Robust neutralizing antibodies to SARS-CoV-2 infection persist for months

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic with millions infected and more than 1 million fatalities. Questions regarding the robustness, functionality, and longevity of the antibody response to the virus remain unanswered. Here, on the basis of a dataset of 30,082 individuals screened at Mount Sinai Health System in New York City, we report that the vast majority of infected individuals with mild-to-moderate COVID-19 experience robust immunoglobulin G antibody responses against the viral spike protein. We also show that titers are relatively stable for at least a period of about 5 months and that anti-spike binding titers significantly correlate with neutralization of authentic SARS-CoV-2.

Our data suggest that more than 90% of seroconverters make detectable neutralizing antibody responses. These titers remain relatively stable for several months after infection.

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after symptom onset for two additional time points. The mean interval between the initial titer measurement and the second was 52 days (range: 33 to 67 days). This set the second time point at a mean of 82 days after symptom onset (range: 52 to 104 days) and the third time point at 148 days after symptom onset (range: 113 to 186 days). In comparing overall titer values, we observed a slight drop from a geometric mean titer (GMT) of 764 to a GMT of 690 from the first to the second time point and another drop to a GMT of 404 for the last time point (Fig. 3A). In the higher titer range of ≥1:2880 and 1:960, we also observed a slow decline in titer over time (Fig. 3B and C). Unexpectedly, but in agreement with earlier observations that seroconversion in mild COVID-19 cases might take a longer time to mount (8), we saw an increase in individuals who had an initial titer of 1:320, 1:160, or 1:80 (Fig. 3, D to F) from day 30 to day 82. Titers in these groups declined to about day 30 levels on day 148. Notably, one individual in the initial 1:80 group dropped from a 1:80 titer to being negative at the day 82 time point, and two others lost reactivity at the day 148 time point, indicating that very low initial titers might drop to undetectable levels over time. Neutralizing antibody titers followed titers measured by ELISA (Fig. 3G), and a good correlation between neutralization and ELISA titers was still observed on day 148 (Fig. 3H). The initial serum antibody titer was likely produced by plasmablasts, and plasmablast-derived antibodies peak 2 to 3 weeks after symptom onset. Given an immunoglobulin G half-life of ~21 days, the sustained antibody titers observed here over time are likely produced by long-lived plasma cells in the bone marrow. Note that our observations contrast with a recent report that found waning titers at 8 weeks after virus infection (13). Especially in asymptomatic cases, antibody responses disappeared after 8 weeks in 40% of individuals in that study. However, the antibodies measured in that paper targeted the NP plus a single linear spike epitope. The same paper also reported relatively stable (slightly declining) neutralizing antibody titers, which shows much higher concordance with our present findings. Thus, the stability of the antibody response over time may also depend on the target antigen.

Correlates of protection have been established for many different viral infections. These correlates are usually based on a specific level of antibody acquired through vaccination or natural infection that substantially reduces the risk of (re)infection. One example is the hemagglutination inhibition titer for the influenza virus, where a 1:40 titer reduces the risk of (re)infection by 50% (14). Similar titers have been established for the measles virus (an ID50 titer of 1:120), hepatitis A virus, hepatitis B virus, and many others (15). These titers have facilitated vaccine development considerably. For some viruses and vaccines, the kinetics of the antibody response is also known, allowing for an accurate prediction of how long protection will last (16).

It is still unclear whether infection with SARS-CoV-2 in humans protects from reinfection and, if it does, for how long. We know from work with common human coronaviruses that neutralizing antibodies are induced and that these antibodies can last for years and provide protection from reinfection or, in the event of reinfection, attenuate disease (17). Furthermore, we now know from nonhuman

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**Fig. 1. SARS-CoV-2 spike antibody titers in 30,082 individuals.** (A) The percentage of individuals with antibody titers of 1:80 (low), 1:160 (low), 1:320 (moderate), 1:960 (high), and ≥1:2880 (high). (B) Absolute numbers of individuals testing positive and percent of individuals with titers of 1:320 over time. Testing of each sample was performed once in a Clinical Laboratory Improvement Amendments (CLIA)–certified laboratory using an assay that received emergency use authorization (EUA) from the U.S. Food and Drug Administration (FDA).

**Fig. 2. Neutralizing activity of serum samples in relation to ELISA titers.** (A) A correlation analysis between ELISA titers on the x axis and neutralization titers in a micro-neutralization assay on the y axis. The Spearman ρ was determined. Red bars indicate the geometric mean. (B) The proportion of sera that exert any neutralizing activity in each of the ELISA titer categories. Testing was performed once, using an FDA EUA ELISA in a CLIA laboratory, or twice, following a standardized neutralization protocol.
primate models that infection with SARS-CoV-2 does protect from reinfection for at least some time (18, 19). We also know that transferring serum of convalescent animals or neutralizing monoclonal antibodies to naïve animals can be protective and reduces virus replication significantly (20, 21). Finally, vaccine-induced neutralizing antibody titers have been established as a correlate of protection in non-human primates (22). Notably, these vaccine-induced titers were relatively low and in the lower range of the titers observed in this study. Our data reveal that individuals who have recovered from mild COVID-19 experience relatively robust antibody responses to the spike protein, which correlate significantly with neutralization of authentic SARS-CoV-2 virus. Furthermore, the vast majority of individuals with antibody titers of 1:320 or higher show neutralizing activity in their serum. We also find stable antibody titers over a period of at least 3 months and only modest declines at the 5-month time point, which is consistent with data for the human coronaviruses SARS-CoV-1 and Middle East respiratory syndrome–related coronavirus (MERS-CoV) (17). We plan to follow this cohort over longer intervals of time. Although we cannot provide conclusive evidence that these antibody responses protect from reinfection, we believe it is very likely that they will decrease the odds ratio of reinfection and may attenuate disease in the case of breakthrough infection. We believe that it is imperative to swiftly perform studies to investigate and establish a correlate of protection from SARS-CoV-2 infection. A correlate of protection, combined with a better understanding of antibody kinetics to the spike protein, would inform policy regarding the COVID-19 pandemic and would be beneficial to vaccine development efforts.

REFERENCES AND NOTES

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SARS-CoV-2 antibodies persist

As the number of daily COVID-19 cases continues to mount worldwide, the nature of the humoral immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains uncertain. Wajnberg et al. used a cohort of more than 30,000 infected individuals with mild to moderate COVID-19 symptoms to determine the robustness and longevity of the anti–SARS-CoV-2 antibody response. They found that neutralizing antibody titers against the SARS-CoV-2 spike protein persisted for at least 5 months after infection. Although continued monitoring of this cohort will be needed to confirm the longevity and potency of this response, these preliminary results suggest that the chance of reinfection may be lower than is currently feared.

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