

Immune Response to SARS-CoV-2 Infection in Children

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SARS-CoV-2 has resulted in more than 540 million cases and more than 6 million deaths globally since the first case was detected in late 2019.¹ Unlike other infections, where children are overrepresented in infection numbers and serve as a reservoir and transmission risk,

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COVID-19 appeared unlikely to cause severe disease in children compared with other age groups. This underappreciation of pediatric infection is misleading because as the pandemic has evolved it has become clear that while children are not at risk of hospitalization and death at comparable rates as older adults, those with certain underlying conditions (for example, diabetes, obesity, neurological conditions) are at risk of severe disease and death.² A recent meta-analysis showed that approximately 3% of infected children are hospitalized.³ Other studies demonstrated that prior to and after the emergence of variants of concern, children with COVID-19 had similar or higher risk of hospitalization, need for life-sustaining therapy, and death as those infected with influenza.^{4,5} Children also are at risk of developing multisystem inflammatory syndrome in children (MIS-C), a rare but severe postinfectious complication, often after asymptomatic or mild infection. While the pathophysiology of MIS-C is as yet poorly understood, it is marked by immune dysregulation. Understanding the normal immune response in children is therefore a priority as we tease out public health implications as SARS-CoV-2 evolves from being a pandemic into an endemic infection. Unfortunately, to date, data on the immune response in children have been relatively sparse.⁶

In this issue of *JAMA Pediatrics*, Yung and colleagues⁷ explore the kinetics of neutralizing antibody levels in children following natural infection with SARS-CoV-2. In a well-designed report, they recruited children aged 0 to 16 years with SARS-CoV-2 infection, confirmed by polymerase chain reaction test results from nasopharyngeal swabs, from a single referral center in Singapore. Children were recruited from early on in the pandemic until September 2021, thereby covering periods from the original Wuhan strain through the emergence of other variants of concern such as Alpha and Delta, although persistence data on the latter variant are, of necessity, limited. This report offers a valuable insight and points to areas for future research. Notably all participants had mild illness, which is the experience of most, but assuredly not all, infected children and approximately one-quarter were asymptomatic. The acute-phase antibody response was most robust in younger children, and unsurprisingly, antibodies peaked in the first months after infection. However, although the numbers are too small to draw definite conclusions, it is somewhat reassuring that neutralizing antibodies persisted for a rea-

sonable interval (9-13 months) following infection. This is encouraging, because although we lack a correlate of immunity and a full understanding of the immune response to SARS-CoV-2, specifically an understanding of the role of cellular immunity, it is hoped that this antibody persistence may at least protect against or ameliorate severe disease, even if it does not prevent subsequent infection. The use of a single center, one that was designated as the national center for diagnostics, ensures consistency in methodology but also limits the generalizability of findings to the wider population and to other populations, since we know that infection rates and severity of disease are influenced by demographics.

How then do we interpret these findings and place them in their proper context? At first glance, it would appear that potentially antibody persistence in younger age groups is more robust, a not altogether unexpected finding given what we know about declining immune responses with age and the decreased likelihood that a pediatric cohort would have associated morbidities or concurrent medications that would interfere with that response. It is also encouraging that contrary to other studies showing that immune response is dependent on severity of illness, in this cohort at least it appeared that mild disease has the potential to confer longer-lasting protection, longer than the 3 to 6 months that is generally considered. Such a duration would allow consideration of potentially longer intervals between vaccine doses as vaccination becomes available for these age groups. Unfortunately this is not likely. Seroprevalence studies estimate that as many as 74% of children have been previously infected with SARS-CoV-2, so if prior infection prevented reinfection, we would not be experiencing rising infection rates at the current time.⁸ The explanation lies in the timing. It is noteworthy that this study preceded the emergence of the Omicron variant in late 2021. Omicron variants contain more than 30 mutations in the SARS-CoV-2 spike protein and resulted in global outbreaks. Further, studies show that the Omicron variant is resistant to neutralizing antibodies induced from prior infections with earlier variants and to vaccination, although the latter was partially overcome with booster doses.⁶ In addition, emerging data suggest that the new BA.2.12.1, BA.4, and BA.5 Omicron subvariants are capable of escaping neutralizing antibodies produced by prior infection with the Omicron BA.1 and BA.2 variants, thus explaining current surges in infection in communities with high rates of prior infection, vaccination, or both.⁹

The novel SARS-CoV-2 virus and COVID-19 pandemic have resulted in a fundamental change in all countries, but as time has passed, adherence to public health guidance regarding mask wearing, handwashing and social distancing has waned. The evolution of novel variants coupled with an incomplete

understanding of both the full spectrum of COVID-19 or associated medium- to long-term sequelae or the kinetics of the immune response underscores the importance of performing studies such as that undertaken by Yung and colleagues and population-based longitudinal studies to fully understand the immune response to SARS-CoV-2 infection and response to vaccination. The virus will continue to mutate and evolve, and with each change, the clinical expression of infection may

change. To date, Omicron has resulted in relatively less severe disease than other variants (for example Delta) but that may not be the case in the future. Such studies need to be performed in all age groups. In pediatrics, it is also encouraging that vaccines are available under emergency use authorization to children as young as 6 months of age, since, despite immune escape, vaccines remain protective against not only severe infection and death, but also potentially against MIS-C.

ARTICLE INFORMATION

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