It’s True Even in a Pandemic: Children are Not Merely Little Adults

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Though separated from family and friends due to physical distancing, my wife’s grandfather celebrated his 104\textsuperscript{th} birthday in April 2020. Born in 1916, in the middle of the First World War, he is now experiencing his 2\textsuperscript{nd} global pandemic and the attendant reality of human mortality. In his toddler years, he belonged to a high-risk population for pandemic influenza – children less than 5 years old, adults >65, and uniquely, young adults 20-40 years of age were disproportionately affected. Now, a century later, he finds himself again in a high-risk population – adults >65 years of age and living in a long-term care facility. Strangely, and to his delight, his great-great grandchildren (of whom there are many) do not seem to share this increased risk for disease.

His endurance and repose during the intervening years point to a principle that each new global threat to human health brings with it something old and something new. Pandemic influenza and coronavirus share transmission characteristics that allow for rapid and dense spread through communities. They share a predilection for severe disease, particularly in high risk hosts, while they also benefit from asymptomatic hosts and minimally symptomatic individuals who are capable of transmission prior to obvious signs of disease. An unusual and new feature of SARS-CoV-2 is the apparent reduced infectivity and relatively low frequency of severe disease in children, an unusual characteristic of a highly contagious respiratory virus. Understanding these similarities and differences will be critically important as we move forward through this pandemic.

In this issue of CID, Mehta et al (CID PAPER) provide a systematic review of pediatric COVID-19, evaluating the available literature to date to glean characteristics of disease and transmission. Though limited by the availability of case reports and case series, many from epicenters in China and Italy, the authors were able to identify a number of studies that were of sufficient quality and granularity to warrant inclusion in the review.

Consistent with local and national experiences, children appear to be less affected by COVID-19 than adults. The authors report that children represent only 5% or less of diagnosed COVID cases and the data available at the time of review suggest that children are less likely to develop either severe pneumonia or the laboratory alterations commonly associated with severe disease, such as lymphopenia and elevated inflammatory markers.
The authors also report that intrauterine transmission appears to be extremely uncommon and that newborns born to infected mothers are likely to experience either asymptomatic disease or mild disease. Taken together, it would appear that children experience a very different response to SARS-CoV-2 infection than adults and raises the hypothesis that dysregulated host responses may be the primary driver of disease severity. In fact, targeting the host response to infection has become the focus of multiple clinical trials, including baricitinib, tocilizumab, ravulizumab, eculizumab, and a host of other drugs aimed at blunting an exuberant immune response.

Using a similar approach, Zimmermann et al recently evaluated available cases of disease in children and neonates [1]. In this review, approximately 35% were asymptomatic and co-infections (namely *Mycoplasma* and influenza) have been identified in many children, complicating how providers attribute symptoms to SARS-CoV-2. Pregnancy outcomes were similarly encouraging, though fetal distress was reported in up to 30% of pregnancies and preterm delivery complicated approximately 35% or reported cases. The authors raise a number of hypotheses that may explain the differences in phenotypes from adults, including differences in immune response, fewer co-morbidities, microbial interactions in the nasal mucosa, differences in ACE2 receptor density in the nasal epithelium [2], and others. The challenge of course, is “what gets us into trouble is not what we don't know; it's what we know for sure that just ain't so” [attribution uncertain]. Shortly after the authors completed their review, reports emerged of a Kawasaki-like illness among Italian children who presented with incomplete Kawasaki Disease, Kawasaki Disease with Septic Shock, or classic Kawasaki Disease. Eight of the 10 children in the report had detectable serum SARS-CoV-2 antibodies and were less likely to be PCR positive [3]. The authors conclude that SARS-CoV-2 may induce an aberrant immune response in some children that resembles Kawasaki Disease (Multisystem Inflammatory Syndrome in Children [MIS-C]). The report, and emerging data from the UK and US, particularly New York City, are particularly intriguing given previous hypotheses regarding the potential role of coronaviruses in the pathogenesis of Kawasaki Disease [4]. In addition, larger case series of pediatric cases are becoming available [5], giving even greater clarity on epidemiology, transmission characteristics, and disease manifestations.
What implications, then, do these early reports of pediatric COVID-19 have for healthcare workers and public policy makers? First, we are early in the pandemic and we simply do not know what we don’t know. For this reason, the Pediatric Infectious Diseases Society (PIDS) has encouraged all its members to contribute to the Pediatric Infectious Diseases Transplant Network (PIDTN) COVID-19 Registry. Prospective collection of data will be essential as we characterize this pandemic in children. Second, the review by Mehta et al should remain encouraging that children are less severely affected overall. In many areas, childcare availability is the *sine qua non* of re-opening local economies. It is nearly impossible to open retail businesses, restaurants, law firms, and government agencies without providing access to school and adequate childcare opportunities for workers. Recent reports from Europe, where schools are reopening in several countries, are encouraging; Denmark reopened nurseries, kindergartens, and primary schools in mid-April and disease activity remains moderate across the country. With that being said, two important caveats remain. Many teachers, administrators, and support staff in local schools and childcare facilities belong to high risk groups as a result of age or comorbidities. We have a duty to protect these individuals as much as possible. Moreover, we must recognize that some proportion of children that are infected will experience either moderate disease, severe disease, or immunologically mediated complications, such as MIS-C. Defining the true burden of disease across pediatrics will be essential as we consider best practices for the start of the 2020-21 academic year.

My wife’s grandfather would likely summarize the issue by saying there is ‘nothing new under the sun.’ Unfortunately, the vast majority of us have not been around the sun as many times as he has. We are still learning what we know, what we don’t know, and what we think we know that just isn’t so. As it relates to children, early reports are encouraging, but the emergence of immunologically mediated complications must give us pause. In this pandemic, at least thus far, children are not merely mirrors of the adult experience but bring their own challenges in diagnosis and treatment.

**Disclosures**

No relevant disclosures to report
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