EDITORIAL

# The Power of Antibody-Based Surveillance

Galit Alter, Ph.D., and Robert Seder, M.D.

Antibodies are immune proteins that mark the evolution of the host immune response to infection. Antibodies can be measured in a sensitive and specific manner, providing an archive that reflects recent or previous infection. If maintained at sufficiently high levels, antibodies can rapidly block infection on reexposure, conferring long-lived protection.

Unlike pathogen detection, which is detectable only transiently, at the time of pathogen shedding at sites where diagnostic material is collected, antibodies represent durable markers of infection, providing critical information on infection rates at a population level. Contrary to recent reports suggesting that SARS-CoV-2 RNA testing alone, in the absence of antibodies, will be sufficient to track and contain the pandemic, the cost, complexity, and transient nature of RNA testing for pathogen detection render it an incomplete metric of viral spread at a population level. Instead, the accurate assessment of antibodies during a pandemic can provide important population-based data on pathogen exposure, facilitate an understanding of the role of antibodies in protective immunity, and guide vaccine development.

In midsummer 2020, studies emerged pointing to rapid waning of antibody immunity,[1,2] with reports across the globe suggesting that antibody responses were inversely correlated to disease severity,[4] even suggesting that asymptomatic infection could occur without seroconversion.[5] Consistently, in a month-long study, antibody titers were noted to wane both in patients with mild infection and in those with severe infection,[2] which raised the possibility that humoral immunity to this coronavirus may be very short-lived.

Stefansson and colleagues now report in the *Journal* their findings on the impact and implications of antibody testing at a population level, capturing insights on prevalence, fatality risk, and durability of immunity.[3] The study was performed in Iceland, where 15% of the country's population was tested for infection with SARS-CoV-2 by quantitative polymerase-chain-reaction (PCR) and antibody testing. The study involved approximately 30,000 persons, including those with hospital, community, and household infections and exposures; sampling of the population was performed in an unbiased manner. Using two highly sensitive and specific assays, Stefansson and colleagues monitored antibody levels and durability over 4 months, whereas previous studies profiled antibody kinetics for only 28 days.[2] Kinetic analyses of various antibody isotypes were captured across different SARS-CoV-2 antigens, offering an unprecedented snapshot of seroconversion rates and seromaintenance.

Coupling PCR and multi-antigen, multi-isotype antibody surveillance, the study provides an internally validated analysis of the power of serologic testing. From their data, Stefansson and colleagues calculate that approximately 56% of seropositive persons also had a confirmed PCR test, demonstrating that antibody testing captured a larger percentage of exposures. It is notable that nearly a third of the infections were detected in persons with asymptomatic infection. This unbiased population-level sampling allowed for the calculation of infection fatality risk at 0.3% in Iceland. Additional observations confirmed elevated antibody levels in older adults and in persons who were hospitalized. Conversely, antibody levels were lower in smokers and in women who had less severe disease.

The most striking observation was that antibodies remained stable over the 4 months after diagnosis, a finding captured in a subgroup of longitudinally monitored subjects. Unlike previous studies,[2] this study suggested stability of SARS-CoV-2 humoral immunity. Discordant results may simply be attributable to sampling biases. Infections and vaccines generate two waves of antibodies: The first wave is generated by early short-lived plasma cells, poised to populate the systemic circulation, but this wave subsides rapidly after resolution of acute infection. The second wave is generated by a smaller number of longer-lived plasma cells that provide long-lived immunity (Fig. 1).[6] Thus, sampling soon after infection, during wave 1, may point toward a robust though transient waning. Conversely, sampling later or over a longer period of time may provide a more accurate reflection of the decay patterns of the immune response. Along these lines, a rise and early decay of antibodies was observed in the Icelandic study, but with limited loss of antibod-

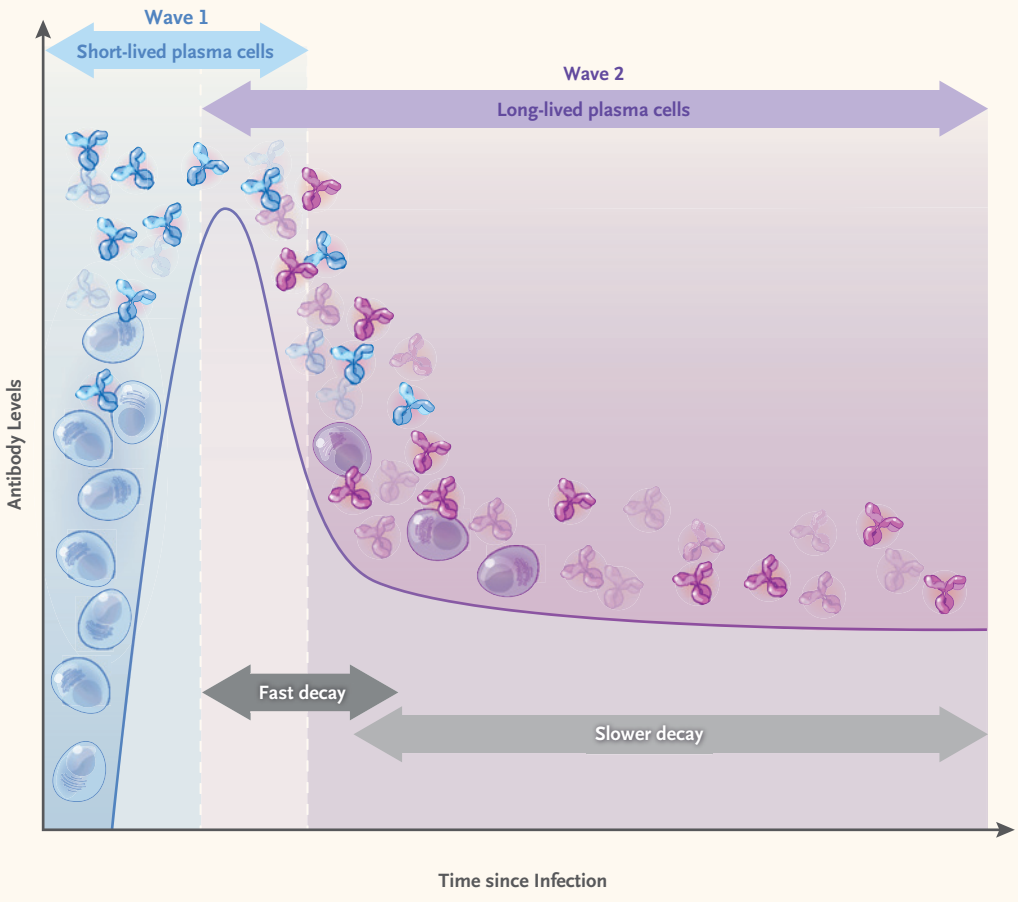


**Figure 1. Humoral Immune Response.**

Shown are the kinetics of the humoral immune response after infection, comprising two waves of antibodies. Wave 1 antibodies are produced by rapidly expanding, short-lived plasma cells aimed at populating the systemic circulation with antibodies that provide some level of defense as more affinity-matured antibodies evolve. Wave 2 antibodies are generated by long-lived plasma cells that, although less common, generate potent high-affinity antibodies that typically confer long-lived immunity. Because the decay kinetics differ considerably between wave 1 and wave 2 antibodies, sampling time can dramatically affect calculations of the rate of decay: rapid decay would be observed at the end of wave 1, whereas slower decay would be observed in wave 2.

ies at later time points, a finding that points to stable SARS-CoV-2 immunity for at least 4 months after infection.

This study focused on a homogeneous population largely from a single ethnic origin and geographic region. Thus, future extended longitudinal studies will be necessary to more accurately define the half-life of SARS-CoV-2 antibodies. That said, this study provides hope that host immunity to this unpredictable and highly contagious virus may not be fleeting and may be similar to that elicited by most other viral infections.

Whether antibodies that persist confer protection and retain neutralizing or other protective effector functions that are required to block reinfection remains unclear. Nevertheless, the data reported by Stefansson and colleagues point to the utility of antibody assays as highly cost-effective alternatives to PCR testing for population-level surveillance, which is critical to the safe reopening of cities and schools, and as biomarkers and possible effectors of immunity — useful tools that we can deploy now, while we scan the horizon (and the pages of medical journals) for the wave of vaccines that will end the pandemic of Covid-19.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

From the Ragon Institute of MGH, MIT, and Harvard, Cambridge, MA (G.A.); and the Vaccine Research Center, National Institutes of Health, Bethesda, MD (R.S.).

This editorial was published on September 1, 2020, at NEJM.org.

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DOI: 10.1056/NEJMe2028079