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Antibodies, Immunity, and COVID-19

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Widespread availability of commercial assays that detect anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies has enabled researchers to examine naturally acquired immunity to coronavirus disease 2019 (COVID-19) at the population level. Several studies have found that the SARS-CoV-2 seroprevalence (the percentage of the population with serum containing antibodies that recognize the virus) has remained below 20% even in the most adversely affected areas globally, such as Spain and Italy.[1-3] In this issue of *JAMA Internal Medicine*, Bajema et al[4] contribute new information on the shifting nature of SARS-CoV-2 seroprevalence in the US. The study uses national data to expand on an earlier US Centers for Disease Control and Prevention study of seroprevalence of antibodies to SARS-CoV-2 in 10 US sites.[3]

Using serum samples from commercial clinical laboratories, the investigators found the highest level of seroprevalence in New York, which surged from 6.9%[3] in March to a peak of approximately 25% before mid-August 2020.[4] For all but a few states, seroprevalence remained below 10% throughout the study period; New York was the only state where seroprevalence increased above 20%. In several states, seroprevalence stayed below 1%. Seroprevalence tended to wane over time, although in a few states, such as Georgia and Minnesota, rates increased over the study period. Thus, the primary takeaway from this study is that despite the pandemic raging across the US, most people do not have evidence of prior COVID-19 infection by antibodies to SARS-CoV-2.

A major strength of the study is its reliance on residual serum that had been sent to national commercial laboratories for routine clinical testing, rather than from patients suspected of having COVID-19. This approach enabled a less biased population sampling than in other studies. The samples were not enriched for people suspected of having infection, and thus the study provides a more accurate read of seroprevalence across disparate populations.

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However, a limitation of this approach is that the people most likely to have positive results for antibodies (those with clinical concern for prior infection) were excluded, which could result in an underestimate of true population-based seroprevalence. Another strength of the study is the testing of more than 130 000 samples from all 50 US states plus Washington D.C. and Puerto Rico. By evaluating seroprevalence over time in each geographical area, the investigators imparted a spatiotemporal dynamic to the results.

The unifying hope for ending the global COVID-19 pandemic is the development of adequate population-level herd immunity to halt the continuing cycles of infection and disease. Although no data exist to define the exact threshold necessary to achieve herd immunity against COVID-19, modeling and extrapolation from similar diseases suggest that more than 60%, and perhaps up to 80%, of the population may need immunity for the viral replication rate to drop below 1, enabling a modest level of disease control.[5] Such immunity may be achieved via recovery of many individuals from widespread infection, or preferably via the availability of safe and effective vaccines.

Unfortunately, history has shown that although herd immunity resulting from infection can curb pandemics, it does not eradicate diseases. The historical precedent that most closely approximates, and was substantially worse than, the current COVID-19 pandemic is the 1918 H1N1 influenza pandemic. After more than 2 years, 500 million infections, and 50 million deaths worldwide, sufficient levels of population-based herd immunity finally halted the continued spread of the virus, and society began to recover. Nevertheless, variants of that influenza virus are still present, such that resurgence of this H1N1 subtype remains a persistent concern.

Similarly, measles, mumps, rubella, polio, and smallpox are respiratory tract viruses that once killed or maimed millions of people annually across the globe, despite inducing long-term protective immunity against reinfection following natural infection. In the prevaccine era, immunity following natural infection allowed people to coexist with these viruses, but never eradicated them. On their advent, vaccines reduced the disease burden of these viruses by more than 99%.[6] Indeed, smallpox remains the only disease in human history to have been eradicated, an achievement of vaccination, not natural immunity.

And yet, until safe and effective vaccines are available, natural immunity and public health measures are the primary approaches to managing pandemics. Unfortunately, it is not yet known if detection of anti-SARS-CoV-2 antibodies by commercial clinical laboratory assays is associated with protective immunity. It is possible that protection requires achieving a specific quantity of a specific subtype of antibody. It is also possible that to achieve protection, antibodies must bind to specific epitopes on the virus, which may differ from the epitopes that are targeted in the commercial assays. Thus, we simply do not know if the seroprevalence of antibodies to SARS-CoV-2 that are detected by commercial assays will ultimately translate into protective herd immunity as the virus continues to spread.

Conversely, it is possible that people exposed to SARS-CoV-2 are protected against future infection regardless of whether they have measurable antibody titers or not. The role of T cells in protective immunity against COVID-19, and the association between immunity

based on antibodies and memory T cells, remains undefined. Indeed, there are reasons to be optimistic that prior exposure to the virus does lead to protective immunity. Nearly a year into the COVID-19 pandemic, there have been more than 30 million confirmed infections, but extremely few documented cases of reinfection with SARS-CoV-2 throughout the world.[7] If natural infection did not lead to a high degree of protection, many more reinfections would be expected. Furthermore, analysis of convalescent plasma reveals that most individuals with symptomatic COVID-19 mount neutralizing antibody responses to SARS-CoV-2.[8] Based on immunological experience with other viruses, the presence of neutralizing antibodies is likely associated with protection. Thus, until more data become available, it is reasonable to assume that natural infection with SARS-CoV-2 may lead to protective immunity and prior infection may be closely associated with protection. Furthermore, protection from natural infection suggests that vaccines should induce protective immunity.

The decline over time of the seroprevalence of antibodies to SARS-CoV-2 in the study by Bajema et al[4] is neither unexpected nor alarming. For all infectious diseases, the waning of antibody titers is normal and does not necessarily indicate the loss of protective long-term immunity. Immunoglobulin G titers rise during the weeks following infection as active plasma cells secrete antibody into systemic circulation. Those titers then wane as the plasma cells actively secreting the antibodies senesce, whereas resting memory B and T lymphocytes continue to circulate for years to decades.[9] These memory lymphocytes can mediate long-term immunity to infection even in the face of waning antibody titers.[9] Thus, at present, no conclusions can be drawn from seroprevalence studies about the duration of immunity to SARS-CoV-2 infection. Experience with other respiratory tract viruses suggests that immunity to specific viral serotypes lasts for many years. This was the case with the H1N1 virus that caused the 1918 influenza pandemic, in which adolescent survivors experienced protection from reinfection into the tenth decade of their lives.[10]

In summary, a robust and well-designed seroprevalence study using residual serum samples from across the US has found that herd immunity to SARS-Cov-2 is nowhere in sight, even as the COVID-19 pandemic has raged on for a year. The good news is that the limited number of reinfections of SARS-CoV-2 to date, and the experience with natural infections with other viruses, suggests that protective immunity to COVID-19 should result, a harbinger for the success of vaccines. The bad news is that, like the 1918 influenza pandemic, achieving herd immunity through natural infections will take years of painful sacrifice that are tallied in numerous deaths, severe long-term health sequelae, and widespread economic disruption and hardship. Let us hope that safe and effective vaccines help avoid the consequences of naturally developing herd immunity to COVID-19, as they have reliably done for so many other respiratory viruses.

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