

New Online

Views **352,883**Citations **0**Altmetric **9944**Comments **1**

CME &amp; MOC

Cite

Permissions

## Research Letter

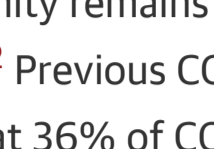
ONLINE FIRST FREE

February 3, 2022

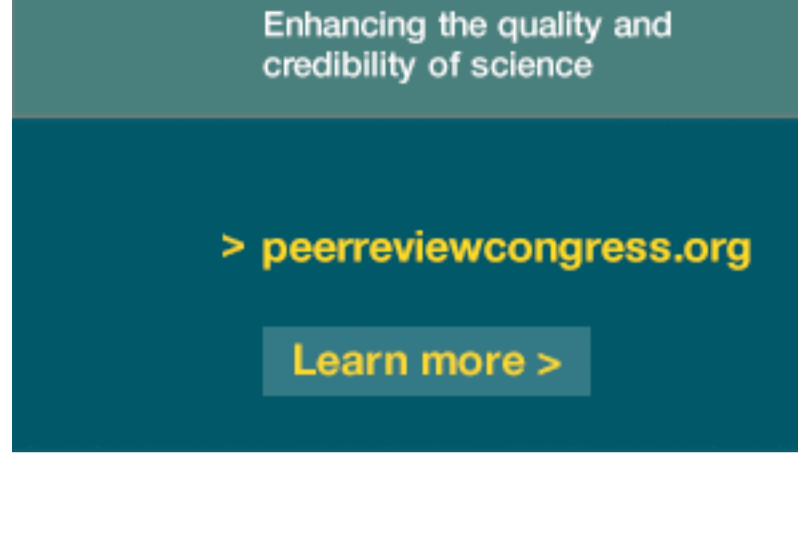
## Prevalence and Durability of SARS-CoV-2 Antibodies Among Unvaccinated US Adults by History of COVID-19

Jennifer L. Alejo, MD<sup>1</sup>; Jonathan Mitchell, MBBS<sup>1</sup>; Amy Chang, MD<sup>1</sup>; et al
[» Author Affiliations](#) | [Article Information](#)

JAMA. Published online February 3, 2022. doi:10.1001/jama.2022.1393



As of December 28, 2021, approximately 27% of the US population was unvaccinated against SARS-CoV-2,<sup>1</sup> yet the prevalence of natural immunity remains unknown. Blood donor studies may have selection bias and lack clinical information.<sup>2</sup> Previous COVID-19 infection is a possible surrogate for natural immunity, but 1 study suggested that 36% of COVID-recovered individuals are serologic nonresponders.<sup>3</sup> 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<sup>1</sup>), 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  $\geq 1.0$ ) and semiquantitative detection of antibodies against the SARS-CoV-2 spike protein receptor-binding domain (RBD) (positive cutoff  $\geq 0.8$  U/mL) were performed (Elecsys; Roche Diagnostics International Ltd). Various cutoffs are reported ( $\geq 250$  U/mL,  $\geq 500$  U/mL,  $\geq 1000$  U/mL), based on reported associations with neutralization.<sup>4</sup>

Population characteristics were compared using  $\chi^2$  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  $\kappa = 0.908$ ).

Among 295 reported COVID-confirmed participants, 293 (99%) tested positive for anti-RBD antibodies ( $\geq 250$  U/mL, 44%;  $\geq 500$  U/mL, 27%;  $\geq 1000$  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 ( $\geq 250$  U/mL, 18%;  $\geq 500$  U/mL, 12%;  $\geq 1000$  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 ( $\geq 250$  U/mL, 2%;  $\geq 500$  U/mL, 2%;  $\geq 1000$  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.<sup>5</sup>

Study limitations include lack of direct neutralization assays, the fact that antibody levels alone do not directly equate to immunity,<sup>4,6</sup> 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.

**Section Editors:** Jody W. Zylke, MD, Deputy Editor; Kristin Walter, MD, Associate Editor.

## Article Information

[Back to top](#)

**Accepted for Publication:** January 26, 2022.

**Published Online:** February 3, 2022. doi:10.1001/jama.2022.1393

**Corresponding Author:** Dorry Segev, MD, PhD, Department of Surgery, Epidemiology Research Group in Organ Transplantation, Johns Hopkins Medical Institutions, 2000 E Monument St, Baltimore, MD 21205 ([dorry@jhmi.edu](mailto:dorry@jhmi.edu)).

**Author Contributions:** Dr Alejo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Segev and Makary contributed equally as senior authors.

**Concept and design:** Alejo, Mitchell, Chang, Segev, Makary.

**Acquisition, analysis, or interpretation of data:** Alejo, Mitchell, Chang, Chiang, Massie, Segev.

**Drafting of the manuscript:** Alejo, Mitchell, Chang, Chiang, Segev.

**Critical revision of the manuscript for important intellectual content:** All authors.

**Statistical analysis:** Alejo, Mitchell, Chang, Chiang, Segev.

**Obtained funding:** Mitchell, Segev, Makary.

**Administrative, technical, or material support:** Alejo, Chang, Chiang, Segev.

**Supervision:** Massie, Segev, Makary.

**Conflict of Interest Disclosures:** Dr Alejo reported receiving a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (T32DK007713). Dr Mitchell reported receiving a grant from the American Society of Transplant Surgeons Jon Fryer Resident Scientist Scholarship. Dr Chang reported receiving a grant from NIDDK (T32DK007732). Dr Massie reported receiving grants from NIDDK. Dr Segev reported receiving consulting and speaking honoraria from Sanofi, Novartis, CLS Behring, Jazz Pharmaceuticals, Veloxis, Mallinckrodt, Thermo Fisher Scientific, AstraZeneca, and Regeneron and receiving grants from NIDDK and the National Institute of Allergy and Infectious Diseases. No other disclosures were reported.

**Funding/Support:** This work was supported by charitable donations from the Ben-Dov family.

**Role of the Funder/Sponsor:** The Ben-Dov family had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data, preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication.

**Additional Contributions:** We thank the following individuals for their assistance with this study, none of whom were compensated for their contributions: Aura T. Abedon, BS, Jake Kim, BS, Alexa A. Jefferis, BS, and Carolyn N. Sidoti, BS (Department of Surgery, Johns Hopkins School of Medicine), for data collection and study coordination; and Daniel S. Warren, PhD (Department of Surgery, Johns Hopkins School of Medicine), William A. Werbel, MD (Department of Medicine, Johns Hopkins School of Medicine), and Macey L. Levan, JD, PhD (Department of Acute and Chronic Care, Johns Hopkins School of Nursing, and Department of Surgery, Johns Hopkins School of Medicine), for administrative and scientific support.

## 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 Vaccination 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 BN-T162b2 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](#)

JAMA®

JAMA Network™

Help



Get the latest from JAMA

Email address

Sign Up

[Privacy Policy](#) | [Terms of Use](#)

© 2022 American Medical Association. All Rights Reserved.

[Terms of Use](#) | [Privacy Policy](#) | [Accessibility Statement](#)

Our website uses cookies to enhance your experience. By continuing to use our site, or clicking "Continue," you are agreeing to our [Cookie Policy](#) | [Continue](#)