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Association Between Anti-S Antibody Levels and SARS-CoV-2 Infection during the First Omicron Wave in Salvador, Brazil

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Abstract

Background: SARS-CoV-2, with its high transmissibility and rapid dissemination, has caused a global public health emergency. The emergence of new variants and mutations of SARS-CoV-2 spike protein antigens has led to concerns about immune escape and the potential for reinfection, even in individuals who have been previously infected or vaccinated. Brazil has been severely affected by the pandemic, especially in its densely populated slum areas. Our study aimed to evaluate the association between anti-S IgG antibody levels and subsequent SARS-CoV-2 infection during the Omicron wave in a susceptible community in Salvador, Brazil, to provide insight into the antibody level necessary for effective protection against infection with heterologous variants in similar settings.

Methods and findings: We conducted this study in a cohort of 1827 residents of Pau da Lima, Salvador, Brazil. We measured serum levels of IgG against the SARS-CoV-2 Spike protein between July and November 2021. From November 2021 to February 2022, during the first Omicron wave, we performed symptom-based screening and PCR testing to identify new infections. We used logistic regression to estimate the association between antibody levels and subsequent PCR-confirmed infection. Among 210 individuals in the cohort who underwent PCR testing, we did not identify any association between antibody levels and PCR-confirmed infection. Among a subset of 84 individuals who did not receive vaccination between the time of antibody measurement and the time of PCR testing, higher antibody levels were associated with increased odds of PCR-confirmed infection.

Conclusion: We did not identify a protective effect of serum anti-S IgG levels on subsequent risk of infection during the Omicron wave. Further studies could address limitations of our study (sample size, confounding) and evaluate the effect of variant-specific antibodies.

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First and foremost, I would like to thank God. He has given me strength and encouragement throughout all the challenging moments. This project would not have been possible without the support of many people. Many thanks to my second advisor, Mariam O. Fofana, who generously provided the datasets for my thesis project, provided necessary help and guidance while I met troubles in the project, most importantly, reviewed the first draft of my thesis. Many thanks to my first advisor, Albert I. Ko, who spent his precious time discussing with me and guiding me through numerous confusions. Also, thanks to all the faculty and staff members in Department of Epidemiology of Microbial Diseases at Yale School of Public Health, who trained me well and prepared me with enough capabilities to complete this project and reach further goals. And finally, thanks to my families, schoolmates, and friends who endured this process with me, and offering support and love.

Table of Contents

Abstract.....**1**

Acknowledgments.....**2**

Introduction.....**4**

Methods.....**5**

Study site and population.....5

Data collection.....6

Data analysis.....7

Ethical consideration.....7

Results.....**8**

Study population and characteristics 8

Antibody levels prior to PCR-confirmed Omicron infection.....13

Antibody levels prior to PCR-confirmed re-infection in the Omicron wave.....15

Longitudinal antibody trends.....16

Discussion.....**19**

Key findings 19

Limitations 20

Conclusion 21

Appendix.....**22**

References.....**23**

Introduction

SARS-CoV-2 is the coronavirus responsible for the COVID-19 pandemic. SARS-CoV-2 spread rapidly worldwide and has continued to cause surges of transmission because of its high transmissibility, ability to disseminate rapidly, and high mutation rate. Analyses of the evolution rate of SARS-CoV-2 suggest that it has acquired on average 2 new mutations per month [1]. The presence of antibodies to the SARS-CoV-2 Spike protein (anti-S antibodies) indicates either prior infection or vaccination. Higher titers of neutralizing and anti-S binding antibodies are associated with greater protection against infection [2]. However, mutations in the SARS-CoV-2 Spike protein antigens have enabled the virus to escape recognition by antibodies generated from a prior infection or vaccination, especially during the Omicron wave that began in late 2021 [3]. Because of this phenomenon of immune escape, people are susceptible to reinfection a few months after a prior infection or when new variants are introduced in their communities [4, 5]. For example, in a cohort study conducted in Norway, even after three doses of vaccination, the Omicron variants' secondary attack rate (SAR) was significantly higher (46%) than the SAR for Delta variants (11%) [6].

Brazil has had one of the highest burdens of COVID-19 cases, ranking fifth in the world with over 37,085,675 cases as of March 2023 [7]. Residents of urban informal settlements suffered a particularly high burden during the early months of the pandemic. In a cross-sectional survey conducted after the first wave of the epidemic among residents of an urban informal settlement in Salvador, Brazil, nearly 50% had been infected with SARS-CoV-2 based on the presence of serum anti-S antibodies [8]. In contrast, surveys of the general population in Brazil reported seropositivity ranging from 10% to 30% around the same

period [9, 10]. Brazil subsequently experienced a wave of transmission associated with the Gamma variant in early 2021, and a wave of transmission associated with the Omicron variant in late 2021 to early 2022 [11].

It remains unclear how effective antibodies generated after infection with one variant protect against re-infection by other variants. Moreover, repeat exposure to the SARS-CoV-2 virus in previously infected individuals may lead to preferential stimulation of memory responses to the virus that caused the initial infection instead of activating *de novo* immune response to the more recent virus [12]. Thus, there is concern that this imprinting of antibody responses decreases immune protection against future variants [13]. In this study we aimed to estimate how well serum anti-S antibodies developed in response to a previous infection and/or vaccination protected against infection with the Omicron variant, in a prospective cohort of residents of Pau da Lima, an urban informal settlement in Salvador, Brazil. We hypothesized that individuals who experienced an infection during the Omicron wave had lower serum anti-S antibodies prior to Omicron infection compared to individuals who did not have an Omicron infection.

Methods

Study site and population

The study was conducted in the community of Pau da Lima in Salvador, the largest city in the northeast of Brazil. Pau da Lima is a low-income urban informal settlement with a population of approximately 25,000 people, living in a densely crowded area [14]. More than 70% of heads of household make less than the Brazilian minimum wage, and over half of households

lack legal tenancy rights [15]. The study site consists of a densely populated area of 0.35 km^2. Individuals who reside within the study area at the time of any survey (defined as sleeping 3 or more nights per week within the study area), who are aged 2 years or older, and who provide informed consent (parental consent for minors aged <18 years) are eligible to participate. For this analysis, we included residents who participated in the second SARS-CoV-2 survey (referred to as "L46"), conducted from July to November 2021.

Data collection

Pau da Lima has been the site of an ongoing cohort study involving semi-annual household-based serological surveys. This is an open cohort, meaning that participants can enter and leave the cohort between surveys. Three surveys have been conducted since the onset of the COVID-19 pandemic: a first survey (L45) from November 2020 to February 2021, a second survey (L46) from July 2021 to November 2021, and a third survey (L47) from March to September 2022. During the serosurveys, field teams visited every household in the study area to identify and recruit eligible individuals. After obtaining informed consent, they administered a standardized questionnaire of sociodemographic and health information and collected a serum sample that was analyzed for the presence of SARS-CoV-2 anti-S antibodies. We also measured the level of antibodies against the Nucleocapsid protein of SARS-CoV-2 (anti-N). Data collected in the questionnaire included sex, age, vaccination status, and the date and formulation of vaccine doses received.

Between the second and third surveys, the study team conducted active screening of SARS-CoV-2 infections. They visited every household in the study area in 2-week cycles to identify individuals with symptoms of an acute viral illness (anorexia, cough, diarrhea, fatigue, fever,

headache, loss of smell, loss of taste, altered mental state, myalgia, nausea, rash, runny nose, chills, shortness of breath, or sore throat). In each household with at least one symptomatic individual, the index individual (symptomatic resident) as well as all residents of the household (household contacts) who consented underwent collection of a nasal swab for RT-PCR detection of SARS-CoV-2 infection.

Data analysis

Our primary exposure was the level of anti-S antibodies as measured during the second survey (L46), and the primary outcome was PCR-confirmed infection during the initial Omicron wave, between November 1, 2021, and February 28, 2022. We report the median and interquartile range (IQR) for continuous variables, and the proportion and 95% confidence interval (95% CI) for categorical variables. For comparisons, we used the Chi-square test for categorical variables and the t-test for continuous variables. We fitted a binary logistic regression model in order to account for potential confounding variables such as age, sex, and waning of antibody levels between the time of measurement and the time of PCR testing. We considered p-values <0.05 to be statistically significant. All analyses were performed by statistical language R (version 4.2.2) in software RStudio (version 2022.12.0).

Ethical considerations

The data for this analysis were collected as part of an approved longitudinal study conducted in Pau da Lima, Salvador, Brazil. The study was approved by the Institutional Review Boards of the Instituto Gonçalo Moniz, Oswaldo Cruz Foundation (Fiocruz) and the Brazilian National Commission for Ethics in Research (CAAE 35405320.0.1001.5030 and

17963519.0.0000.0040), and the Yale University Human Research Protection Program (2000031554).

Results

Study population and characteristics

A total of 1827 individuals participated in the L46 survey (July to November 2021). Survey participants were predominantly female (69.0%), which is consistent with previous surveys conducted in this cohort. Overall, the study population was relatively young, with a median age of 29.0 years (interquartile range [IQR] 2.00 - 85.0]). Most participants in this study reported their ethnicity as Brown (49.0%) or Black (46.2%), and 42.9% reported having 6 or fewer years of formal education. Compared to the overall study population, participants who underwent PCR testing during the active screening period were more likely to have experienced a prior SARS-CoV-2 infection (43.3% vs. 34.7%, p = 0.0165). Nearly half of participants (45.4%) had received at least one dose of a COVID-19 vaccine prior to the L46 survey. Details of the sociodemographic characteristics of the study population are shown in **Table 1**.

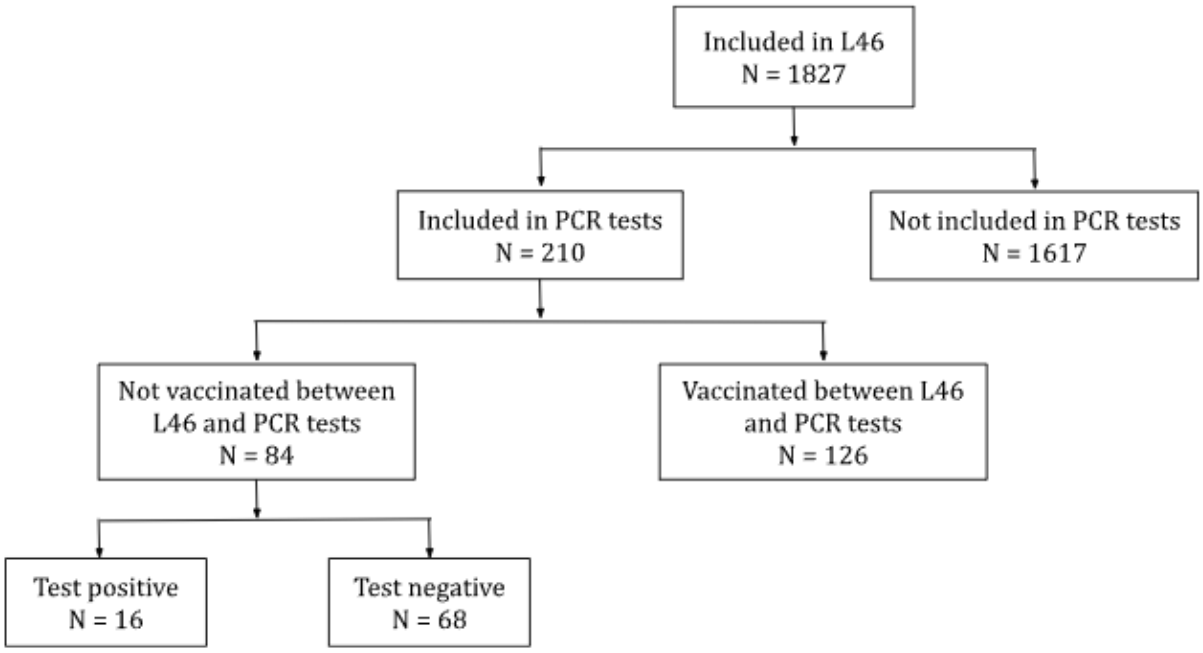
Among the 1827 individuals who participated in the L46 survey, 210 subsequently underwent PCR testing for SARS-CoV-2 during the period of active screening from November 2021 to February 2022. Of those 210, 126 received at least one vaccine dose between the time of serum collection in the L46 survey and the time of their PCR test, such that their antibody measurements were not reflective of their immune status at the time of the PCR test. The remaining 84 individuals who did not receive any vaccine dose between the time of

serum antibody measurement and the time of PCR testing were selected for further analyses (**Figure 1**).

Table 1: Characteristics of study population and participants who underwent PCR testing

	Included in L46 (N=1827)	Underwent PCR testing (N=210)	P
Age			
Mean (SD)	31.4 (18.2)	33.8 (18.4)	0.0718
Median [Min, Max]	29.0 [2.00, 85.0]	32.0 [3.00, 77.0]	
Missing	5 (0.3%)	0 (0%)	
Age group			
2-17	500 (27.4%)	51 (24.3%)	0.718
18-34	562 (30.8%)	63 (30.0%)	
35-49	416 (22.8%)	51 (24.3%)	
50-64	239 (13.1%)	32 (15.2%)	
65+	90 (4.9%)	13 (6.2%)	
Missing	20 (1.1%)	0 (0%)	
Sex			
Female	1060 (58.0%)	145 (69.0%)	***0.00265***
Male	767 (42.0%)	65 (31.0%)	
Race			
Black	841 (46.0%)	97 (46.2%)	0.986
Brown	894 (48.9%)	103 (49.0%)	
White	89 (4.9%)	10 (4.8%)	
Other	1 (0.1%)	0 (0%)	
Don't know	2 (0.1%)	0 (0%)	
Education			
>9	648 (35.5%)	73 (34.8%)	0.966
0-6	783 (42.9%)	90 (42.9%)	
7-9	396 (21.7%)	47 (22.4%)	
Prior infection (L46)			
No	1193 (65.3%)	119 (56.7%)	***0.0165***
Yes	634 (34.7%)	91 (43.3%)	
Vaccination status (L46)			
No	627 (34.3%)	85 (40.5%)	0.437
Unclear	87 (4.8%)	7 (3.3%)	
Yes	829 (45.4%)	108 (51.4%)	
Missing	284 (15.5%)	10 (4.8%)	
Vaccination between L46 and PCR test			
Yes		126 (60.0%)	
No		84 (40.0%)	
Missing		0 (0%)	

Figure 1: Flow chart



Overall, women were more likley to have undergone PCR testing during the period of active screening. Individuals who underwent PCR testing were also more likely to have had a prior infection (**Table 2**). Among the 210 individuals who underwent PCR testing, those who received at least one dose of a vaccine between the L46 survey and the time of PCR test were older. Children were particularly less likely to have received a vaccine dose between the L46 survey and the time of PCR testing (**Table 3**). Receipt of a vaccine dose between the time of antibody measurement at L46 and the time of PCR testing was also associated with vaccination prior to L46 and more years of formal education, likely because vaccine eligibility in Brazil was initially determined by age group, with older individuals becoming eligible first.

Table 2: Characteristics of participants who underwent PCR testing

	No vaccine between L46 and PCR test (N=84)	Vaccinated between L46 and PCR test (N=126)	P
Age			
Mean (SD)	28.9 (20.0)	37.0 (16.5)	***0.00164***
Median [Min, Max]	26.5 [3.00, 77.0]	36.0 [12.0, 75.0]	
Age group			
2-17	35 (41.7%)	16 (12.7%)	***< 0.001***
18-34	20 (23.8%)	43 (34.1%)	
35-49	13 (15.5%)	38 (30.2%)	
50-64	12 (14.3%)	20 (15.9%)	
65+	4 (4.8%)	9 (7.1%)	
Sex			
Female	52 (61.9%)	93 (73.8%)	0.0938
Male	32 (38.1%)	33 (26.2%)	
Race			
Black	36 (42.9%)	61 (48.4%)	0.363
Brown	42 (50.0%)	61 (48.4%)	
White	6 (7.1%)	4 (3.2%)	
Education			
>9	22 (26.2%)	51 (40.5%)	***0.0073***
0-6	47 (56.0%)	43 (34.1%)	
7-9	15 (17.9%)	32 (25.4%)	
Prior infection (L46)			
No	50 (59.5%)	69 (54.8%)	0.589
Yes	34 (40.5%)	57 (45.2%)	
Vaccination status (L46)			
No	32 (38.1%)	53 (42.1%)	***0.0206***
Unclear	6 (7.1%)	1 (0.8%)	
Yes	36 (42.9%)	72 (57.1%)	
Missing	10 (11.9%)	0 (0%)	

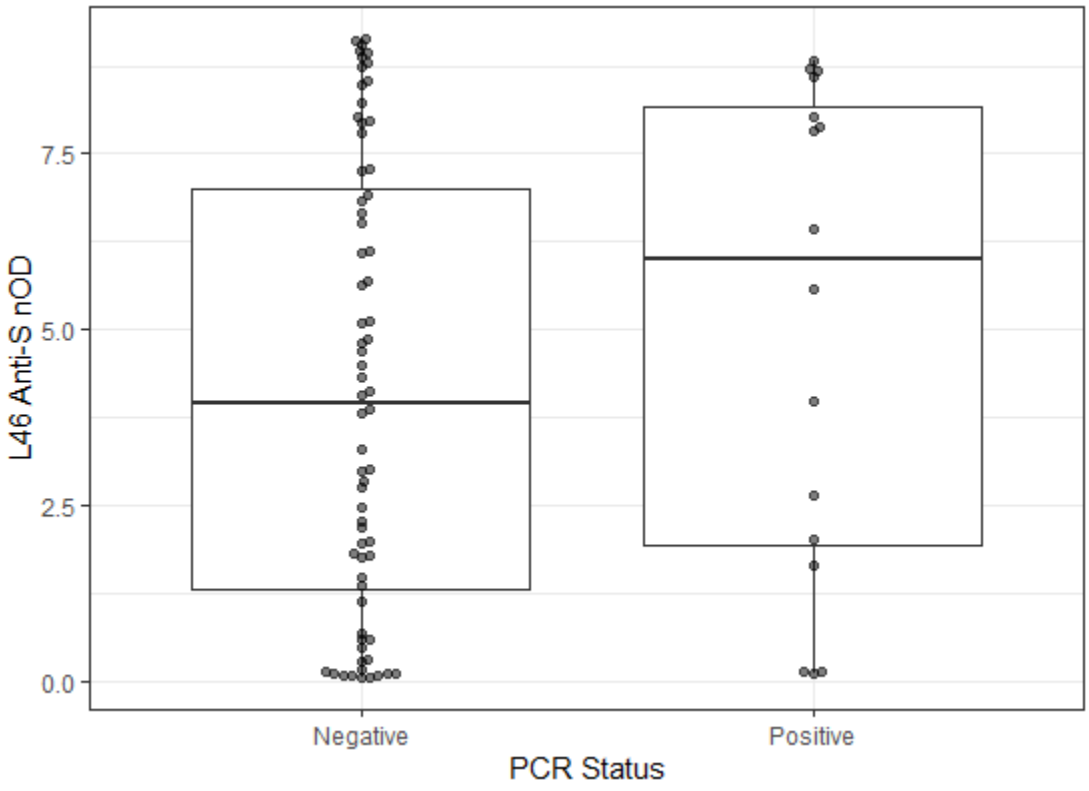
Table 3: Characteristics of participants who were not vaccinated between L46 and PCR testing

	PCR-negative (N=68)	PCR-positive (N=16)	P
Age			
Mean (SD)	28.1 (19.8)	32.6 (20.9)	0.422
Median [Min, Max]	23.0 [3.00, 77.0]	28.5 [7.00, 69.0]	
Age group			
2-17	30 (44.1%)	5 (31.3%)	0.835
18-34	15 (22.1%)	5 (31.3%)	
35-49	11 (16.2%)	2 (12.5%)	
50-64	9 (13.2%)	3 (18.8%)	
65+	3 (4.4%)	1 (6.3%)	
Sex			
Female	44 (64.7%)	8 (50.0%)	0.422
Male	24 (35.3%)	8 (50.0%)	
Race			
Black	30 (44.1%)	6 (37.5%)	0.134
Brown	35 (51.5%)	7 (43.8%)	
White	3 (4.4%)	3 (18.8%)	
Education			
>9	18 (26.5%)	4 (25.0%)	0.787
0-6	37 (54.4%)	10 (62.5%)	
7-9	13 (19.1%)	2 (12.5%)	
Prior infection (L46)			
No	41 (60.3%)	9 (56.3%)	0.989
Yes	27 (39.7%)	7 (43.8%)	
Vaccination status (L46)			
No	26 (38.2%)	6 (37.5%)	0.437
Unclear	6 (8.8%)	0 (0%)	
Yes	28 (41.2%)	8 (50.0%)	
Missing	8 (11.8%)	2 (12.5%)	

Antibody levels prior to PCR-confirmed Omicron infection

We compared anti-S antibody levels measured at the L46 survey (July to November 2021), among 84 individuals who subsequently tested positive or negative for SARS-CoV-2 during the active screening period (November 2021 to February 2022) and did not receive any vaccination between L46 and the time of their PCR test (**Figure 2**). Overall, the distributions of measured antibody levels overlapped between individuals who tested positive (median 6.00, IQR 0.114 – 8.83) and those who tested negative (median 3.97, IQR 0.0571 – 9.14), and we did not identify any statistically significant difference (t-test p-value 0.337).

Figure 2: Anti-S IgG levels at L46 by PCR status



In a logistic regression analysis (**Table 4**), we did not observe a statistically significant association between antibody levels measured at L46 and subsequent PCR-confirmed infection. A longer interval between antibody measurement (coefficient –0.02 [95% CI –0.03 - (-0.00)], OR 0.98 [95% CI 0.970 – 1.00], p-value = 0.043) and time of PCR testing was associated with lower odds of having a positive PCR.

Table 4: Unadjusted and adjusted associations between anti-S IgG levels and PCR-confirmed infection

	Positive PCR (Unadjusted)			**Positive PCR (Adjusted)**		
Predictors	*Coefficient*	*CI*	*P-Value*	*Coefficient*	*CI*	*P-Value*
Intercept	1.13	0.99 – 1.27	**<0.001**	0.80	0.49 – 1.11	**<0.001**
L46 Anti-S IgG OD	0.01	-0.01 – 0.04	0.298	0.02	-0.01 – 0.04	0.261
Age (decade)				0.01	-0.04 – 0.05	0.814
Sex (Male)				0.09	-0.09 – 0.26	0.327
Weeks from L46 OD measurement				-0.02	-0.03 – -0.00	**0.043**
Observations	84			84		
R^2	0.013			0.082		

Antibody levels prior to PCR-confirmed re-infection in the Omicron wave

We then compared anti-S antibody levels measured at the L46 survey (July to November 2021), among a subset of 34 individuals who had evidence of a prior infection, and subsequently underwent PCR testing during the active screening period (**Figure 3**). Overall, individuals who tested positive on PCR had higher antibody levels (median 7.88, IQR 5.57 – 8.83) compared to those who tested negative (median 4.69, IQR 1.78 – 9.12), and this difference was statistically significant (t-test p-value <0.01). In a logistic regression analysis (**Table 5**), higher antibody level at L46 was associated with increased risk of subsequent positive PCR test (coefficient 0.06 [95% CI 0.00 – 0.12], OR 1.06 [95% CI 0.00 – 1.13]).

Figure 3: Anti-S IgG levels at L46 by PCR status among individuals with a prior infection

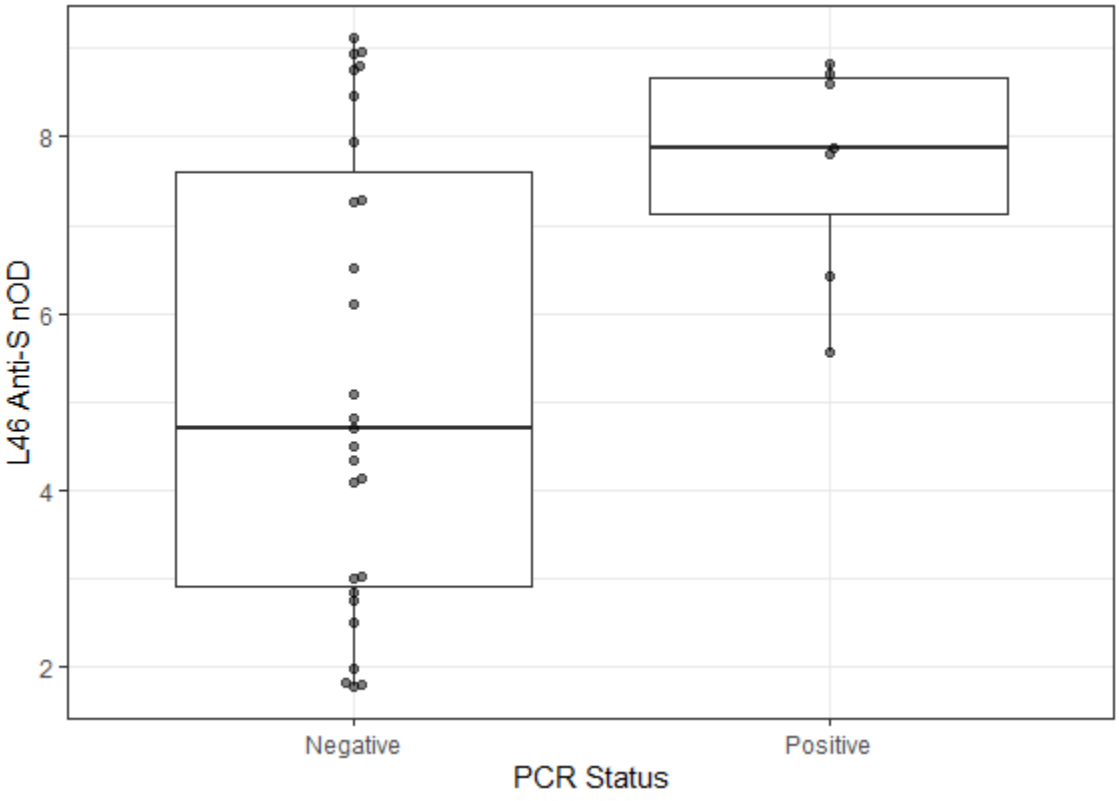


Table 5: Unadjusted and adjusted associations between anti-S IgG antibody levels and PCR-confirmed re-infection

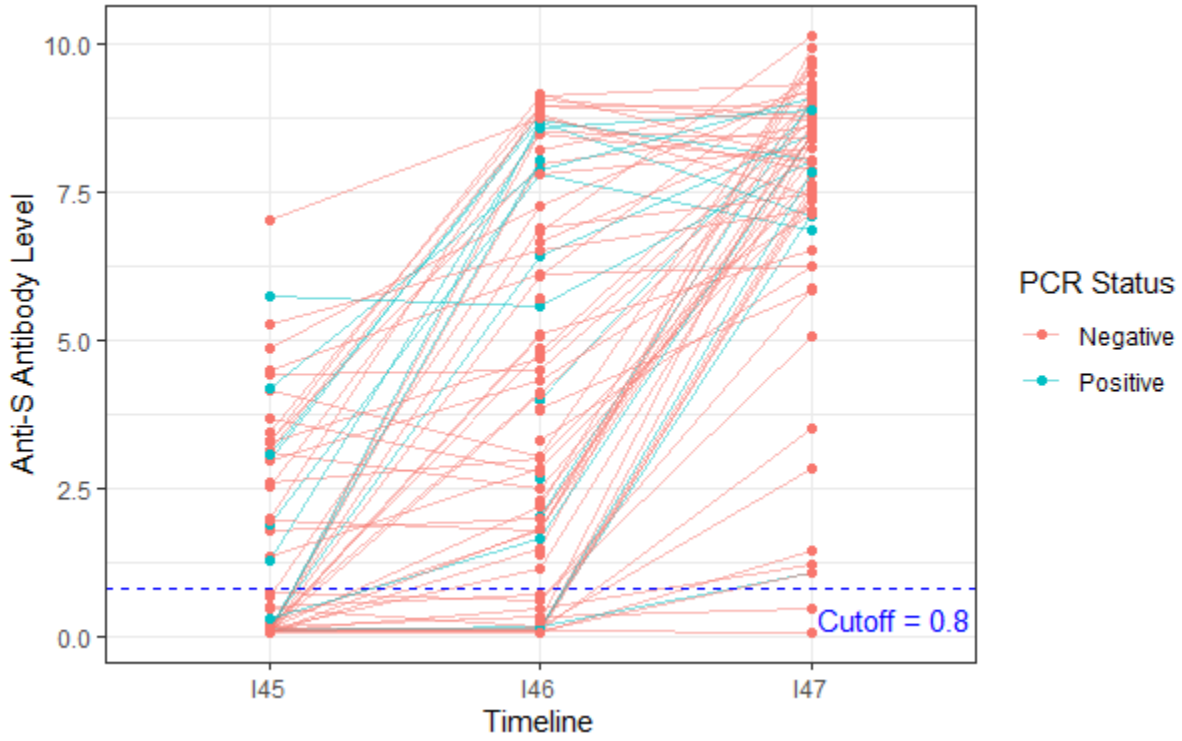
	Positive PCR (Unadjusted)			Positive PCR (Adjusted)		
Predictors	*Coefficient*	*CI*	*P-Value*	*Coefficient*	*CI*	*P-Value*
Intercept	0.85	0.53 – 1.17	**<0.001**	0.45	-0.14 – 1.05	0.132
L46 Anti-S IgG OD	0.06	0.01 – 0.11	**0.016**	0.06	0.00 – 0.12	**0.040**
Age (decade)				0.01	-0.07 – 0.09	0.789
Sex (Male)				0.11	-0.17 – 0.39	0.444
Weeks from L46 OD measurement				-0.02	-0.04 – 0.01	0.163
Observations	34			34		
R^2	0.154			0.225		

Longitudinal antibody trends

Although most of our study population (1617/1827) did not undergo PCR testing, we suspected that some individuals who were not tested nevertheless experienced an infection. We therefore examined longitudinal trends in antibody levels to identify individuals who may have had an infection between the second (L46, July to November 2021) and third (L47, March to September 2022) surveys but did not undergo a PCR test. As shown in **Figure 4**, among the 84 individuals who did not receive a vaccine dose between the L46 survey and the time of PCR testing, a large proportion had an increase in anti-S antibody levels,

suggesting that they experienced an infection during that interval. Many of these people had tested negative on PCR, indicating that they had an infection that was not detected during our active screening period.

Figure 4: Longitudinal changes in anti-S antibody levels by PCR status



Overall, the change in anti-S antibody levels between the second and third surveys was similar among individuals who tested positive on PCR (median ratio 1.45, IQR 0.817 – 68.7) and those who tested negative (median ratio 1.89, IQR 0.529 – 131.0), and there was no statistically significant difference (t-test p-value = 0.964, **Figure 5**). Finally, we examined the levels of anti-N antibody levels measured during the third survey (L47), as elevated anti-N levels could be reflective of a recent infection (**Figure 6**). We found that the levels of anti-N antibodies were similar between individuals who tested negative on PCR (median 2.41, IQR

0.0625 – 7.78) and those who tested positive (median 1.81, IQR 0.355 – 5.55), and there was no statistically significant difference between these two groups (p = 0.851).

Figure 5: Ratio of change in anti-S antibody levels from survey 2 (L46) to survey 3 (L47)

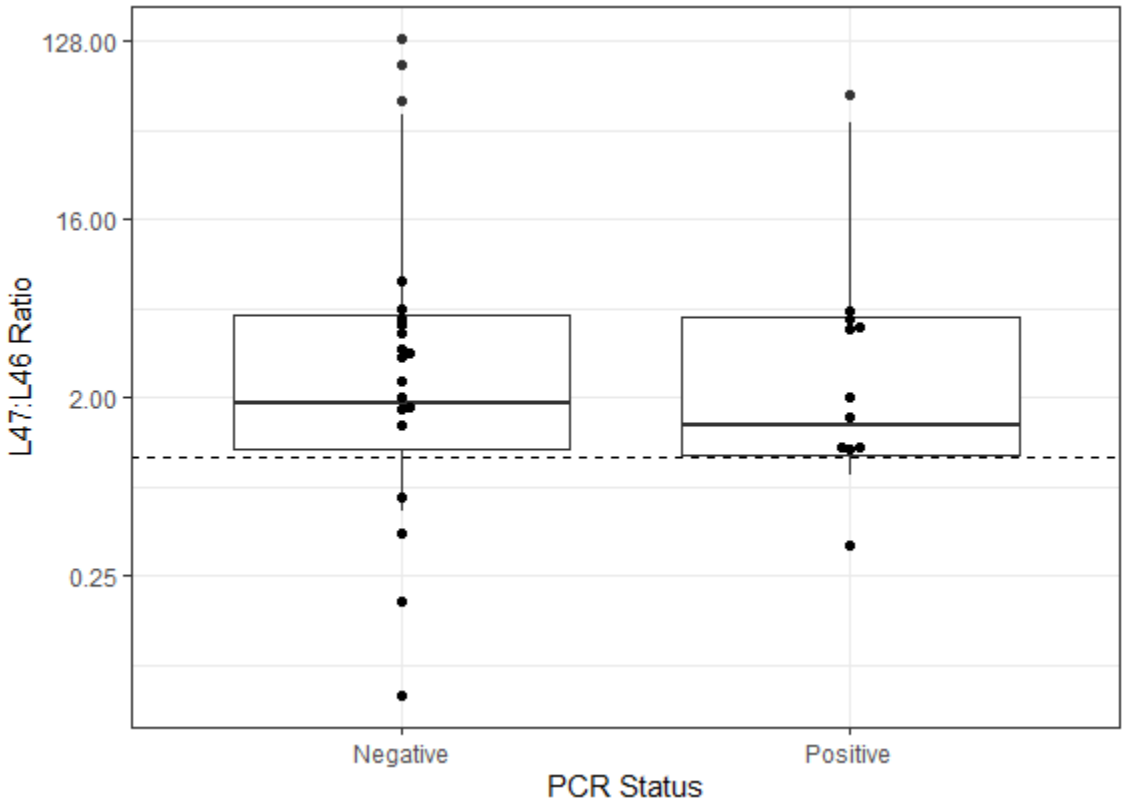
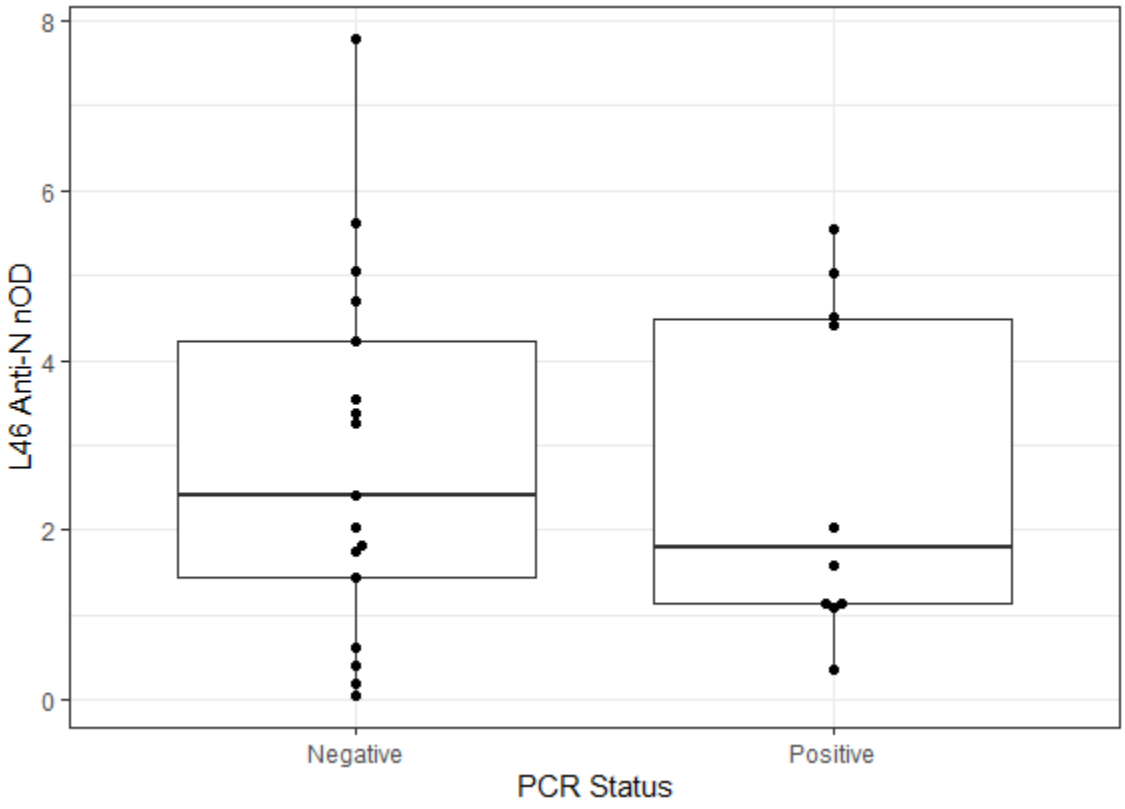


Figure 6: Anti-N antibody levels at survey 3 (L47) by PCR status



Discussion

Key findings

A key strength of our study is that we were able to follow individuals longitudinally. Overall, we found that there is no evidence to support our hypothesis that the risk of virologically confirmed SARS-CoV-2 infection during the first Omicron wave is inversely correlated to the level of pre-existing anti-S antibodies from exposure to previous variants. On the contrary, among the subset of individuals who had a prior history of SARS-coV-2 infection, we found that higher L46 anti-s IgG antibody levels were associated with a higher risk of re-infection during the first Omicron wave.

There are several reasons why we may have observed these results. It is possible that individuals who had lower antibody levels during the L46 survey became infected shortly after their antibody levels were measured, and thus had increased immunity during the period of active screening. In fact, longer durations from time of antibody measurement to time of PCR testing were associated with decreased odds of testing positive on PCR during the period of active screening. Thus, the antibody levels measured at L46 may not have been reflective of the true immunity status during the active screening. An alternative explanation is that more robust antibody responses generated by earlier variants result in decreased immunity against the Omicron variant, due to imprinting. Finally, we only measured one type of antibody (serum anti-S IgG), and it is possible that while anti-S IgG is not associated with protection from infection, other types of antibodies are better corelates of protection.

Limitations

Some limitations of our study include the small sample size of individuals who underwent PCR testing, and undetected infections in our study population. Because only individuals who were symptomatic, or in a household with a symptomatic person, were tested, we were not able to reliably detect asymptomatic infections. We may also have missed the ideal time window to test infected individuals. Moreover, most individuals in our population received at least one vaccine dose between the time that their antibody levels were measured and the time that they underwent PCR testing. This further reduced the number of individuals in whom we could truly evaluate the association between antibody levels measured at L46 and subsequent PCR-confirmed infection.

It is likely that our study was subject to selection bias. For example, female residents were more likely to participate in the serological surveys and more likely to undergo PCR screening. Women were also more likely to stay in the cohort at the third survey (**Appendix Table 6**). This may be partly because women in this community are less likely to be employed outside of the home, and thus more likely to be present during study visits. Moreover, we noted that individuals who underwent PCR screening were more likely to have had a prior SARS-CoV-2 infection. This may be because they have a higher underlying risk of infection (e.g., differences in household crowding, or risk mitigation behaviors such as mask usage). Alternatively, it is possible that individuals who had a prior infection were more likely to be aware of symptoms and/or be willing to get tested.

Conclusions

In this population of residents in an urban informal settlement with high exposure to SARS-CoV-2, higher antibody levels as measured by serum anti-S IgG were not associated with protection from subsequent infection during the first Omicron wave. Counter-intuitively, we found that among those with a prior infection, higher antibody levels were associated with higher risk of reinfection. In order to better understand these observed findings, future studies could be conducted with a larger sample size to improve the statistical power of the analysis. Additionally, improving the sensitivity of the screening protocol could minimize false negatives. One possible approach would be implementing systematic bi-weekly testing for all individuals, rather than relying on symptom-based testing. Last but not least, it may be beneficial to examine variant-specific antibodies in future studies, rather than relying on a single type of antibody.

Appendix

Table 6: Sociodemographic characteristics of study population compared to individuals who were retained at survey 3 (L47)

	Included in L46 (N=1827)	Included in L46 & L47 (N=702)	P
Age			
Mean (SD)	31.4 (18.2)	32.6 (18.6)	0.128
Median [Min, Max]	29.0 [2.00, 85.0]	31.0 [2.00, 82.0]	
Missing	5 (0.3%)	0 (0%)	
Age group			
2-17	500 (27.4%)	185 (26.4%)	0.461
18-34	562 (30.8%)	200 (28.5%)	
35-49	416 (22.8%)	170 (24.2%)	
50-64	239 (13.1%)	99 (14.1%)	
65+	90 (4.9%)	44 (6.3%)	
Missing	20 (1.1%)	4 (0.6%)	
Sex			
Female	1060 (58.0%)	446 (63.5%)	***0.013***
Male	767 (42.0%)	256 (36.5%)	
Race			
Black	841 (46.0%)	321 (45.7%)	0.698
Brown	894 (48.9%)	353 (50.3%)	
White	89 (4.9%)	28 (4.0%)	
Other	1 (0.1%)	0 (0%)	
Don't know	2 (0.1%)	0 (0%)	
Education			
>9	648 (35.5%)	247 (35.2%)	0.941
0-6	783 (42.9%)	306 (43.6%)	
7-9	396 (21.7%)	149 (21.2%)	
Prior infection (L46)			
No	1193 (65.3%)	420 (59.8%)	***0.0119***
Yes	634 (34.7%)	282 (40.2%)	
Vaccination status (L46)			
No	627 (34.3%)	308 (43.9%)	0.117
Unclear	87 (4.8%)	43 (6.1%)	
Yes	829 (45.4%)	337 (48.0%)	
Missing	284 (15.5%)	14 (2.0%)	

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