Research Letter

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Prevalence and Durability of SARS-CoV-2 Antibodies Among Unvaccinated US Adults by History of COVID-19

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As of December 28, 2021, approximately 27% of the US population was unvaccinated against SARS-CoV-2,[1] yet the presence of natural immunity remains unknown. Blood donor studies may have selection bias and lack clinical information.[2] Previous COVID-19 infection is a possible surrogate for natural immunity, but 1 study suggested that 36% of COVID-recovered individuals are serologic nonresponders.[3] Even among individuals who develop antibodies, durability of this response beyond 6 months remains unknown. We characterized natural immunity and long-term durability among unvaccinated individuals using anti-spike antibodies, the first line of defense against SARS-CoV-2.

Methods

Healthy adults who reported no SARS-CoV-2 vaccination were recruited via 1 public Twitter post and 1 public Facebook advertisement between September 11, 2021, and October 8, 2021. Participants completed an online questionnaire about demographics, COVID-19 status, and mask use. Using weighted random sampling (relative weights based on the estimated unvaccinated US population by age, race and ethnicity, and education[1]), we created 3 equally sized sample groups among those who reported a test-confirmed COVID-19 infection ("COVID-confirmed"), believed they had COVID-19 but were never tested ("COVID-unconfirmed"), and did not believe they ever had COVID-19 and never tested positive ("no-COVID"). These groups were invited to undergo antibody testing at LabCorp facilities nationwide.

Qualitative detection of antibodies against the SARS-CoV-2 antinucleocapsid (N) protein (positive cutoff index ≥1.0) and semiquantitative detection of antibodies against the SARS-CoV-2 spike protein receptor-binding domain (RBD) (positive cutoff ≥0.8 U/mL) were performed (Elecsys; Roche Diagnostics International Ltd). Various cutoffs are reported (≥250 U/mL, ≥500 U/mL, ≥1000 U/mL), based on reported associations with neutralization.[4]

Population characteristics were compared using χ^2 test for categorical (Fisher exact test for rare outcomes) and Wilcoxon rank-sum test for continuous variables. We used linear regression to analyze the association between time after infection and log antibody titer. The threshold for statistical significance was $P < .05$ (2-sided). All analyses were performed using Stata 17.0/SE (StataCorp). The study was approved by the Johns Hopkins institutional review board. Participants provided electronic informed consent.

Results

Of 1580 individuals invited to undergo serologic testing, 816 (52%) did so between September 24, 2021, and November 5, 2021. Participants had a mean age of 48.0 years, 421 (52%) were women, and 669 (82%) were White (**Table**). Fourteen percent reported routine mask use in public. Anti-RBD and anti-N antibody presence/absence were correlated (95%; Cohen κ=0.908).

Among 295 reported COVID-confirmed participants, 293 (99%) tested positive for anti-RBD antibodies (≥250 U/mL, 44%; ≥500 U/mL, 27%; ≥1000 U/mL, 15%). A median of 8.7 (IQR, 1.9-12.9; range, 0-20) months passed since reported COVID-19 diagnosis. The median anti-RBD level among those who tested positive was 205 (IQR, 61-535) U/mL. There was no evidence of association between time after infection and antibody titer (0.8% increase [95% CI, -2.4% to 4.2%] per month, $P = .62$) (**Figure**).

Among 275 reported COVID-unconfirmed participants, 152 (55%) tested positive for anti-RBD antibodies (≥250 U/mL, 18%; ≥500 U/mL, 12%; ≥1000 U/mL, 6%). The median level among those who tested positive was 131 (IQR, 35-402) U/mL.

Among 246 reported no-COVID participants, 11% tested positive for anti-RBD antibodies (≥250 U/mL, 2%; ≥500 U/mL, 2%; ≥1000 U/mL, 2%). The median level among those who tested positive was 82 (IQR, 19-172) U/mL.

Discussion

In this cross-sectional study of unvaccinated US adults, antibodies were detected in 99% of individuals who reported a positive COVID-19 test result, in 55% who believed they had COVID-19 but were never tested, and in 11% who believed they had never had COVID-19 infection. Anti-RBD levels were observed after a positive COVID-19 test result up to 20 months, extending previous 6-month durability data.[3]

Study limitations include lack of direct neutralization assays, the fact that antibody levels alone do not directly equate to immunity,[4,5] the cross-sectional study design, a convenience sample with an unknown degree of selection bias due to public recruitment, self-reported COVID-19 test results, the study population being largely White and healthy, and lack of information on breakthrough infections. Participants were given only 1 month to complete antibody testing, which may have contributed to the 52% rate among those invited to test.

Although evidence of natural immunity in unvaccinated healthy US adults up to 20 months after confirmed COVID-19 infection is encouraging, it is unclear how these antibody levels correlate with protection against future SARS-CoV-2 infections, particularly with emerging variants. The public health implications and long-term understanding of these findings merit further consideration.

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References

1. USAFacts. Secondary US Coronavirus vaccine tracker 2021. Accessed December 28, 2021. https://usafacts.org/issues/coronavirus/
2. Jones JM, Stone M, Sulaeman H, et al. Estimated US infection- and vaccine-induced SARS-CoV-2 seroprevalence based on blood donations, July 2020-May 2021. *JAMA*. 2021;326(14):1400-1409. doi:10.1001/jama.2021.15161
Article | PubMed | Google Scholar | Crossref
3. Liu W, Russell RM, Bibollet-Ruche F, et al. Predictors of nonseroconversion after SARS-CoV-2 infection. *Emerg Infect Dis*. 2021;27(9):2454-2458. doi:10.3201/eid2709.211042
PubMed | Google Scholar | Crossref
4. Gilbert PB, Montefiori DC, McDermott AB, et al; Immune Assays Team; Moderna Inc Team; Coronavirus Vaccine Prevention Network (CoVPN)/Coronavirus Efficacy (COVE) Team; US Government (USG)/CoVPN Biostatistics Team. Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. *Science*. 2022;375(6576):43-50. doi:10.1126/science.abm3425
PubMed | Google Scholar | Crossref
5. Israel A, Shenhar Y, Green I, et al. Large-scale study of antibody titer decay following BNT162b2 mRNA vaccine or SARS-CoV-2 infection. *Vaccines (Basel)*. 2021;10(1):64. doi:10.3390/vaccines10010064
PubMed | Google Scholar | Crossref
6. Lustig Y, Sapir E, Regev-Yochay G, et al. BNT162b2 COVID-19 vaccine and correlates of humoral immune responses and dynamics: a prospective, single-centre, longitudinal cohort study in health-care workers. *Lancet Respir Med*. 2021;9(9):999-1009. doi:10.1016/S2213-2600(21)00220-4
PubMed | Google Scholar | Crossref