VIEWPOINT

COVID-19: BEYOND TOMORROW

COVID-19 and Postinfection Immunity
Limited Evidence, Many Remaining Questions

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Viewpoint

In the absence of effective treatment or biomedical prevention, efforts to control the coronavirus disease 2019 (COVID-19) pandemic have relied on nonpharmaceutical interventions such as personal preventive actions (eg, handwashing, face covers), environmental cleaning, physical distancing, stay-at-home orders, school and venue closures, and workplace restrictions adopted at the national, state, and local levels. In addition to these public health interventions, development of herd immunity could also provide a defense against COVID-19. However, whether immunity occurs among individuals after they have recovered from COVID-19 is uncertain. Many human infections with other viral pathogens, such as influenza virus, do not produce a durable immune response.

Understanding whether and how recovery from COVID-19 confers immunity to, or decreased severity of, reinfection is needed to inform current efforts to safely scale back population-based interventions, such as physical distancing. Understanding potential postinfection immunity also has important implications for epidemiologic assessments (eg, population susceptibility, transmission modeling), serologic therapies (eg, convalescent plasma), and vaccines. In this Viewpoint, we describe what is currently known about the immune response to COVID-19, highlight key gaps in knowledge, and identify opportunities for future research.

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COVID-19 is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Following infection, detectable IgM and IgG antibodies develop within days to weeks of symptom onset in most infected individuals.[1-3] Why some patients seem not to develop a humoral immune response, as reflected by detectable antibodies, is uncertain. Adding to this uncertainty is the unclear relationship between antibody response and clinical improvement. The findings from a small study of 9 patients with COVID-19 found that greater clinical severity produced higher antibody titers.[1] However, antibody detection and higher titers have not always been found to correlate with clinical improvement in COVID-19.[2,3] Moreover, mild COVID-19 symptoms can resolve prior to seroconversion (as reflected by detectable IgM and IgG), although detectable IgM and IgG antibodies have preceded declines in SARS-CoV-2 viral loads.[2,3]

What appears more certain is that viral burden typically peaks early in illness, and then declines as antibodies develop and antibody titers rise over the subsequent 2 to 3 weeks.[2,3] Success in culturing virus from nasopharyngeal specimens declines quickly during the first week of mild illness, but the absolute duration that a patient might shed infectious virus is unknown.[2] Persistent detection of viral RNA many days to weeks after recovery from COVID-19 at concentrations near the detection limit of available assays likely does not represent a meaningful clinical or public health risk, especially in the absence of symptoms[2]; however, definitive evidence does not yet exist.

The durability of neutralizing antibodies (NAbs, primarily IgG) against SARS-CoV-2 has yet to be defined; persistence up to 40 days from symptom onset has been described.[1] Duration of antibody responses against other human coronaviruses may be relevant in this context. For example, following infection with SARS-CoV-1 (the virus that caused SARS), concentrations of IgG remained high for approximately 4 to 5 months before subsequently declining slowly during the next 2 to 3 years.[4] Similarly, NAbs following infection with MERS-CoV (the virus that caused Middle East respiratory syndrome) have persisted up to 34 months in recovered patients.[5]

Detection of IgG and NAbs is not synonymous with durable immunity. With regard to COVID-19, a small, nonpeer-reviewed, preprint report provides the only data thus far on possible postinfection immunity in primates.[6] In this study, 4 rhesus macaques were infected with SARS-CoV-2, and following recovery did not become reinfected when rechallenged with the same virus 28 days after the first inoculation.[6] Whether persons can be reinfected with SARS-CoV-1 and MERS-CoV is unknown; SARS has not reemerged since 2004 and MERS cases remain sporadic. Reinfections can occur with at least 3 of the other 4 common human coronaviruses—specifically, 229E, NL63, and OC43—all of which generally cause milder respiratory illnesses.[7] The reasons for this reinfection are not fully known, but evidence suggests that possibilities include both short-lived protective

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immunity and reexposure to genetically distinct forms of the same viral strain.

To date, no human reinfections with SARS-CoV-2 have been confirmed. Evidence of reinfection typically requires culture-based documentation of a new infection following clearance of the preceding infection or evidence of reinfection with a molecularly distinct form of the same virus. In one report, among 2 otherwise healthy individuals who had recovered from COVID-19 and had 2 or more sequentially polymerase chain reaction (PCR)–negative upper respiratory specimens at least 24 hours apart, SARS-CoV-2 RNA was detected again in throat swabs sporadically for up to 10 days.[8] SARS-CoV-2 RNA has also been detected in throat or nasopharyngeal swabs more than 20 days after negative test results.[9] In another report among 18 patients, viral burdens (as determined by PCR cycle threshold) were generally lower than, and had declined substantially from, values during peak of illness.[10] At the time of postrecovery positive test results, the patients described in these reports had few, if any, symptoms, and when radiographically examined, they demonstrated stable or improving pneumonia.[8,10] There is also no evidence at present that such persons transmitted SARS-CoV-2 to others after they had clinically recovered. However, this possibility of transmission cannot be ruled out, especially for persons who may be predisposed to prolonged shedding of other pathogens, such as due to immunocompromised states.

It is also possible these cases represent persistent or recrudescent COVID-19 illness or even true reinfection. On the other hand, these cases may also represent prolonged sporadic viral RNA shedding at or near the limit of assay detection or variation in collection technique, specimen handling, or storage conditions affecting test performance. Data to effectively differentiate these possibilities are lacking, highlighting an area of substantial uncertainty. Routine collection of such data, specifically viral burden (as measured by PCR assay cycle threshold) and viral culture, and from a larger sample of patients under standard protocols, is needed.

Serological assays to detect SARS-CoV-2 antibodies are rapidly becoming available and will be critical to estimate the prevalence of infections, including those that are asymptomatic. However, it is presently premature to use such assays to determine whether individuals are immune to reinfection. Performance standards, including sensitivity and specificity, for the burgeoning number of serologic assays and the potential for cross-reactivity with other coronaviruses (yielding false-positives) have yet to be determined. Widespread testing of persons who have not had COVID-19, a population with low SARS-CoV-2 prevalence, can generate more false-positives than true-positives. This phenomenon may complicate clinical and epidemiologic interpretation of results, especially if the serologic tests do not have high specificity or some form of confirmatory testing is not used. More fundamentally, it remains to be determined whether a robust IgG response corresponds with immunity. Well-designed longitudinal cohort studies of persons who recovered from COVID-19 are needed to monitor for signs and symptoms of recurrent illness. Such longitudinal studies could also document possible reexposure events, all linked with clinical and laboratory investigations of other alternate etiologies, serologic testing, attempts to isolate virus by culture, and viral genomic comparisons of isolated viral specimens. However, in the short-term, possible recurrences of infection can be identified by monitoring surveillance data and by requesting clinicians and public health authorities to report and investigate cases of possible recurrence to determine whether recurrence can be confirmed.

In summary, existing limited data on antibody responses to SARS-CoV-2 and related coronaviruses, as well as one small animal model study, suggest that recovery from COVID-19 might confer immunity against reinfection, at least temporarily. However, the immune response to COVID-19 is not yet fully understood and definitive data on postinfection immunity are lacking. Amidst the uncertainty of this public health crisis, thoughtful and rigorous science will be essential to inform public health policy, planning, and practice.

ARTICLE INFORMATION

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