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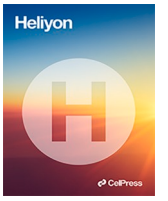

Research article

Diverse immune responses in vaccinated individuals with and without symptoms after omicron exposure during the recent outbreak in Guangzhou, China

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ABSTRACT

Objectives: During the recent wave of coronavirus disease 2019 (COVID-19) infections in China, most individuals have been vaccinated and exposed to the omicron variant. In the present study, two cohorts were observed in the vaccinated population: vaccinated individuals with symptoms (VIWS) and those without symptoms (VIWOS). Our study aimed to characterize the antibody response in two cohorts: VIWS and VIWOS.

Methods: A questionnaire survey was conducted in the community. Blood and saliva samples were collected from 124 individuals in the VIWS and VIWOS cohorts. Capture enzyme-linked immunosorbent assay (ELISA) was performed to detect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) specific antibodies.

Results: The questionnaire survey revealed that 30.0 % (302/1005) of individuals in the older adult group (≥65 years) experienced no symptoms, whereas the rate of individuals without symptoms in the younger group (<65 years) was 17.8 % (166/932). Nucleocapsid (N)-specific IgM (N-IgM) was detected in the blood samples at a rate of 69.2 % (54/78) in the VIWS cohort. The positivity rate for N-specific IgA (N-IgA) was 93.6 % (73/78). In addition, the positivity rates of spike (S)-specific IgA (S-IgA) and N-IgA detected in saliva samples were 42 % (21/50) and 54 % (27/50), respectively. Both N-IgA positivity and negativity were observed in the VIWOS cohort. The detection rate of N-IgM positivity was 57.1 % (12/21) in the N-IgA-positive group. In addition, 54.3 % (25/46) of the vaccinated individuals without symptoms were IgA-negative.

Conclusions: Our study indicates that substantial N-specific antibodies were induced during omicron infection and that testing for N-IgA in both blood and saliva may aid in the diagnosis of SARS-CoV-2 infection in vaccinated populations.

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1. Introduction

The emergence of the omicron variant has led to extreme rates of coronavirus disease 2019 (COVID-19) occurrence worldwide [1]. Omicron has been associated with a milder disease than that caused by previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strains [2–4]. Individuals with omicron infection may present with symptoms such as fever, sore throat, fatigue, cough, body aches, runny nose, loss of taste or smell, nausea, and vomiting, or may be asymptomatic but test positive for viral nucleic acid [5–7]. Asymptomatic individuals have a viral load in the upper respiratory tract [8] and can unknowingly spread the virus.

Owing to the cancellation of the zero-COVID policy, SARS-CoV-2 omicron (BA5.2 and BF.7) spread rapidly throughout the population in mainland China within 1 month from early December 2022. This new outbreak resulted in a significant increase in the number of infected cases, with a seropositivity rate of up to 80 % [9]. However, a small number of individuals had no symptoms despite a confirmed history of exposure to SARS-CoV-2 (living with infected persons). This raises the question of whether they are truly asymptomatic or simply not infected.

Typically, viral shedding peaks at 5–6 d after the onset [8]. Therefore, antibody testing for SARS-CoV-2 has become increasingly important for tracking latent and asymptomatic infections [10,11]. Anti-spike (anti-S) and anti-nucleocapsid (anti-N) antibodies are produced during SARS-CoV-2 infection. However, anti-S antibodies have also been detected [12–15]. The types of vaccines include messenger RNA (mRNA) vaccines, vector vaccines, protein subunit vaccines, and inactivated whole virus vaccines, which produce or contain the S protein. In addition, whole-virus inactivated vaccines can induce anti-N antibodies in vaccinees; but the level of anti-N Abs in vaccinees without infection is lower than that in infected individuals [16–20]. Anti-N IgG is commonly used to investigate past or current COVID-19 infections in vaccinated population [6,10,18]. Recently, anti-SARS-CoV-2 IgA has been used to diagnose breakthrough infections in vaccinees [11,21]. However, the anti-N antibody response in inactivated virus vaccinees with omicron infections is not well understood.

During this new omicron surge in China, two cohorts were observed in the vaccinated population: vaccinated individuals with symptoms (VIWS) and vaccinated individuals without symptoms (VIWOS). In this study, we characterized the antibody response in both cohorts, VIWS and VIWOS, in a community-based population, with a focus on the anti-N antibody response. Our results indicate that testing for N-IgA in both blood and saliva may aid in the diagnosis of SARS-CoV-2 infection in vaccinated populations, especially in inactivated vaccine-immunized populations.

2. Materials and methods

2.1. Study population and sampling

The study was conducted with the approval of the Human Ethics Committee of Guangzhou Eighth People's Hospital (202115202).

All individuals (n = 1937) enrolled in this study resided in one community (Jiahe Street, Guangzhou, China) during the SARS-CoV-2 outbreak in Guangzhou between early December 2022 and January 2023 (Fig. 1), regardless of age and vaccination status. The questionnaires were collected between February 2023 and March 2023. The two groups were categorized based on the presence or absence of the symptoms listed in the questionnaire (Supplementary Table 1) [22–24]. Owing to the high vaccination rate in the population, individuals who were not vaccinated were excluded from subsequent antibody testing. Therefore, two cohorts of vaccinated individuals with symptoms (VIWS, n = 78) and vaccinated individuals without symptoms (VIWOS, n = 46) were enrolled for antibody testing (Fig. 1). In the VIWOS cohort, exposure to omicron infection was confirmed by living with infected individuals. A total

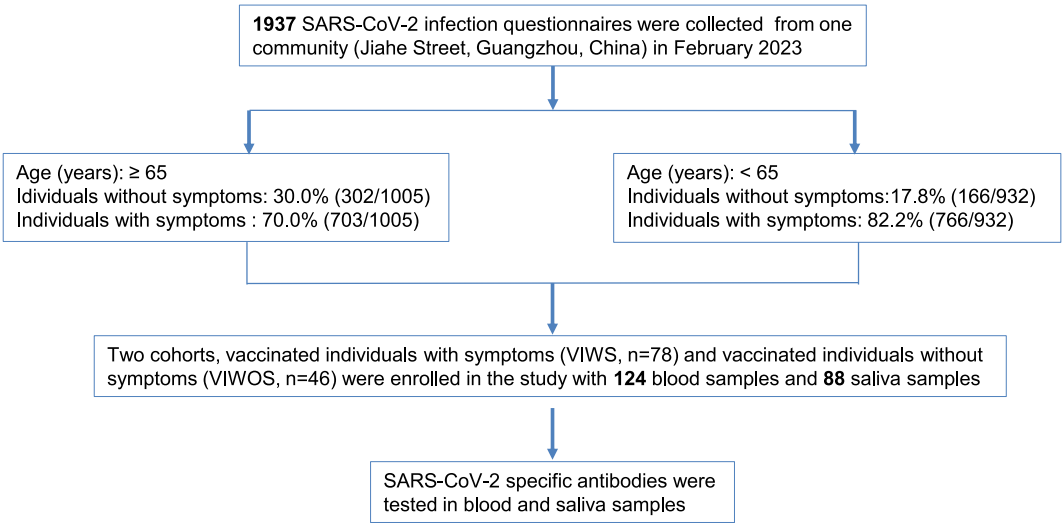

Fig. 1. Study design of the VIWS and VIWOS cohorts for the detection of SARS-CoV-2 specific antibodies.

of 124 blood and 88 saliva samples from each of the two cohorts (Table 1) were collected between February and March 2023 after each participant provided written informed consent.

Plasma samples were clarified, aliquoted, and stored at −80 °C until use. The saliva samples were added to an equal volume of diluent (1 % NP-40 and 0.5 % Trition-X-100 in phosphate-buffered saline [PBS]), mixed, and allowed to stand for 10 min. The mixtures were then centrifuged at 2500 rpm for 10 min, and the supernatants were collected and stored at −20 °C until use.

2.2. Detection of SARS-CoV-2 specific IgM, IgA, and IgG

IgM, IgA, and IgG against the S and N proteins of SARS-CoV-2 in blood and saliva samples were measured using capture enzyme-linked immunosorbent assay (ELISA) [25].

The recombinant S or N protein with a D7 tag at the C-terminus was captured in 96-well plates using a pre-coated D7-tag capture antibody [26]. A 1:100 or 1:4 dilution of the plasma or saliva antibody was used in the capture ELISA. All samples were tested in duplicates. Optical density (OD) at 450 nm was measured using a microplate reader spectrophotometer (Varioskan lux, ThermoFisher, USA). The threshold value was calculated from the OD value of the negative controls with the standard deviation (SD) in each microplate.

2.3. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics software (version 27.0; SPSS Inc., Chicago, IL, USA). Categorical variables were compared using the chi-square test ($\chi 2$) or Fisher's exact test. Continuous variables were analyzed using the Mann-Whitney *U* test. The OD values of the ELISA are expressed as mean values. Differences between the two groups were compared using the Mann–Whitney *U* test. $p < 0.05$ was considered statistically significant.

3. Results

3.1. Some individuals exhibited no symptoms during this new omicron outbreak

A survey was conducted in the Jiahe Street community in Guangzhou, China using a questionnaire applet, and information was collected from 1937 respondents (Fig. 1). Among individuals aged ≥65 years (n = 1005), 30.0 % (302/1005) had no symptoms of omicron infection. In the <65 years age group (n = 932), the rate of individuals with no symptoms was 17.8 % (166/932).

Table 1
Demographics, symptoms, prior infections, and vaccine regimens of the VIWOS and VIWS cohorts.

Characteristics	VIWOS cohort (n = 46)	VIWS cohort (n = 78)	*p* value
Age, years			
Median(IQR)	48.5(33.75–56.25)	37.5 (30.25–46.25)	0.018
Sex			
Female	17 (37.0 %)	49 (62.8 %)	0.005
Male	29 (63.0 %)	29 (37.2 %)	
Symptoms			
Fever	No	61 (78.2 %)	
Sore throat	No	50 (64.1 %)	
Fatigue	No	46 (59.0 %)	
Cough	No	39 (50.0 %)	
Body aches	No	38 (48.7 %)	
Runny nose	No	28 (35.9 %)	
Loss of taste or smell	No	20 (25.6 %)	
Nausea or vomiting	No	11 (14.1 %)	
Unknown	No	7 (9.0 %)	
Previous SARS-CoV-2 infection			
No previous infection	45 (97.9 %)	69 (88.5 %)	0.131
Previous infection before this outbreak	0	4 (5.1 %)	0.296
Unknown	1 (2.1 %)	5 (6.4 %)	0.529
Vaccine			
Inactived vaccine	37 (80.4 %)	62 (79.5 %)	0.899
Non-replicating vector vaccine	5 (10.9 %)	4 (5.1 %)	0.405
Protein subunit vaccine	0	2 (2.6 %)	0.53
Unknown	4 (8.7 %)	10 (12.8 %)	0.684
Days between last vaccination and blood collection			
Median(IQR)	441.5 (145.3–497.8)	439.5 (384.0–509.0)	0.426

VIWOS, vaccinated individuals without symptoms; VIWS, vaccinated individuals with symptoms.

3.2. Comparison of IgM, IgA, and IgG antibodies detected in the VIWS and VIWOS cohorts

As described in the Materials and Methods section 2.1. The two cohorts, vaccinated individuals with symptoms (VIWS) and vaccinated individuals without symptoms (VIWOS), were grouped into a community-based population. In total, 124 blood samples were collected from the VIWS (n = 78) and VIWOS (n = 46) cohorts. Viral antigen capture ELISA was performed on 124 blood samples to detect IgM, IgA, and IgG antibodies directed against the S and N proteins of wild-type SARS-CoV-2 (Fig. 2A–C, Supplementary Tables 2–3).

S-specific IgM (S-IgM) was not detected in either the VIWOS (0/46) or the VIWS cohorts (0/78, Fig. 2A). In contrast, we detected IgM against the conserved N protein (N-IgM) in 69.2 % (54/78) of the individuals in the VIWS cohort. Notably, both S-IgA and N-IgA were detected in 15.4 % (12/78) and 93.6 % (73/78) of the patients in the VIWS cohort, respectively (Fig. 2B). As expected, all IgG antibodies detected in the VIWS cohort were positive for either S or N protein (Fig. 2C).

SARS-CoV-2 specific antibodies, IgM IgA, and IgG antibodies were also detected in the VIWOS cohort. However, the levels of the N-specific antibodies N-IgM, N-IgA, and N-IgG were notably lower than those in the VIWS cohort ($p = 0.0001$, Fig. 2A–C). For S-specific antibodies, the positive rate for S-IgG in the VIWOS cohort was 91.3 % (42/46); however, the level of S-IgG was lower than that in the VIWS cohort ($p = 0.0001$, Fig. 2C). Our data indicate that omicron infection induces substantial N-specific antibodies, as well as S-IgG, in a vaccinated population.

3.3. Comparison of IgM and IgG antibodies detected in the VIWOS with N-IgA-positive and -negative cohorts

The positivity rate for N-IgA was higher than that for N-IgM in the VIWS cohort (93.6 % [73/78] vs. 69.2 % [54/78], $p < 0.001$). The N-IgA level in the VIWS cohort was higher than that in the VIWOS cohort ($p = 0.0001$; Fig. 2B). We hypothesized that asymptomatic individuals may exist in the VIWOS cohort and be N-IgA-positive. Based on the N-IgA test results, the VIWOS cohort was further classified into two groups: IgA-positive (n = 21) and IgA-negative (n = 25) (Fig. 2D and E, Supplementary Table 3). In the N-IgA-positive group, the detection rate of N-IgM was 57.1 % (12/21), whereas that in the N-IgA-negative group the detection rate was 4.0 % (1/25) (Fig. 2D). Differences in N-IgG and S-IgG levels were also observed between the N-IgA positive and N-negative VIWOS groups ($p = 0.0001$, Fig. 2E). In addition, 54.3 % (25/46, Supplementary Table 3) of the vaccinated individuals without symptoms were IgA-negative.

3.4. Detection of specific IgA and IgG in saliva

SARS-CoV-2-specific IgA and IgG assays were performed on 88 saliva samples collected from 124 individuals (Fig. 3, Supplementary Tables 2–3). As shown in Fig. 3A, the positivity rates for S-IgA and N-IgA were 42 % (21/50) and 54 % (27/50), respectively, among individuals in the VIWS cohort. Additionally, S-IgA (13.2 %, 5/38) and N-IgA (21.5 %, 8/38) were detected in the VIWOS cohort, which was significantly different from the rates in the VIWS cohort ($p = 0.07$ for S-IgA and $p = 0.02$ for N-IgA). The positive

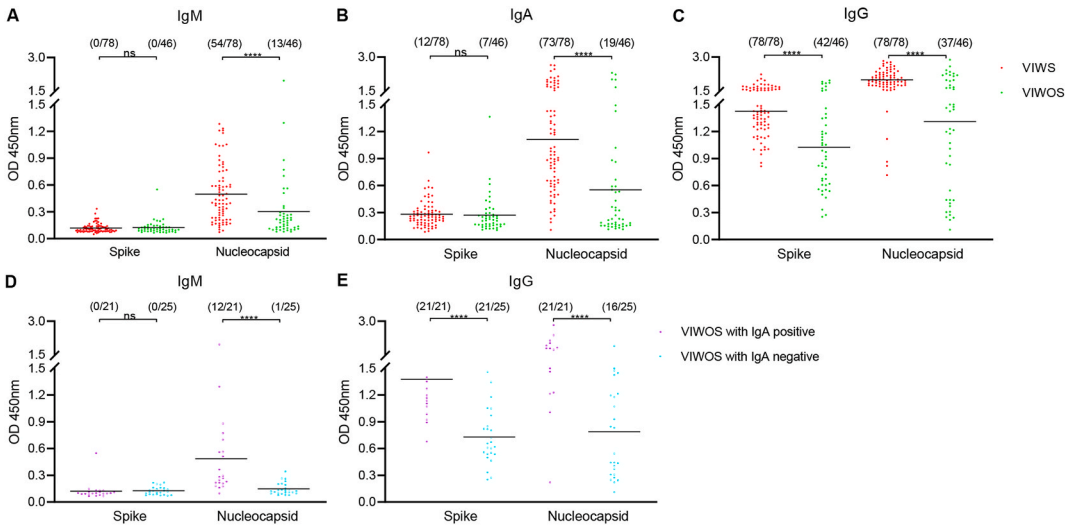

Fig. 2. Quantification of SARS-CoV-2 specific antibodies in blood using ELISA. The OD values and positive rates of IgM, IgA, and IgG in blood detected in the VIWS and VIWOS cohorts (A–C) and in the VIWOS with IgA positive and IgA negative (D–E). Plasma Ab at a 1:100 was used in the capture ELISA. All samples were assayed in duplicate. The threshold value was calculated from the OD value of the negative controls with SD in each microplate. The OD values of the ELISA were expressed as the mean value. Differences between two groups were compared using the Mann-Whitney *U* test. Statistical significance was set at $p < 0.05$. VIWS, vaccinated individuals with symptoms; VIWOS, vaccinated individuals without symptoms; ns, not significant; ****$p < 0.0001$.

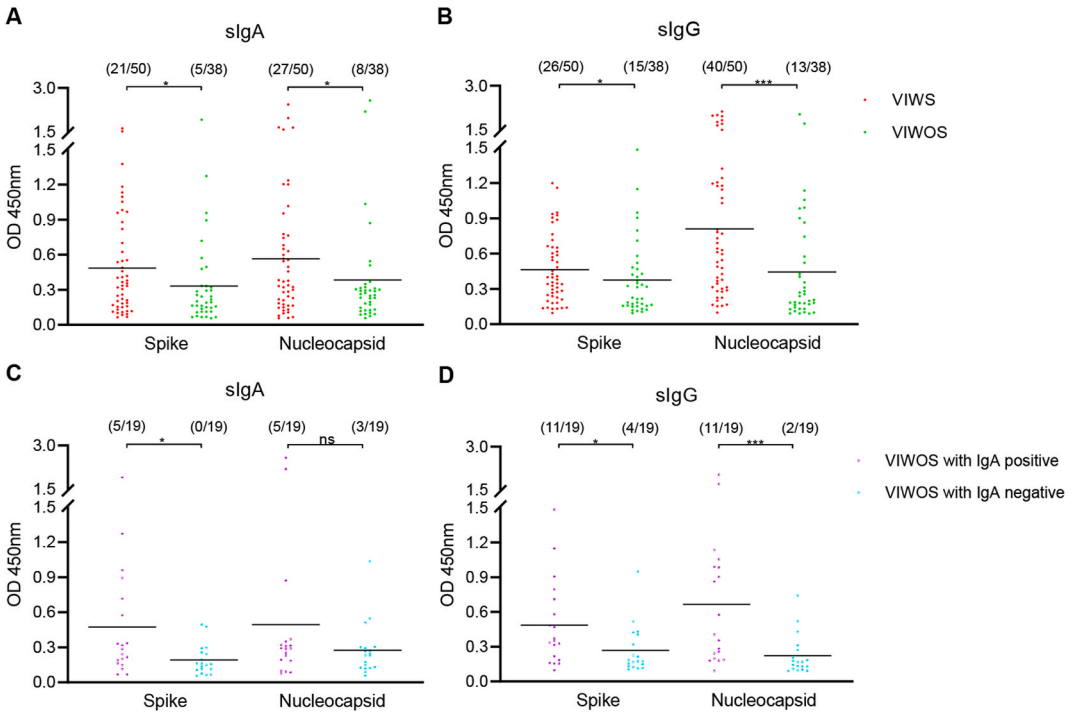

Fig. 3. Quantification of SARS-CoV-2 specific antibodies in saliva using ELISA. The OD values and positive rates of IgA and IgG in saliva detected in the VIWS and VIWOS cohorts (A–B) and in the VIWOS with IgA positive and IgA negative (C–D). Saliva Ab at a 1:4 dilution was used in the capture ELISA. All samples were assayed in duplicate. The threshold value was calculated from the OD value of the negative controls with SD in each microplate. The OD values of the ELISA were expressed as the mean value. Differences between two groups were compared using the Mann-Whitney *U* test. $p < 0.05$ was considered statistically. sIgA, salivary IgA; sIgG, salivary IgG; VIWS, vaccinated individuals with symptoms; VIWOS, vaccinated individuals without symptoms; ns, not significant; $*p < 0.05$; $***p < 0.001$.

rates for S-IgG and N-IgG were also higher in the VIWS cohort than those in the VIWOS cohort (Fig. 3B), especially for N-IgG (80 %, [40/50] vs. 34.2 %, [13/38], $p < 0.001$). A similar trend in the positive rates of IgG was observed between the two groups of the VIWOS cohort with IgA positivity and IgA negativity (Fig. 3C and D).

4. Discussion

Omicrons tend to cause relatively mild symptoms or no symptoms at all in vaccinated individuals [2–4]. Among omicron variant-positive individuals, 25.5–32.4 % of asymptomatic infections have been reported [5,27]. Due to strict control measures for COVID-19 in China, most people will remain vaccinated until the new SARS-CoV-2 (BA5.2 and BF.7) outbreak starts in early December 2022. In our study 84.4%–92.7 % of the individuals were vaccinated with two or more doses of the vaccine (Supplementary Table 1). Our survey showed that most people exposed to SARS-CoV-2 during this outbreak developed illness, presenting with fever (63 %), sore throat (48.6 %), and cough (48.2 %), whereas a minority (17.8%–30.0 %) showed no symptoms.

Conventionally, the presence of virus-specific IgM antibodies indicates a recent infection [28]. However, in the present study, S-IgM was undetectable in both the VIWS and VIWOS cohorts. This could be attributed to the vaccinated individuals, as S-IgM may not have been sufficiently elicited by subsequent omicron infections (mainly BA.5.2 in Guangzhou). As expected, N-IgM was detected in 69.2 % of the symptomatic individuals. Notably, the N-IgA positivity rate in the VIWS cohort was 93.6 %. Most individuals ($\sim$ 79.5 %, Table 1) were vaccinated with to 2–3 doses of an inactivated COVID-19 vaccine, which can induce low levels of SARS-CoV-2-specific IgA [21]. Because the interval between the last dose injection and the blood sample collection was >1 year, with a median of 439.5 d (IQR, 384.0–509.0, Table 1), the S-IgA and N-IgA detected in the symptomatic group were likely to have originated from the recent omicron infection. The potential use of IgA in serosurveys has not been established [11,21]. Our results suggest that N-IgA is more appropriate than N-IgM for diagnosing omicron infections in vaccinated populations. Our study also demonstrated that SARS-CoV-2 specific IgG (S-IgG and N-IgG) was induced during omicron infections in a vaccinated population. Because of pre-existing IgG antibodies in the vaccinated individuals, samples from two time points, pre-epidemic and post-epidemic, were required for the diagnosis of infection.

Interestingly, among the individuals with no symptoms, N-IgA-positive and N-IgA-negative groups could be categorized, and the detection rate of N-IgM was 57.1 % in the N-IgA-positive group, suggesting that some individuals may have developed asymptomatic infections while still eliciting adaptive immune responses to SARS-CoV-2 infection. Additionally, we observed that 54.3 % of the N-IgA-negative individuals in the VIWOS cohort, except for one N-IgM-positive patient (Supplementary Table 3), remained asymptomatic

during this new omicron outbreak, indicating potential resistance to the SARS-CoV-2 variant infection [29]. Further understanding of the protective immune response against SARS-CoV-2 infection in these exposed but uninfected individuals will inform vaccine development.

Secretory IgA (SIgA), the dominant antibody class in mucosal secretions, is also present in saliva and breast milk [30]. In our study, the positivity rates of S-IgA and N-IgA were 42 % and 54 %, respectively, in symptomatic individuals. Saliva is easily accessible and noninvasive, making the detection of salivary N-IgA a valuable tool for the diagnosis of SARS-CoV-2 infection.

In conclusion, our study suggests that substantial N-specific antibodies are induced during omicron infection, and that testing for N-IgA in both blood and saliva may aid in the diagnosis of SARS-CoV-2 infection in vaccinated populations. The antibody responses we have characterized here in both the VIWS and VIWOS cohorts, particularly the specific IgA response, will inform the diagnosis of other respiratory viral infections and the management of post-COVID19 syndrome in the future.

Our study had several limitations. First, participants received the survey via a questionnaire applet, which may have led to potential underreporting of manifestations owing to unawareness of some minor symptoms, especially in the older adult population. Second, the number of samples in each VIWS or VIWOS cohort was small, and the samples were collected 2–3 months after the outbreak. The kinetic levels of specific antibodies are lacking. Although the limited sample size may not fully represent the broader population, it still provides insights into the characteristics of the antibody response in the two cohorts, VIWS and VIWOS, in a community-based population.

Ethics statement

This study was reviewed and approved by the Human Ethics Committee of Guangzhou Eighth People's Hospita, with the approval number: 202115202. All participants provided informed consent to participate in the study.

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Data availability statement

The data supporting the findings of this study are available in the manuscript or supplementary tables.

CRediT authorship contribution statement

Ming Gao: Writing - original draft, Resources, Methodology, Investigation. **Xiaomin Xing:** Writing - original draft, Methodology, Investigation. **Wenbiao Hao:** Resources, Methodology. **Xulei Zhang:** Methodology, Investigation. **Kexin Zhong:** Methodology, Investigation. **Canhui Lu:** Supervision, Resources. **Xilong Deng:** Supervision, Resources, Investigation, Funding acquisition, Conceptualization. **Lei Yu:** Writing - review & editing, Writing - original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e24030.

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