Integrating SARS-CoV-2 Antibody Results in Children Into Pandemic Response

Andrea T. Cruz, MD, MPH,[a] Mark R. Denison, MD[b]

The report by Messiah et al[1] in this issue of *Pediatrics* provides useful data on the duration of the nucleocapsid antibody response in children after SARS-CoV-2 infection. As our current SARS-CoV-2 vaccines elicit antibodies to the spike protein, antibodies to the nucleocapsid represent past infection, rather than vaccine response. The authors found that, in this cohort of 218 children, ~45% had antibodies to the nucleocapsid protein during the time that the predominant circulating variants were alpha and delta. The frequency of nucleocapsid antibody detection was no different by age, body habitus, or severity of infection. More than 95% of children who had positive nucleocapsid antibody test results at the onset of the study still had detectable antibodies at least 6 months later. This study, in which enrollment began before vaccinations were available to children and ended before *o* became the predominant circulating variant, provides some reassuring data regarding the durability of the response.

However, there remains much we still do not know about the immune response to SARS-CoV-2. First, this study qualitatively evaluated the nucleocapsid antibody response. Quantitative results, which would have allowed for evaluation of the potential degradation of the nucleocapsid antibody response over time, were not available. As we do not know what nucleocapsid antibody levels are associated with protective immunity, it is possible that the qualitative nucleocapsid antibody response detected may have been below the threshold conferring immunity. Studies on the duration of the SARS-CoV-2 nucleocapsid antibody response in children have provided conflicting results. Some data suggest that children may have a more attenuated nucleocapsid antibody response than adults.[2] However, other studies have found that antibodies to the spike protein were high in children, even in those who had negative nucleocapsid antibody test results, suggesting that exposure to previous endemic coronaviruses may lead to cross-protection for SARS-CoV-2 infection.[3,4]

Second, more than one half of children still did not have a detectable nucleocapsid antibody response even >1 year into the pandemic. This percentage has undoubtedly declined since the study closed, given the high rates of the omicron variant in children,[5] and it is possible that recent infection may not have been detected through nucleocapsid antibody testing. Nonetheless, a substantial proportion of children have not developed neutralizing antibodies at all, or have developed nucleocapsid antibodies, but the immune response after wild-type infection may not result in protective immunity. This may be particularly true for the omicron variant, for which convalescent sera offered little to no neutralizing

[a]*Department of Pediatrics, Baylor College of Medicine, Houston, Texas; and* [b]*Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee*

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Address correspondence to Andrea Cruz, MD, MPH, Department of Pediatrics, Sections of Emergency Medicine and Infectious Diseases, Baylor College of Medicine, 6621 Fannin St, Ste A2210 Houston TX 77030. E-mail: acruz@bcm.edu

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activity. However, in 1 study, investigators found that administration of a booster dose did result in a neutralizing response to omicron.[6] Consequently, and as the authors point out, the emphasis on vaccinating children and administration of boosters to combat waning immunity[7] must persist. Whereas this study did not look at nucleocapsid antibody response in children <5 years of age who remain vaccine ineligible to date, the youngest age cohort included (5–9 years of age) had substantially lower frequencies of antibody detection than older children at all time points in the study. This suggests that the protection offered by vaccination may be highest for the youngest children. However, vaccination will be a crucial part of pandemic control for children of all ages. Natural infection with coronaviruses confers only transient humoral immune responses; in contrast, mRNA vaccines have less decay in antibody responses over time and may also result in cell-mediated immunity.[8]

Third, in this study, the presence of symptoms did not correlate with the presence or absence of nucleocapsid antibodies. This is not surprising given the frequency of asymptomatic infection[4] and the symptomatology shared by SARS-CoV-2 and other respiratory viral pathogens.[9] Thus, a child having had an upper respiratory tract infection, or a febrile illness should not provide false reassurance that the illness was caused by SARS-CoV-2, that SARS-CoV-2 immunizations should be delayed, or that the child subsequently may be protected.

The duration of a nucleocapsid antibody response is somewhat reassuring, particularly given that many children[10] are unable to receive the benefits of vaccination either because of their age or vaccine hesitancy. However, a qualitative antibody response should not provide false reassurance. In the absence of a correlation with quantitative nucleocapsid antibody levels and protective immunity, there are reasons that we do not currently integrate antibody testing into decisions to vaccinate.

ABBREVIATION

SARS-CoV-2: severe acute respiratory coronavirus 2

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