1   **Research Letter: Incidence of SARS-CoV-2 infection among unvaccinated US adults during the Omicron**

2   **wave**

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4   Jennifer L. Alejo, MD[1], Teresa PY Chiang, MD, MPH[1], Jonathan Mitchell, MBBS[1], Aura T. Abedon, BS[1],

5   Alexa A. Jefferis, BS[1], William Werbel, MD[1], Allan B. Massie PhD, MHS[2], Martin A. Makary MD, MPH*[1],

6   Dorry L. Segev, MD PhD*[2]

7   *Senior authors contributed equally

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9   (1) Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD.

10   (2) Department of Surgery, NYU Grossman School of Medicine, New York, NY.

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15   Contact Information:

16   Dorry Segev, M.D., Ph.D.

17   Professor of Surgery

18   NYU Grossman School of Medicine

19   dorry@nyulangone.org

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53   **Abstract**

54   As of 4/20/2022, approximately 23% of the eligible US population was unvaccinated. We studied COVID-

55   19 infections during the Omicron (B.1.1.529) wave in unvaccinated US adults, stratified by pre-Omicron

56   antibody levels. Anti-spike serologic testing was performed prior to the Omicron wave in the United

57   States (9/23/21-11/5/21) and participants were surveilled to determine incident COVID-19. Only 12% of

58   those who entered the wave with antibodies reported a test-confirmed COVID-19 infection, compared

59   to 35% of those without antibodies prior to the Omicron wave. Effectiveness of these anti-RBD

60   antibodies in this unvaccinated population was 67%. Among people with antibodies, titer did not appear

61   to be associated with risk of test-confirmed Omicron infection.

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64   As of 4/20/2022, approximately 23% of the eligible US population has not received at least one SARS-

65   CoV-2-vaccine dose.[1] We recently reported that 99% of unvaccinated US adults who had a test-

66   confirmed SARS-CoV-2 infection had detectable anti-RBD antibodies up to 20 months after their positive

67   COVID-19 test.[2] However, whether these antibodies can be used as a clinical marker of protection

68   against new variants is undescribed. To better understand protective correlates, we studied COVID-19

69   infections during the Omicron (B.1.1.529) wave in unvaccinated US adults, stratified by pre-Omicron

70   antibody levels.

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72   Methods

73   Self-described healthy adults who reported never receiving a SARS-CoV-2 vaccine were recruited for this

74   national cohort study between (9/11/2021-10/8/2021).[2] Anti-spike serologic testing was performed

75   prior to the Omicron wave (9/23/21-11/5/21), and categories of antibody titers were created based on

76   reported associations with neutralization.[3-4] Participants completed a follow-up questionnaire

77   (1/19/2022-2/7/2022) about COVID-19 test status and symptoms (since 12/1/2021): tested positive for

78   COVID-19, suspected COVID-19 but never tested positive, or no suspected infection or positive test, and

79   classified symptoms as severe, moderate, mild, or none.

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81   Population characteristics were compared using Fisher's exact test for categorical variables and

82   Wilcoxon rank-sum test for continuous variables. All analyses were performed using Stata 17.0/SE. The

83   study was approved by the Johns Hopkins institutional review board. Participants provided informed

84   electronic consent.

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86   Results

87   Of 843 unvaccinated adults with anti-RBD measured within two months preceding the Omicron wave,

88   566 (67%) completed the follow-up survey between 1/19/2022-2/7/2022. 20 reported interval COVID-

89   19 vaccination and were excluded. The median (interquartile range, IQR) age was 48 (37-59) years, 295

90   (54%) were women, 453 (83%) were white, 203 (37%) reported having a test-confirmed COVID-19

91   diagnosis before the Omicron wave, and 328 (60%) had anti-RBD antibodies before the Omicron wave.

92   446 (82%) reported no regular public mask use since December 1, 2021. Participants with and without

93   anti-RBD antibodies were similar with respect to age, sex, race, ethnicity, and mask use (Table).

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95   35% of unvaccinated individuals without preexisting antibodies (anti-RBD<0.8 U/mL, n=218) reported

96   test-confirmed COVID-19; an additional 12% reported suspected/unconfirmed COVID-19 during the

97   Omicron wave. In contrast, 12% of unvaccinated individuals with preexisting antibodies (anti-RBD$\geq$0.8

98   U/mL, n=328) reported test-confirmed COVID-19 and an additional 15% reported

99   suspected/unconfirmed COVID-19 during the Omicron wave. Among those with anti-RBD 0.8-1000 U/mL

100   (n=284), 12%/16% reported confirmed/suspected COVID-19, and among those with anti-RBD$\geq$1000

101   U/mL (n=44), 9%/7% reported confirmed/suspected COVID-19 (Supplementary Figure).

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103   Having antibodies was 67% effective against reporting test-confirmed COVID-19(35% vs 12% p<0.001).

104   Among those with test-confirmed COVID-19 who answered symptom questions (n=115), those with

105   antibodies reported shorter symptom duration than their antibody-negative counterparts (median[IQR]

106   3.5 [3, 5] vs. 6 [3, 8] days, p=0.013). There was a higher proportion of antibody-negative participants (vs.

107   positive) in the COVID-19-confirmed (38% vs 24%, p=0.15), and suspected/unconfirmed groups (22% vs.

108   6%, p=0.06), but neither difference was statistically significant.

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110   <u>Discussion</u>

111   In this national longitudinal study of incident COVID-19 among unvaccinated adults during the Omicron

112   wave, only 12% of those who entered the wave with anti-RBD antibodies reported a test-confirmed

113   COVID-19 infection, compared to 35% of those without antibodies prior to the Omicron wave.

114   Effectiveness of these anti-RBD antibodies, presumably derived from previous infection, in this

115   unvaccinated population was 67%. Recently, reduced vaccine efficacy against Omicron has been

116   described among 4x-vaccinated Israelis, and the additional protection of a 4th dose peaked four weeks

117   post-fourth dose and waned in later weeks.[4-5] Our results add valuable information to the discussion

118   of vaccine versus infection-derived immune protection against Omicron.[6-7]

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120   Study limitations include lack of information about direct neutralization against Omicron (though anti-

121   RBD correlation with neutralization is described), lack of viral sequencing (though follow-up occurred

122   when Omicron became the dominant strain in the US), self-reported COVID-19 test results, limited

123   availability of COVID-19 testing during the follow-up period which could lead to underreporting of

124   COVID-confirmed cases, and survivor bias.[3]

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126   In conclusion, the presence of anti-RBD antibodies in an unvaccinated healthy adult (natural immunity)

127   was associated with 23% decreased relative risk for COVID-19 reinfection and shorted symptom

128   duration versus those without pre-existing anti-RBD antibodies during the Omicron wave. Among people

129   with antibodies, titer did not appear to be associated with risk of test-confirmed Omicron infection,

130   although our sample size for those ≥1000 U/mL may have been inadequate to detect such a difference

131   in that range. It is important to note that while disease severity for hospitalized Omicron patients was

132   somewhat lower for Omicron versus other variants, patients hospitalized with COVID-19 remain at

133   substantial risk of critical illness and death. [8] Our findings shed some light on COVID protection among

134   the unvaccinated-immune.

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159   **Table.** Participant demographics and clinical characteristics, by pre-Omicron anti-RBD level

	Total, No. (%)	Anti-RBD Antibody		P value[a]
		Negative	Positive	
No.	546	218	328	
Age, median (IQR), y	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), d [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), d [d]	4 (3, 5)	5 (3, 6)	4 (2, 5)	0.04
Omicron-wave-none	355 (65%)	114 (52%)	241 (73%)	<0.001

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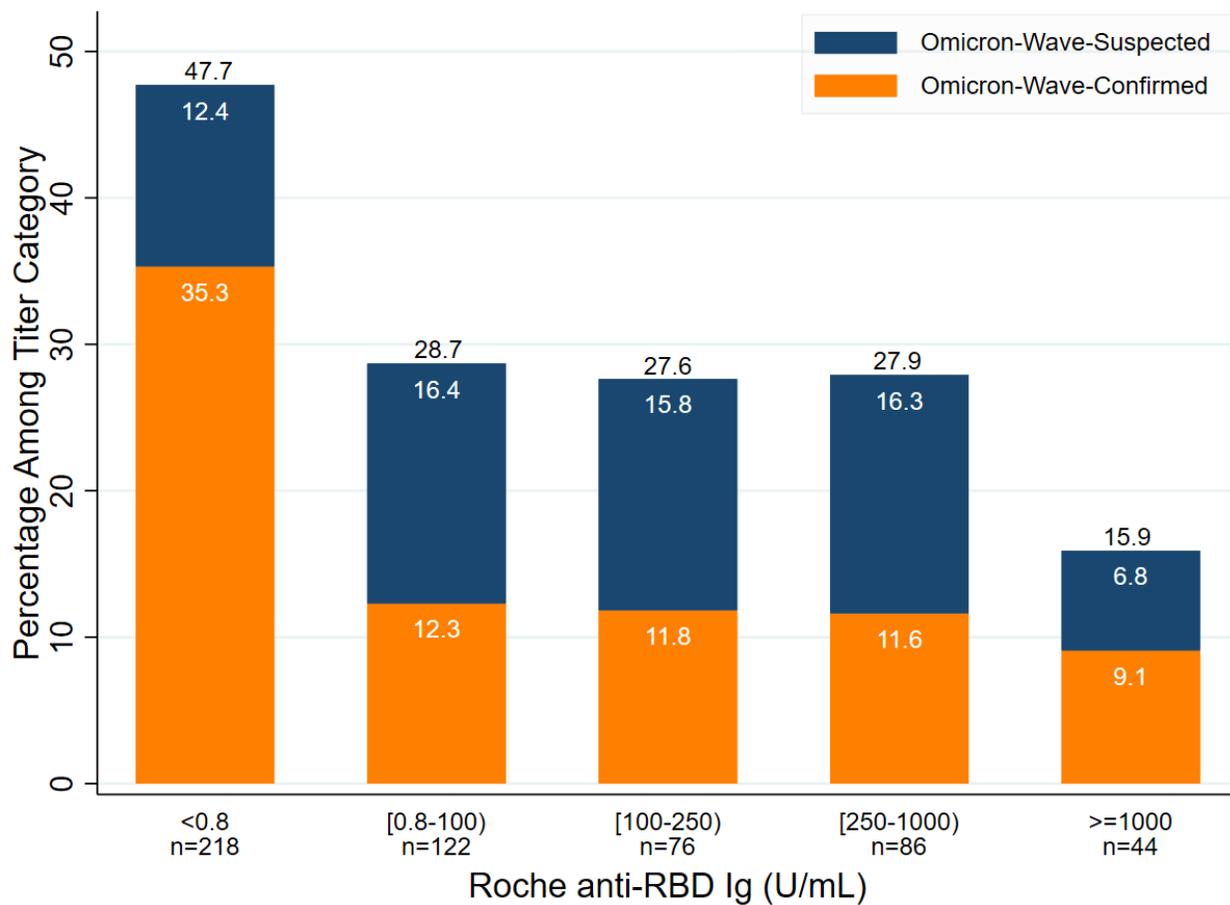161   Abbreviation: RBD, receptor-binding domain.

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

163   [b] Race and ethnicity were collected during recruitment to perform weighted random sampling among

164   the 3 groups for antibody testing. Participants could select from African-American/Black, Asian, White,

165   or other. Ethnicity was self-reported. Participants could select from Hispanic/Latino: yes/no.

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

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

168   **Figure. Distribution of self-reported COVID-19 infections after December 1, 2021 among unvaccinated**

169   **US Adults, stratified by pre-Omicron wave anti-RBD antibody level.**

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