantly been obtained through real time reverse transcriptase polymerase chain reaction (RT-PCR) of nasopharyngeal or oropharyngeal swabs (10, 12–15). While some studies have evidenced uneven distribution of infection among males and females, with a slightly larger proportion of infections observed among males (10, 13, 15), sex has not been identified as a risk factor for severe infection in the pediatric population (12). Among youth, the clinical course of symptomatic SARS-CoV-2 infection has been documented to be generally mild to moderate in severity, with most patients experiencing only mild symptoms of respiratory infection such as fever and dry cough, and less commonly, rhinorrhea, nasal congestion, fatigue, and sore throat (12, 13, 15). The large majority of pediatric patients who were hospitalized have not required oxygen nor ventilation assistance, and most have been observed to recover within 1 to 2 weeks of disease onset during acute infection (12, 15). Interestingly, the most commonly reported chest computed chromatography abnormality in patients were nodular and bilateral ground-glass opacities, which were suggestive of pneumonia, but were observed irrespective of symptom presentation (12, 15, 16).

While a small percentage of pediatric cases of severe COVID-19 has been documented, they have generally been represented among patients possessing pre-existing comorbidities such as congenital anomalies, chronic lung diseases such as asthma, or other immunosuppressive disorders (16, 17). However, the overall reported intensive care unit

(ICU) mortality rates for pediatric patients who experienced critical illness has been significantly smaller than that for adults presenting with severe COVID-19 (17).

Currently, a more pressing matter of concern has been the increase in reports of MIS-C in pediatric patients following previous exposure to SARS-CoV-2 as indicated by positive RT-PCR or antibody testing, or an epidemiological link to a person with confirmed infection (18). Although initially documented in a small cluster of older school-aged children in England in April 2020, cases of MIS-C have since emerged from multiple areas within Europe and the United States (19, 20). In response, the European and United States Centres for Disease Control and Prevention (CDC) and the WHO have established case definitions for MIS-C to aid physicians in recognizing patients presenting with symptoms of this syndrome (21, 22). A number of studies have remarked the similarities in some clinical manifestations of MIS-C to Kawasaki disease, an acute pediatric vasculitis that may cause coronary-artery aneurysms, and even toxic shock syndrome (18, 23, 24). Common clinical presentations of MIS-C include persistent fever, asthenia, erythematous rash, multiorgan dysfunction including manifestations of abdominal pain and cardiac dysfunction, and in a substantial number of cases, cardiovascular shock (18, 23, 24). Laboratory features have been suggestive of hyperinflammation and cytokine storm, such as observations of elevated serum IL-6 levels, C-reactive protein, ferritin, along with other markers of an inflammatory state (18, 23, 24). Affected patients with MIS-C frequently required ICU admission for inotropic support and management of cardiovascular failure, with ranges of 20-100% of patients requiring hospitalization (24). What has warranted significant alarm, has been the failure to identify underlying health conditions that may function as risk factors for the development of MIS-C, with most patients reporting to be previously healthy and only mildly symptomatic or asymptomatic during acute SARS-CoV-2 infection (18, 19). While the majority of patients with MIS-C have appeared to recover within a week of hospitalization (18), the moderate- to long-term outcomes along with the pathophysiology of this syndrome remains to be determined.

What is the current predicted role of children and adolescents in SARS-CoV-2 transmission? To assess the degree to which the pediatric population may contribute to viral spread, some groups have undertaken efforts to establish computational mathematical models to evaluate the impact of school closures on case incidence within the community of interest. Using line list data released from published reports on case incidence, in addition to city-specific age-distribution data and previously measured contact matrixes, Davies et al. simulated the impacts of a 3-month long school closure in their simulations of COVID-19 epidemic in 3 different cities across the globe (25). Similarly, Abdollahi et al. constructed and parameterized an age-stratified computational model using demographic data for the province of Ontario, Canada, and the most recent estimates of COVID-19 epidemiological characteristics at the time of study to simulate disease spread and the effects of a 3-16 week school closure on mitigating community disease burden (26). In both studies, the effectiveness of school closures on reducing the incidence of SARS-CoV-2 infection and the burden of COVID-19 was minimal.

Alternative to computational modelling, Ismail et al. performed a prospective, cross-sectional analysis to assess the results of the partial re-opening of school settings in England between the months of June and July, 2020 (27). Despite a median daily attendance of 928 000 students across a median of 57 600 partially re-opened school settings, the total incidence of SARS-COV-2 infection related to these educational environments was limited. Identified cases of infection were primarily among staff, and the majority of cases linked to outbreaks were also identified in staff. In contrast, the determined rates of infection and outbreak were lower in children, and transmission between students was described as rare.

Together, the results of these studies may lead some to conclude that children and adolescents play a negligible role in the COVID-19 pandemic, and that interventions directed towards this subpopulation may have limited success in minimizing community transmission. However, in particular to the studies based on computational modelling, initial results may be skewed and constrained by model predictions that relied on early estimates and preliminary information available at the onset of the pandemic. Although alluded to even shortly

following the declaration of the COVID-19 pandemic, the concern regarding the covert presentation of SARS-CoV-2 infection and thus, the potential for underestimating transmission among youth has recently been emphasized (13, 28). An assessment of reported pediatric cases of COVID-19 in the cities of Ningbo and Wenzhou in China by Qiu et al. in March of 2020 identified 28% of all confirmed cases as asymptomatic (13). In conducting a systematic review on pediatric COVID-19, Hoang et al. similarly determined that just under 20% of identified cases of SARS-CoV-2 infection among children were asymptomatic (15). Given that we prioritized identification of symptomatic cases of SARS-CoV-2 infection at the onset of the pandemic, it is indeed likely that the rate of infection in youth may be dramatically under-reported. Ismail et al. even briefly recognized that the results of their study may have been constrained by the lack of wide-spread testing in school settings; instances where further symptom-agnostic testing was pursued, additional cases of infection were identified.

In addition to the prevalence of asymptomatic pediatric cases of SARS-CoV-2 infection, the lack of knowledge on the infectiousness of asymptomatic and paucisymptomatic cases relative to symptomatic cases also complicates our ability to conclusively determined the role of children and adolescents in viral transmission. It is possible that milder causes may have reduced infectiousness due to the lack of symptom presentation that may otherwise contribute to viral dissemination (25). However, asymptomatic patients who were later identified as positive for SARS-CoV-2 infection have contributed to chains of viral transmission within communities (29). A number of reports have noted the absence of significant differences in viral load between patients regardless of symptom presentation, determined using RT-PCR of collected naso- or oro-pharyngeal swabs over the period of hospitalization (13). Yet, differences in viral load between symptomatic and asymptomatic patients ultimately requires further elucidation.

How might we be able to address the current gaps in our knowledge moving forward?
Addressing the current knowledge gaps regarding SARS-CoV-2 infection among children and adolescents requires further investigations on the newly emerged condition classified as MIS-C, in addition to elucidating the rate and role of asymptomatic pediatric infection. These steps are imperative to effectively manage disease burden in this subpopulation and the global community.

Speaking first to the topic of MIS-C, the pathophysiology of this syndrome and the moderate- to long-term outcomes are currently unknown. At the moment, patients who have met the case definition criteria for MIS-C upon clinical presentation have been treated with immunomodulatory therapies and offered vasopressor or vasoactive support, typical of treatment of Kawasaki Disease, due to the overlapping similarities of the conditions (18, 24). The possibility of MIS-C being the result of delayed hyperinflammation following SARS-CoV-2 infection has resulted in the administration of interleukin-6 inhibitors in the treatment of some patients; however, whether treatment with antiviral therapies is beneficial to patients who concurrently tested RT-PCR positive for SARS-CoV-2 infection has been discussed (24). Determining both the pathogenesis and pathophysiology of MIS-C may optimize treatment methods, clinical management, and potentially aid early detection and prevention efforts. Furthermore, given the relative recency in the emergence of MIS-C and its unclear prognosis, monitoring of patients following hospital discharge may be necessary to mitigate the risk of possible long-term cardiac manifestations or further complications (18, 24).

Early predictions on the rate of viral transmission owed to children and adolescents may have been constrained by preliminary reports of infection that largely overlooked asymptomatic and paucisymptomatic individuals. The value in expanding diagnostic testing efforts has been highlighted in a study put forward by Han and colleagues, where they noted that without the extensive contact tracing and testing efforts employed, up to 93% of children who were identified and tested positive for SARS-CoV-2 would have gone undetected (10). The contributions of asymptomatic and mildly symptomatic cases in viral shedding, and effectively, community spread has also been debated. Semi-quantitative efforts have used cycle threshold (Ct) in RT-PCR of naso- and oro-pharyngeal swabs to predict viral load in patients, with higher Ct indicating lower viral load; however, these studies are few and further

investigation is required (9,10). Elucidating the rate of viral transmission and infectiousness of asymptomatic cases may offer a more comprehensive understanding of the role that children and adolescents may play in this unprecedented global pandemic.

CONCLUSIONS

The rapid emergence of SARS-CoV-2 has resulted in an unprecedented public health and economic burden across the globe. A year after the declaration of the COVID-19 global pandemic by the WHO, the international collaborative efforts of researchers, clinicians, and public health officials has resulted in significant progress in clinical characterization of SARS-CoV-2 infection, vaccine development, and investigations of therapeutic treatments to mitigate the strain of the disease. While commendable advancement has been made, much remains unknown in regards to SARS-CoV-2 pathology and long-term outcomes of viral infection. These gaps in our knowledge warrant concern and should motivate continued investigative efforts. The introduction of new circulating variants of concern with reports of increased transmissibility and potential ability for immune evasion further consolidates this necessity (30, 31). This article in particular, emphasizes the need for increased assessment of SARS-CoV-2 infection among children and adolescents, who were initially believed to be spared from severe disease and perhaps prematurely concluded to play a relatively limited role in viral transmission.

Increasing reports of a multisystem inflammatory syndrome that appears to have a temporally delayed association with SARS-CoV-2 infection in children has raised alarm in clinical settings. Currently unidentified host risk factors, and observations of MIS-C causing hyperinflammatory shock and cardiovascular failure in previously healthy children who reported no underlying comorbidities urges additional examination on this potentially life-threatening syndrome. Identification and validation of early biomarkers indicative of MIS-C along with long-term follow-up of affected patients may offer aid in future case detection, clinical management, and reduce the risk of unmitigated progression of cardiac complications.

On the other hand, our initial understanding of viral infection in the pediatric population was hindered by the focus on identifying symptomatic cases of infection at the onset of the pandemic. It is now apparent that a significant portion of children and adolescents who have been infected with SARS-CoV-2 remain asymptomatic, or only mildly symptomatic and were thus undetected and remain under-reported as a result of early diagnostic efforts. Therefore, predictions that this subpopulation holds a negligible role in viral transmission due to decreased susceptibility of case incidence may be flawed. The expansion of large-scale, rapid diagnostic testing in school settings may be a strategy that would allow us to acquire an updated, and perhaps more comprehensive understanding of the role that children and adolescents hold in viral spread. Throughout a number of provinces in Canada, rapid diagnostic testing pilot projects in university and school settings have been initiated (32–34). As these data continue to emerge, amendments to the initial parameters in previously established computational models may refine predictions of viral spread, and better inform public health policy and control interventions.

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