Duration of Effective Antibody Levels After COVID-19

Andrea T. Cruz, MD, MPH,[a] Steven L. Zeichner, MD, PhD[b]

After having coronavirus disease 2019 (COVID-19), patients develop a humoral immune response thought to protect against reinfection, but antibody levels can decline over time. Understanding how long antibody levels remain high enough to prevent infection is important in understanding, absent vaccination, whether children may be vulnerable to COVID-19 and in modeling how COVID-19 spreads through the population.

The levels of antibodies capable of neutralizing the virus (neutralizing antibodies [nAbs]) provide a direct marker of a protective humoral immune response. The nAbs can be measured directly by determining how well a patient's serum inactivates virus when a known amount of virus is placed on cells in tissue culture, which is known as a plaque reduction neutralization test. The remarkably safe and effective approved COVID-19 vaccines elicit potent antibody responses against portions of the virus mediating attachment to host cells and viral entry, the spike protein and its receptor-binding domain. The concentration of antibodies a patient has against spike protein and receptor-binding domain provides a marker of susceptibility to infection or reinfection.[1–3]

In their study in *Pediatrics*, Bonfante et al[4] report that preschool-aged children with asymptomatic or mildly symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection had high levels of nAbs and that these levels remained high for the duration of their 7- to 8-month follow-up period. In contrast, lower nAb levels and more transient nAb responses were seen in school-aged children and adults.

These findings are intriguing for several reasons. First, nAbs persisted in younger children at high levels for several months. This is in contrast to the experience with both adults and with non–SARS-CoV-2 coronavirus infections. In one study, researchers found that after COVID-19, only one-third of adults had detectable nAbs and, even in those patients, nAb levels decayed rapidly over a few months.[5] For non–SARS-CoV-2 coronaviruses, nAbs wane within several months of infection, resulting in repetitive infections by many coronaviruses that cause a significant fraction of viruses causing common colds.[6] Reasons for the enhanced persistence of nAbs in younger children is unclear. One explanation may be that the immune response in adults, who have had repetitive exposure to endemic coronaviruses, may target these previous viruses and may not respond as easily to SARS-CoV-2 as the relatively less experienced (and potentially more flexible) immune response seen in young children. This concept is called original antigenic sin.[7] Although original antigenic sin may result in a more robust response to viral strains previously encountered, antibodies made against a newly encountered coronavirus in patients who have

[a]*Department of Pediatrics, Baylor College of Medicine, Houston, Texas; and* [b]*Departments of Pediatrics and Microbiology, Immunology, and Cancer Biology, School of Medicine, University of Virginia, Charlottesville, Virginia*

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Address correspondence to: Andrea T. Cruz, Department of Pediatrics, Baylor College of Medicine, 6621 Fannin St, Suite A2210, Houston, TX 77030. E-mail: acruz@bcm.edu

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had many coronavirus infections may bind suboptimally to strains with more antigenic drift.

The ability to generate an immune response in younger children was not contingent on illness severity. In adults, several studies have shown that antibody responses were higher in more severely ill than in mildly ill patients.[8] Given that up to 50% of children with SARS-CoV-2 have subclinical or mild symptoms,[9] the ability to mount an immune response that yields good nAb levels for at least several months is reassuring because vaccines remain unavailable to younger children. Even after vaccines are approved for the youngest children, barriers to vaccine uptake (including vaccine hesitancy and logistic barriers to widespread global distribution) mean that many children will not benefit from vaccination in the near future. As such, the data presented in this study suggest that reinfection may be a less common occurrence, given the magnitude and durability of the antibody response.

This does not mean that children who have already had SARS-CoV-2 should remain unimmunized once vaccines are approved for younger children. Recent data from vaccinated individuals and convalescent adult cohorts indicate that nAb levels are highly correlated with immunity.[10] The mean nAb levels seen after vaccination are higher than levels seen in convalescent adults.[10,11] Levels of nAbs decay with time, so the efficacy of a vaccine will not remain static over time. This may be a reason that boosters will be necessary, and boosters may also be needed to target newer SARS-CoV-2 variants for which existing vaccines may provide inadequate protection. Another reason for previously infected individuals to be vaccinated is that nAbs are only part of the host immune response. Immunoprotection may stem from other arms of the immune system, some of which may be more durable (eg, memory B-cell or T-cell responses). For example, in one study, researchers evaluated how immunity to endemic coronaviruses may impact host response to SARS-CoV-2. They found that, although there was little evidence of cross-reactive SARS-CoV-2 serum antibodies, preexisting memory B cells were activated during SARS-CoV-2 infection.[12] The study by Bonfante et al was focused on the patients' antibody responses to SARS-CoV-2, but it is important to remember that cellular immunity plays an important role in the ability of a patient to control SARS-CoV-2.[13] To fully understand the durability immune responses of children to COVID-19 and how these differ from those in adults, it will be necessary to describe pediatric long-term, cell-mediated immune responses in addition to humoral responses.

Although many aspects of what comprises an effective immune response to SARS-CoV-2 require additional study, the work of Bonfante et al advances our understanding, demonstrating a more durable (and likely effective) response in younger children. Because children constitute an important contribution to the spread of COVID-19 through the population,[13] knowledge of the potential susceptibility of children to reinfection is important in modeling COVID-19 epidemiology.

ABBREVIATIONS

COVID-19: coronavirus disease 2019
nAb: neutralizing antibody
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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