Incidence of SARS-CoV-2 infection among unvaccinated US adults during the Omicron wave

Dear Editor,

As of 20 April 2022, approximately 23% of the eligible US population has not received at least one SARS-CoV-2-vaccine dose [1]. We recently reported that 99% of unvaccinated US adults who had a test-confirmed SARS-CoV-2 infection had detectable anti-receptor-binding domain (anti-RBD) antibodies up to 20 months after their positive COVID-19 test [2]. However, whether these antibodies can be used as a clinical marker of protection against new variants is undescribed. To better understand protective correlates, we studied COVID-19 infections during the Omicron (B.1.1.529) wave in unvaccinated US adults, stratified by pre-Omicron antibody levels.

Self-described healthy adults who reported never receiving a SARS-CoV-2 vaccine were recruited for this national cohort study between 11 September 2021 and 8 October 2021 [2]. Using weighted random sampling with relative weights based on demographics (age, race, ethnicity, education) and geographic regions proportional to the population of the United States (using US Census regions, treating the Pacific division as a separate region), a subgroup of survey respondents was invited to undergo anti-spike serologic testing (Elecsys; Roche Diagnostics International; positive cutoff $\geq$ 0.8 U/ml) prior to the Omicron wave (23 September 2021 to 5 November 2021) [3]. Pre-Omicron antibody titers were stratified based on reported associations with neutralization [4, 5]. Participants completed a follow-up questionnaire (19 January 2022 to 7 February 2022) about COVID-19 test status and symptoms (since 1 December 2021): tested positive for COVID-19, suspected COVID-19 but never tested positive, or no suspected infection or positive test. Symptoms were classified as severe, moderate, mild, or none.

Population characteristics were compared using Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. All analyses were performed using Stata 17.0/SE.

The study was approved by the Johns Hopkins institutional review board. Participants provided informed electronic consent.

Of 843 unvaccinated adults with anti-RBD measured within 2 months preceding the Omicron wave, 566 (67%) completed the follow-up survey between 19 January 2022 and 7 February 2022. Twenty participants reported receiving at least one SARS-CoV-2 vaccine since enrollment and were excluded from the analysis. The median (interquartile range, IQR) age was 48 (37–59) years, 295 (54%) were women, 453 (83%) were white, 203 (37%) reported having a test-confirmed COVID-19 diagnosis before the Omicron wave, and 328 (60%) had anti-RBD antibodies before the Omicron wave. Note that 446 (82%) reported no regular public mask use since December 1, 2021. Participants with and without anti-RBD antibodies were similar with respect to age, sex, race, ethnicity, and mask use (Table 1).

Note that 35% of unvaccinated individuals without pre-existing antibodies (anti-RBD < 0.8 U/ml, $n = 218$) reported test-confirmed COVID-19; an additional 12% reported suspected/unconfirmed COVID-19 during the Omicron wave. In contrast, 12% of unvaccinated individuals with pre-existing antibodies (anti-RBD $\geq$ 0.8 U/ml, $n = 328$) reported test-confirmed COVID-19 and an additional 15% reported suspected/unconfirmed COVID-19 during the Omicron wave. Among those with anti-RBD 0.8–1000 U/ml ($n = 284$), 12%/16% reported confirmed/suspected COVID-19, and among those with anti-RBD $\geq$ 1000 U/ml ($n = 44$), 9%/7% reported confirmed/suspected COVID-19 (Fig. 1).

Having antibodies was 67% effective against reporting test-confirmed COVID-19 (35% vs. 12%, $p < 0.001$). Among those with test-confirmed COVID-19 who answered symptom questions ($n = 115$), those with antibodies reported shorter symptom duration than their antibody-negative counterparts (median [IQR] 3.5 [3, 5] vs. 6 [3, 8]

Table 1. *Participant demographics and clinical characteristics by pre-Omicron anti-receptor-binding domain (anti-RBD) level*

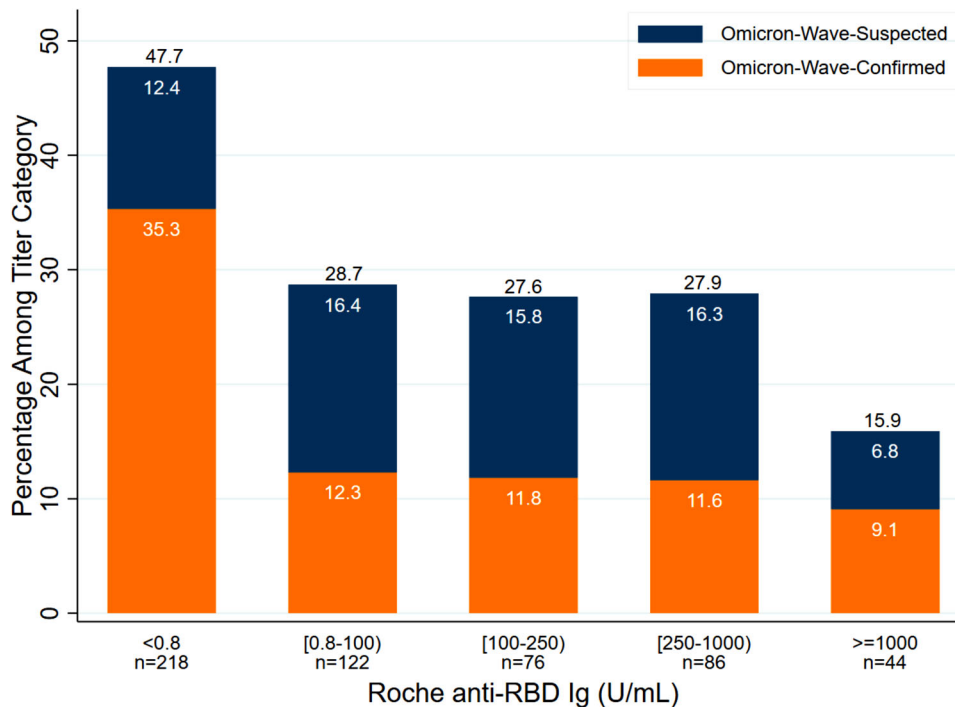|		Anti-RBD antibody		
	Total, No. (%)	Negative	Positive	*p* Value[a]
No.	546	218	328	
Age, median (IQR), years	48 (37, 59)	48 (37, 62)	48 (37, 58)	0.41
Male	251 (46%)	104 (48%)	147 (45%)	0.54
Race[b]				0.34
African American/Black	7 (1%)	2 (1%)	5 (2%)	
Asian	23 (4%)	10 (5%)	13 (4%)	
White	453 (83%)	187 (86%)	266 (81%)	
Other	63 (12%)	19 (9%)	44 (13%)	
Hispanic[b]	67 (12%) (*n* = 543)	24 (11%)	43 (13%)	0.51
Mask use since Dec. 1, 2021				0.20
Yes	96 (18%)	44 (20%)	52 (16%)	
No	446 (82%)	173 (79%)	273 (83%)	
Declined to answer	4 (1%)	1 (<1%)	3 (1%)	
Anti-RBD median (IQR)	34.6 (<0.8, 228.7)	<0.8 (<0.8, <0.8)	168 (56, 499)	<0.001
Prior COVID Infection				
Prior COVID confirmed	203 (37%)	2 (1%)	201 (61%)	<0.001
Prior COVID unconfirmed	183 (34%)	71 (33%)	112 (34%)	
No prior COVID	160 (29%)	145 (67%)	15 (5%)	
Omicron-wave-confirmed	115 (21%)	77 (35%)	38 (12%)	<0.001
Symptoms: severe or moderate	38 (33%)	29 (38%)	9 (24%)	0.15
Severe[c]	1 (1%)	1 (1%)	0 (0%)	
Moderate[c]	37 (32%)	28 (36%)	9 (24%)	
Symptoms: mild or none	77 (67%)	48 (62%)	29 (76%)	
Mild[c]	74 (64%)	45 (58%)	29 (76%)	
None[c]	3 (3%)	3 (4%)	0 (0%)	
Symptom duration median (IQR), days[c]	5 (3, 7)	6 (3, 8)	3.5 (3, 5)	0.01
Omicron-wave-suspected	76 (14%)	27 (12%)	49 (15%)	<0.001
Symptoms: severe or moderate	9 (12%)	6 (22%)	3 (6%)	0.06
Severe[d]	0 (0%)	0 (0%)	0 (0%)	
Moderate[d]	9 (12%)	6 (22%)	3 (6%)	
Symptoms: mild or none	67 (88%)	21 (77%)	46 (94%)	
Mild[d]	64 (84%)	19 (70%)	45 (92%)	
None[d]	3 (4%)	2 (7%)	1 (2%)	
Symptom duration median (IQR), days[d]	4 (3, 5)	5 (3, 6)	4 (2, 5)	0.04
Omicron-wave-none	355 (65%)	114 (52%)	241 (73%)	<0.001

Abbreviation: RBD, receptor-binding domain.

[a]Fisher's exact test used for categorical variables and Wilcoxon rank-sum test for continuous variables.

[b]Race and ethnicity were collected during recruitment to perform weighted random sampling among the three groups for antibody testing. Participants could select from African American/Black, Asian, White, or other. Ethnicity was self-reported. Participants could select from Hispanic/Latino: yes/no.

[c]Among Omicron-wave-confirmed, *N* = 115.

[d]Among Omicron-wave-unconfirmed, *N* = 76.

Fig. 1 *Distribution of self-reported COVID-19 infections after December 1, 2021 among unvaccinated US adults, stratified by pre-Omicron wave anti-receptor-binding domain (anti-RBD) antibody level.*

days, $p = 0.013$). There was a higher proportion of antibody-negative participants (vs. positive) in the COVID-19-confirmed (38% vs. 24%, $p = 0.15$), and suspected/unconfirmed groups (22% vs. 6%, $p = 0.06$), but neither difference was statistically significant (Fig. 1).

In this national longitudinal study of incident COVID-19 among unvaccinated adults during the Omicron wave, only 12% of those who entered the wave with anti-RBD antibodies reported a test-confirmed COVID-19 infection, compared to 35% of those without antibodies prior to the Omicron wave. The attributable risk reduction of these anti-RBD antibodies—presumably derived from previous infection—in this unvaccinated population was 67%. Recently, reduced vaccine efficacy against Omicron has been described among 4x-vaccinated Israelis, and the additional protection of a fourth dose peaked 4 weeks after fourth dose and waned in later weeks [4–6]. Our results add valuable information to the discussion of vaccine versus infection-derived immune protection against Omicron [7, 8].

Study limitations include lack of information about direct neutralization against Omicron (though anti-RBD correlation with neutralization is described), lack of viral sequencing (though follow-up occurred when Omicron became the dominant strain in the United States), self-reported COVID-19 test results, and survivor bias [4].

In conclusion, the presence of anti-RBD antibodies in an unvaccinated healthy adult (natural immunity) was associated with 23% absolute risk reduction for COVID-19 reinfection and shortened symptom duration versus those without pre-existing anti-RBD antibodies during the Omicron wave. Among people with antibodies, titer did not appear to be associated with risk of test-confirmed Omicron infection, although our sample size for those ≥ 1000 U/ml may have been inadequate to detect such a difference in that range. It is important to note that while disease severity for hospitalized Omicron patients was somewhat lower for Omicron versus other variants, patients hospitalized with COVID-19 remain at substantial risk of critical illness and death [9]. Our findings

shed some light on COVID protection among the unvaccinated-immune.

Conflict of interest

D. L. Segev has the following financial disclosures: consulting and speaking honoraria from Sanofi, Novartis, CLS Behring, Jazz Pharmaceuticals, Veloxis, Mallinckrodt, Thermo Fisher Scientific, Astra Zeneca, and Regeneron. The remaining authors of this manuscript have no conflict of interest.

Author contributions

Jennifer L. 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. *Concept and design, and critical revision of the manuscript*: Jennifer L. Alejo, Teresa P. Y. Chiang, Jonathan Mitchell, William Werbel, Allan B. Massie, Martin A. Makary, and Dorry L. Segev. *Acquisition, analysis, and interpretation of data; drafting of the manuscript; and administrative, technical, or material support*: All authors. *Statistical analysis*: Jennifer L. Alejo, Teresa P. Y. Chiang, Allan B. Massie, and Dorry L. Segev. *Received funding*: Segev. *Supervision*: Allan B. Massie, Martin A. Makary, and Dorry L. Segev.

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References

1 Centers for Disease Control and Prevention. COVID-19 vaccinations in the United States. https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-people-onedose-pop-5yr Accessed 2 Feb 2022.

2 Alejo JL, Mitchell J, Chang A, Chiang TPY, Massie AB, Segev DL, et al. Prevalence and durability of SARS-CoV-2 antibodies among unvaccinated US adults by history of COVID-19. *JAMA.* https://doi.org/10.1001/jama.2022.1393

3 US Census Bureau. Census regions and divisions of the United States. https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf Accessed 8 Oct 2021.

4 Gilbert PB, Montefiori DC, McDermott AB, Fong Y, Benkeser D, Dengh W, et al. Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. *Science.* 2022; **375**(6576):43–50. https://doi.org/10.1126/science.abm3425

5 Rössler A, Riepler L, Bante D, Von Laer D, Kimpel J. SARS-CoV-2 omicron variant neutralization in serum from vaccinated and convalescent persons. *N Engl J Med.* 2022;**386**:698–700. https://doi.org/10.1056/nejmc2119236

6 Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Amir O, Freedman L, et al. Protection by a fourth dose of BNT162b2 against Omicron in Israel. *N Engl J Med.* 2022;**386**:1712–20. https://doi.org/10.1056/nejmoa2201570

7 Lauring AS, Tenforde MW, Chappell JD, Gaglani M, Ginde AA, McNeal T, Ghamande S, et al. Clinical severity of, and effectiveness of mRNA vaccines against, covid-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. *BMJ.* 2022:e069761. https://doi.org/10.1136/bmj-2021-069761

8 Accorsi EK, Britton A, Fleming-Dutra KE, Zachary R, Smith MA, Nong S, et al. Association between 3 doses of mRNA COVID-19 vaccine and symptomatic infection caused by the SARS-CoV-2 Omicron and delta variants. *JAMA.* 2022;**327**:639–51. https://doi.org/10.1001/jama.2022.0470

9 Regev-Yochay G, Gonen T, Gilboa M, Mandelboim M, Indenbaum V, Amit S, et al. Efficacy of a fourth dose of Covid-19 mRNA vaccine against Omicron. *N Engl J Med.* 2022; **386**(14):1377–80. https://doi.org/10.1056/nejmc2202542

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