Boosting of serum neutralizing activity against the Omicron variant among recovered COVID-19 patients by BNT162b2 and CoronaVac vaccines

Lu Lu,[a,1] Lin-Lei Chen,[a,1] Ricky Rui-Qi Zhang,[b,1] Owen Tak-Yin Tsang,[c,1] Jacky Man-Chun Chan,[c] Anthony Raymond Tam,[d] Wai-Shing Leung,[c] Thomas Shiu-Hong Chik,[c] Daphne Pui-Ling Lau,[c] Chris Yau-Chung Choi,[c] Carol Ho-Yan Fong,[a] Jian-Piao Cai,[a] Hoi-Wah Tsoi,[a] Charlotte Yee-Ki Choi,[a] Xiaojuan Zhang,[a] Syed Muhammad Umer Abdullah,[a] Brian Pui-Chun Chan,[a] Kwok-Hung Chan,[a,f] Kwok-Yung Yuen,[a,e,f,g] Ivan Fan-Ngai Hung,[b,d] and Kelvin Kai-Wang To [a,e,f,g]*

[a]State Key Laboratory for Emerging Infectious Diseases, Carol Yu Centre for Infection, Department of Microbiology, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong Special Administrative Region, China
[b]Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong Special Administrative Region, China
[c]Department of Medicine and Geriatrics, Princess Margaret Hospital, Hong Kong Special Administrative Region, China
[d]Department of Medicine, Queen Mary Hospital, Pokfulam, Hong Kong Special Administrative Region, China
[e]Department of Microbiology, Queen Mary Hospital, Pokfulam, Hong Kong Special Administrative Region, China
[f]Centre for Virology, Vaccinology and Therapeutics, Hong Kong Science and Technology Park, Hong Kong Special Administrative Region, China.
[g]Department of Clinical Microbiology and Infection Control, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China

Summary

Background SARS-CoV-2 Omicron variant evades immunity from past infection or vaccination and is associated with a greater risk of reinfection among recovered COVID-19 patients. We assessed the serum neutralizing antibody (NAb) activity against Omicron variant (Omicron NAb) among recovered COVID-19 patients with or without vaccination.

Methods In this prospective cohort study with 135 recovered COVID-19 patients, we determined the serum NAb titers against ancestral virus or variants using a live virus NAb assay. We used the receiver operating characteristic analysis to determine the optimal cutoff for a commercially-available surrogate NAb assay.

Findings Among recovered COVID-19 patients, the serum live virus geometric mean Omicron NAb titer was statistically significantly higher among BNT162b2 recipients compared to non-vaccinated individuals (85.4 vs 5.6, $P < 0.0001$). The Omicron seropositive rates in live virus NAb test (NAb titer $\geq$10) were statistically significantly higher among BNT162b2 (90.6% [29/32];$P < 0.0001$) or CoronaVac (36.7% [11/30]; $P = 0.0115$) recipients when compared with non-vaccinated individuals (12.3% [9/73]). Subgroup analysis of CoronaVac recipients showed that the Omicron seropositive rates were higher among individuals with two doses than those with one dose (85.7% vs 21.7%; $P = 0.0045$). For the surrogate NAb assay, a cutoff of 109.1 AU/ml, which is 7.3-fold higher than the manufacturer's recommended cutoff, could achieve a sensitivity and specificity of 89.5% and 89.8%, respectively, in detecting Omicron NAb.

Interpretation Among individuals with prior COVID-19, one dose of BNT162b2 or two doses of CoronaVac could induce detectable serum Omicron NAb. Our result would be particularly important for guiding vaccine policies in countries with COVID-19 vaccine shortage.

Funding Health and Medical Research Fund, Richard and Carol Yu, Michael Tong (see acknowledgments for full list).

eBioMedicine 2022;79: 103986
Published online xxx
https://doi.org/10.1016/j.ebiom.2022.103986

*Corresponding author at: Department of Microbiology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Block T, Queen Mary Hospital, Pokfulam, Hong Kong Special Administrative Region, China.
E-mail address: kelvinto@hku.hk (K.K.-W. To).

[1] These authors contribute equally to this work.

Keywords: COVID-19; SARS-CoV-2; Omicron variant; Neutralizing antibody; Surrogate neutralizing antibody test; Spike protein receptor binding domain; Beta variant; Delta variant; mRNA vaccine; Inactivated vaccine

Research in context

Evidence before this study

SARS-CoV-2 Omicron variant has become the dominant variant circulating globally in late 2021/early 2022. The main aim of this study is to assess the neutralizing antibody against the Omicron variant among individuals with prior COVID-19. We searched PubMed without language restrictions on 4th February 2022 for articles using the terms "COVID-19" or "SARS-CoV-2", and "Omicron variant", and "neutralizing antibody". Several studies assessed the neutralizing antibody response against the Omicron variant among recovered COVID-19 patients, but most did not include sera collected more than 1 year post-infection. Two studies included CoronaVac recipients who had prior COVID-19. However, none assessed the difference between one or two doses of CoronaVac among these recovered individuals.

Added value of this study

We found that among individuals with prior COVID-19, BNT162b2 or CoronaVac recipients had a higher geometric mean neutralizing antibody titer and seropositive rate against the Omicron variant than those without vaccination. One dose of BNT162b2 achieved detectable live virus NAb against the Omicron, Beta and Delta variant for most individuals with prior COVID-19. In contrast, individuals with two doses of CoronaVac had a significantly better NAb response than those with a single dose. Surrogate NAb level correlate with live virus NAb titers, but a higher cutoff of surrogate NAb level is required to predict a seropositive result in the live virus NAb assay.

Implications of all the available evidence

Our results showed that one dose of BNT162b2 or two doses of CoronaVac would be sufficient to induce neutralizing antibody activity against the Omicron variant in the majority of recovered COVID-19 patients, although the protective titer for Omicron variant is yet to be determined. Our findings would be especially important in countries where there is a shortage of COVID-19 vaccines. Furthermore, as CoronaVac is used in over 50 countries worldwide, our study could help guide vaccination policies in such countries.

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic has led to over 5.6 million deaths globally since first reported in late 2019.[1] Severe cases have overwhelmed the healthcare system. COVID-19 vaccines have been proven to be highly effective in clinical trials and in post-marketing surveillance, especially against severe disease.[2]

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to circulate across the globe due to the high prevalence of reinfection and vaccine-breakthrough infections, which in turn are associated with waning neutralizing antibody (NAb) titers among COVID-19 patients or vaccine recipients.[3–7] The persistence of SARS-CoV-2 in the human population is also contributed by the appearance of variants, especially those designated as Variants of Concern (VOCs) by the World Health Organization (WHO). VOCs are known to be highly transmissible and able to partially evade immunity induced by natural infection or vaccination.[8] The Alpha and Delta variants have been associated with more severe disease and higher transmissibility.[9–11] The Beta variant can partially evade neutralizing antibodies and poses a higher risk of reinfection,[8,12,13] but is outcompeted by the Alpha variant in competition experiments.[14] The combined effect of enhanced transmissibility and partial immune escape make it difficult to control the pandemic even when the population is immune to the previously circulating variants.[15]

The recently emerged Omicron variant, first found in South Africa, Botswana, and Hong Kong in November 2021,[16] has spread at an unprecedented speed, with a doubling time of only 2–3 days.[17] The household transmission risk is higher for the Omicron variant compared to the Delta variant,[18] and the Omicron variant has been observed to be transmitted between travelers in a quarantine hotel in Hong Kong without any apparent direct contact.[16] As the Omicron variant carries numerous mutations at the spike protein receptor binding domain (RBD) which is the main target of neutralizing antibodies, there is a concern that this variant can evade humoral immunity induced by natural SARS-CoV-2 infection or COVID-19 vaccine. Recent studies have shown that sera collected from vaccine recipients of different platforms have poor NAb titers against the Omicron variant.[19–25] Preliminary analysis showed that vaccine effectiveness against symptomatic diseases caused by the Omicron variant is lower compared to Delta variant.[26,27] A retrospective analysis in South Africa showed that the Omicron variant was associated with an increased risk of reinfection.[28]

As there are already over 280 million confirmed COVID-19 cases worldwide and seroprevalence studies

suggest that the true number of infected individuals can be much higher,[29–31] there is an urgent need to assess the risk of recovered COVID-19 patients from reinfection by the Omicron variant. Hence, in this study, we assessed the serum neutralizing activity against Omicron variant among recovered patients. In particular, we compared the NAb titers against the Omicron variant (Omicron NAb) between individuals without vaccination and those who received BNT162b2 (Pfizer-BioNTech) or CoronaVac (SinoVac) vaccines after recovery from COVID-19. For CoronaVac recipients, we compared the NAb titer after 1 and 2 doses. We also determined the utility of a commercially-available surrogate NAb assay on the prediction of Omicron NAb.

Methods

Human subjects

This is a part of a prospective study conducted at Queen Mary Hospital and Princess Margaret Hospital in Hong Kong. We included patients who had RT-PCR confirmed SARS-CoV-2 infection. These patients were initially hospitalized for COVID-19 between January 2020 and February 2021. We excluded patients if they were aged 17 years or younger, or if serial specimens were not collected. Serial blood samples were collected during follow-up visit at out-patient clinics. Some patients in the vaccinated cohort were included in our previous study.[32] Under elimination strategy, all individuals with laboratory-confirmed COVID-19 are isolated in hospitals. For asymptomatic patients, the day of hospitalization was used as the date of symptom onset.

Ethics statement

Written informed consent was obtained from all recruited patients. The Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 13–265 and UW 21–214) and the Kowloon West Cluster REC (KW/EX-20-038 [144–26]) have approved this study.

Viral culture

Viral culture was performed in a biosafety level 3 facility as we described previously.[19] Briefly, TMPRSS2-expressing VeroE6 (VeroE6/TMPRSS2) cells (JCRB Cat#JCRB1819; RRID:CVCL_YQ49) were seeded with 100 μL of minimum essential medium (MEM) (Gibco®, Thermo Fisher Scientific; Cat#11095) with 10% fetal bovine serum (FBS) and 5 mg/mL G418 (Gibco®, Thermo Fisher Scientific; Cat# 10131027) at 4×10^4 cells in 96-well plate (TPP™ 96-Well, Cell Culture-Treated, Flat-Bottom Microplate; Cat#92096). The plates were incubated at 37 °C in a carbon dioxide incubator until confluence for inoculation. Each well was inoculated with 30 μL of clinical specimen. One hour after incubation, the clinical specimen was removed and cells were replenished with 100 μL of MEM medium with 1% FBS, 100 U/ml penicillin-streptomycin (Gibco®, ThermoFisher Scientific; Cat# 15140122), 100 U/ml of nystatin (Gibco®, ThermoFisher Scientific; Cat# 15340029), and 25 mM HEPES (Gibco®, ThermoFisher Scientific; Cat# 15630080). The cells were incubated at 37 °C with 5% CO_2 and observed 2,3 times per day for virus-induced cytopathic effect (CPE). Cultures with more than 50% virus-induced cytopathic effect were expanded to large volume in VeroE6/TMPRSS2 cells with the same culture condition. The 50% tissue culture infective doses ($TCID_{50}$) were determined in VeroE6/TMPRSS2 cells.

The whole genome sequence of the culture isolates was determined using nanopore sequencing (Oxford Nanopore Technologies) in our previous studies.[12,19] The SARS-CoV-2 ancestral virus isolate belong to a lineage A virus (GISAID accession number: EPI_ISL_434571). The three variants included a Beta variant isolate (GISAID accession number: EPI_ISL_2423556), a Delta variant isolate (GISAID accession number: EPI_ISL_3221329), and an Omicron variant BA.1 isolate (GISAID accession number EPI_ISL_7138045).

Live virus neutralization antibody assays

Live virus NAb assay was performed on VeroE6/TMPRSS2 cells and the live virus NAb titer was determined as we described previously.[19] Briefly, serum samples were heat inactivated at 56 °C for 30 min and were serially diluted in 2-folds with MEM containing 1% FBS. Duplicates of each diluted serum were mixed with a SARS-CoV-2 virus isolate to reach final concentration of 100 $TCID_{50}$ per 100 µl of serum-virus mixture and were incubated at 37 °C for 1 h. After incubation, the 100 μL of the serum-virus mixture was then added to VeroE6/TMPRSS2 cells that were seeded in 96-well plates 24 h before infection. The cells were incubated with the mixture at 37 °C. After incubation for 3 days, CPE was examined (Supplementary Fig. S1). The live virus NAb titer was determined as the highest dilution with 50% inhibition of CPE. A live virus neutralizing antibody titer of $\geq$10 was considered positive. For statistical analysis, a value of 5 was assigned if the live virus neutralizing antibody titer is <10.

Surrogate neutralizing antibody and binding antibody assays

Commercially available RBD IgG, spike IgM, N IgG, N IgM and surrogate NAb assay used in this study are listed in Supplementary Table S1.[33]

Statistical analysis

All statistical analysis was performed using SPSS 26.0 (IBM SPSS Statistics; RRID:SCR_019096) or

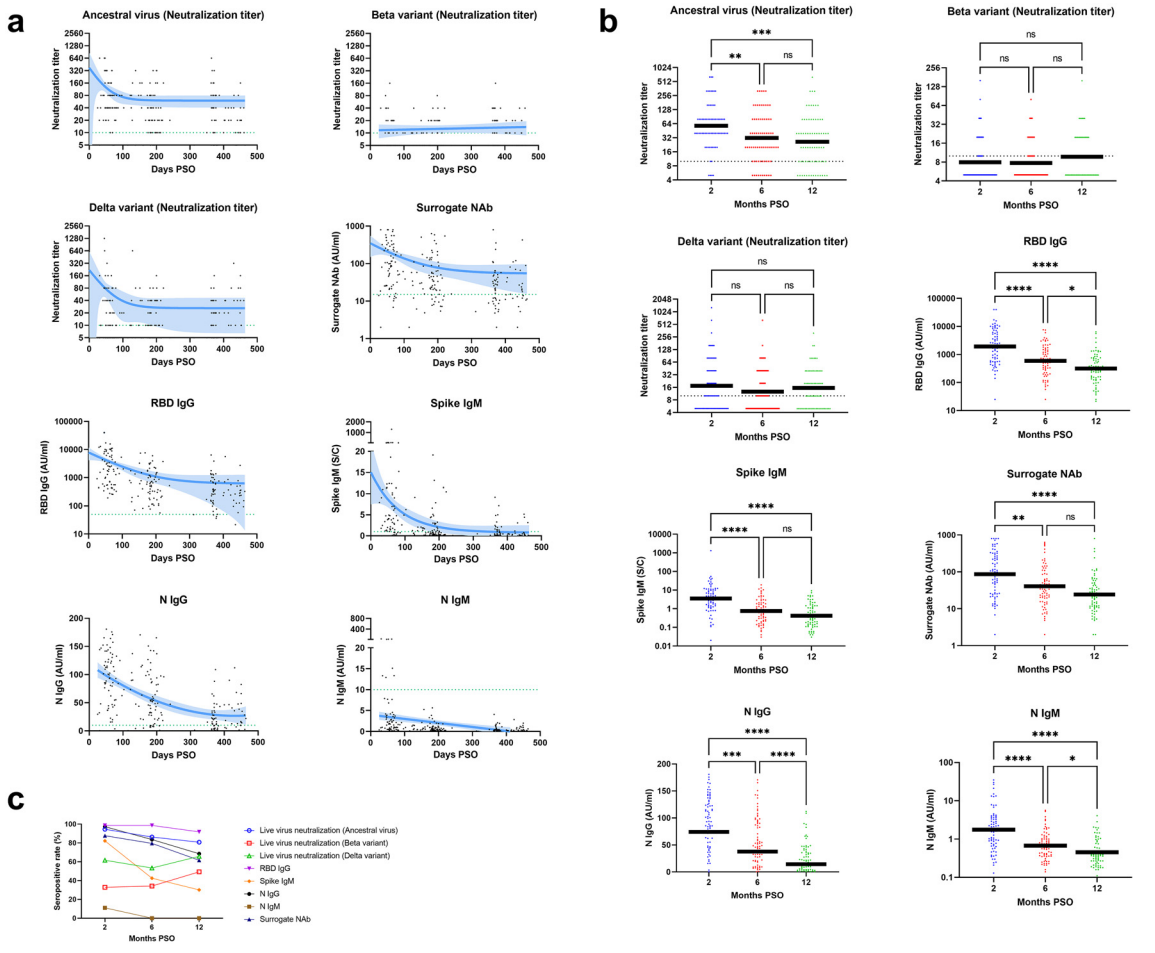

Figure 1. Long term antibody kinetics in 73 non-vaccinated recovered COVID-19 patients.

(a) Each black dot represents a serum sample from a recovered patient. The thick blue line represents the best fit curve whereas the surrounding blue area represents the 95% confidence interval. Horizontal green dotted line represents either the limit of detection or the cutoff recommended by the manufacturer. For the purpose of calculating the trend, we have excluded one outlier for spike IgM, and 4 outliers for RBD IgG. The *p*-values for selecting the best fit curves for each dataset are given in Supplementary Table S2. Abbreviations: N, nucleoprotein; NAb. Neutralizing antibody; PSO, post-symptom onset; RBD, receptor binding domain; S/C: signal-to-cutoff ratio.

(b) Antibody titers at different periods. For x-axis, the median interval between symptom onset and sample collection of the 2 months, 6 months and 12 months time points are 61 days, 184 days and 376 days. The thick black horizontal line indicates the geometric mean. Statistical analysis was performed using Kruskal-Wallis test. ns, not significant; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$.

(c) Comparison of seropositive rate between live virus neutralizing antibody, surrogate neutralizing antibody, and binding antibody assays. For live virus neutralizing antibody assay, a serum specimen is considered to be seropositive if the neutralizing antibody titer was ≥10.

GraphPad Prism 9.3.1.471 for Windows (GraphPad Software, San Diego CA, USA. RRID:SCR_002798). For the longitudinal analysis of antibody results in Figure 1, a best fit curve was computed and overlaid on each plot. We tested whether the data fit a linear model, a one phase decay model, a two phase decay model, or a second order polynomial model, and chose the best model via an extra sum-of-squares F test as described.[34] We performed pairwise comparisons of all models, with the assumption that the data followed either a model specified by the null hypothesis or one specified by an alternate hypothesis. When the *P* value could be explicitly computed, we picked the null hypothesis when $P \geq 0.05$, or the alternate hypothesis when $P < 0.05$. For scenarios when it was not possible to compute the *P* value, we retained the simpler model. The results are summarized in Supplementary Table S2.

For the purpose of statistical analysis, a live virus NAb titer of <10 was considered as 5, and log-transformed titers were used for the calculation of statistical

differences. Fisher's exact test was used in assessing proportions and Mann Whitney U test was used to compare continuous variables between two groups. The non-parametric ANOVA Kruskal Wallis test or Friedman's test were used in comparing the three patient groups (non-vaccinated, BNT162b2 recipient, CoronaVac recipient) or the four viruses (ancestral virus, Beta variant, Delta variant, Omicron variant). Correlation of antibody titers were determined using Spearman rho. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff for the surrogate NAb assay. We chose the cutoff which maximized the summation of sensitivity and specificity.[35] Multivariate analysis was performed using backward stepwise multivariate regression analysis, and included variables with a P value of <0.1 in the univariate analysis. A P value of <0.05 was considered to be statistically significant.

Role of funding source

The funding source had no role in the study design, data collection, data analysis, interpretation, or writing of the manuscript.

Results

Antibody kinetics of recovered COVID-19 patients prior to vaccination

First, we assessed the antibody kinetics of 73 recovered COVID-19 adult patients without SARS-CoV-2 vaccination during the time of serum sample collection (Supplementary Table S3). Serial samples were collected from each patient at about 2 months (median: 61 days; interquartile range [IQR]: 50–70 days), 6 months (median: 184 days, IQR: 176–199 days) and 12 months (median: 376 days, IQR: 369–433 days) post symptom onset (PSO). For all antibody assays, there was a general trend in decreasing antibody titers except for live virus NAb against the Beta variant (Figure 1a). The decline of live virus NAb titers against the ancestral virus and the Delta variant, the surrogate NAb titer and the levels of IgG against RBD occurred mainly during the first few months after symptom onset. There was a statistically significant decrease in live virus NAb titers against the ancestral virus at 6 or 12 months when compared with 2 months (Figure 1b). However, there was no significant difference in the live virus NAb titer against the Beta or Delta variants among the 3 times periods, likely because many of the samples had NAb titer below the detection threshold. There was a significant decrease in the levels of surrogate NAb and all IgM or IgG when compared with previous time periods.

For live virus NAb assay, 94.5% (69/73) of serum specimens at 2 months PSO had a detectable NAb against the ancestral virus, but has decreased to 80.8% (59/73) at 12 months PSO (Figure 1c). However, the percentage of serum specimens with detectable NAb against the Beta and Delta variants were similar for all 3 periods. Notably, the seropositive rate of RBD IgG remained >90% throughout all time periods, but the seropositive rate of IgM against spike and N protein were particularly low.

BNT162b2 and CoronaVac enhanced the neutralizing antibody response against the Omicron variant in recovered COVID-19 patients

Next, we determined the serum live virus NAb titers against ancestral virus and different variants among non-vaccinated individuals and those who have received BNT162b2 or CoronaVac after recovery from COVID-19. The vaccinated group consisted of a total of 62 patients, including 32 who received BNT162b2 and 30 who received CoronaVac (Supplementary Table S3). The serum specimens in the vaccinated group were collected at a median of 386 days PSO (IQR 368–458 days), which was not statistically significantly different from the collection date for the "12-month" sample for the non-vaccinated group (P = 0.1456; Mann Whitney U test). There was no statistically significant differences in the age, sex, disease severity and comorbidities between the 62 vaccinated and the 73 non-vaccinated individuals. There was no statistically significant difference in the median days after the first dose of vaccine between BNT162b2 and CoronaVac (34 days [IQR: 26-57] vs 42.5 days [IQR: 29-56], P = 0.3602, Mann Whitney U test).

BNT162b2 and CoronaVac recipients had significantly higher geometric mean NAb titer against ancestral virus, Beta variant and Delta variant than those of non-vaccinated individuals (Figure 2a–c). BNT162b2 recipients also had significantly higher geometric mean Omicron NAb titer than those of non-vaccinated individuals (85.4 vs 5.6, P < 0.0001; Kruskal-Wallis test) (Figure 2d). CoronaVac recipients had a higher geometric mean NAb titer against Omicron variant than the non-vaccinated individuals, though not reaching statistical significance (8.5 vs 5.6, P = 0.1171; Kruskal-Wallis test) (Figure 2d). The seropositive rates for live virus NAb against ancestral virus and all variants were significantly higher for either BNT162b2 or CoronaVac recipients than those for non-vaccinated individuals (Table 1). In particular, there was a large difference in the seropositive rate for live virus Omicron NAb between the vaccinated (BNT162b2, 90.6% [29/32]; CoronaVac, 36.7% [11/30]) and non-vaccinated individuals (12.3% [9/73]) (BNT162b2 vs non-vaccinated, P < 0.0001; CoronaVac vs non-vaccinated, P = 0.0115; Fisher's exact test). Univariate analysis showed that receiving BNT162b2 is statistically significantly associated with detectable NAb (P < 0.001; Fisher's exact test), and multivariate analysis confirmed that receiving BNT162b2 was the only

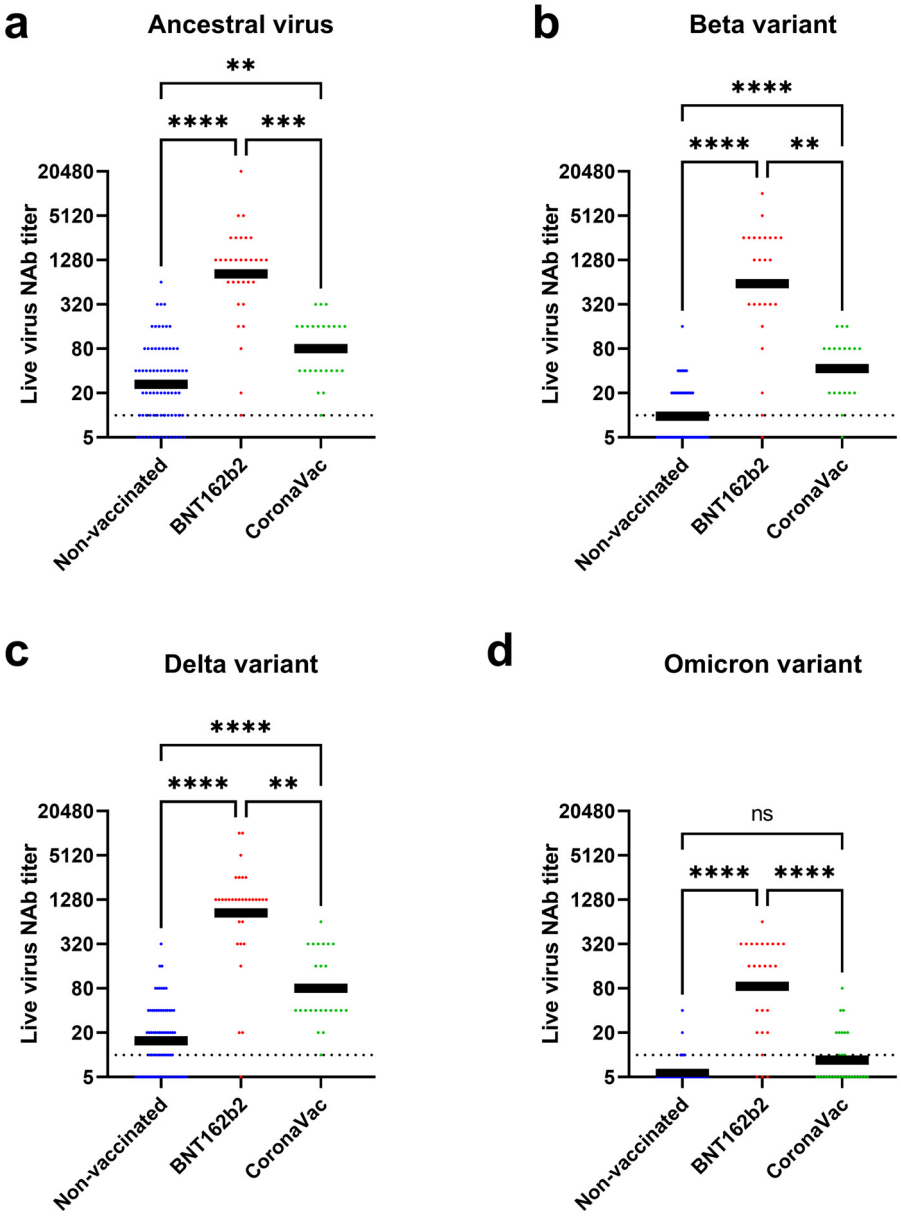

Figure 2. Comparison of live virus neutralizing antibody titer against ancestral virus and variants between recovered COVID-19 patients who are non-vaccinated ($n = 73$) and those who have received BNT162b2 ($n = 32$) or CoronaVac ($n = 30$). (a) Ancestral virus; (b) Beta variant; (c) Delta variant; (d) Omicron variant. The serum specimens were for all groups were collected at a median of 12 months post-symptom onset. Thick black horizontal bars indicate the geometric mean neutralizing antibody titer. Horizontal dotted line represents the limit of detection for the live virus neutralizing antibody assay. Statistical analysis was performed using Kruskal-Wallis test. ns, not significant; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$.

factor that is independently associated with NAb seropositivity against the Omicron variant ($P < 0.001$; multivariate logistic regression) (Table 2).

For non-vaccinated individuals, there were statistically significant reduction in live virus NAb against Beta (2.7-fold reduction, $P < 0.0001$, Friedman test), Delta (1.7-fold reduction, $P = 0.0063$, Friedman test) or Omicron variant (4.7-fold reduction, $P < 0.0001$, Friedman test) when compared with those against the ancestral virus (Figure 3a). For both BNT162b2 and CoronaVac recipients, there was also a statistically significant reduction in the geometric mean NAb titer between ancestral virus and Omicron variant (BNT162b2: 9.7-fold reduction, $P < 0.0001$; CoronaVac: 9.4-fold reduction; $P < 0.0001$, Friedman test) (Figure 3b and c). However, there was no statistically significant difference in the

	Non-vaccinated (*n* = 73)	BNT162b2 recipient (*n* = 32)[a]	*P* value[b] (BNT162b2 vs non-vaccinated)	CoronaVac recipient (*n* = 30)[c]	*P* value[b] (CoronaVac vs non-vaccinated)
Ancestral virus	59 (80.8)	32 (100)	0.0049	30 (100)	0.0090
Beta variant	36 (49.3)	31 (96.9)	<0.0001	29 (96.7)	<0.0001
Delta variant	48 (65.8)	31 (96.9)	0.0004	30 (100)	<0.0001
Omicron variant	9 (12.3)	29 (90.6)	<0.0001	11 (36.7)	0.0115

***Table 1*: Seropositive rate of live virus neutralization antibody assay against ancestral virus and different variants Data expressed as no. (%).**

[a] Overall, serum specimens were collected at a median of 34 days (Interquartile range [IQR]: 26−57 days) after the 1st dose of BNT162b2. Among the 30 patients who received only 1 dose of BNT162b2, the serum specimens were collected at a median of 33 days (IQR: 26−51 days) after the 1st dose of BNT162b2.

[b] Fisher's exact test

[c] Overall, serum specimens were collected at a median of 42.5 days (IQR]: 29-56 days) after the 1st dose of CoronaVac. Among the 23 patients who received only 1 dose of CoronaVac, the serum specimens were collected at a median of 38 days (IQR: 27−51 days) after the 1st dose of CoronaVac. Among the 7 patients who received 2 doses of CoronaVac, the serum specimens were collected at a median of 55 days (IQR: 53−68 days) after the 1st dose of CoronaVac.

	Neutralization Ab titer		*P* value[a]	
	<10 (*n* = 22)	≥10 (*n* = 40)	Univariate analysis	Multivariate analysis
Demographics				
Age in years, median (range)	53 (21-85)	57 (23-76)	0.073	0.083
Female sex, no. (%)	11 (50.0)	22 (55.0)	0.793	N/A
Disease severities				
Require oxygen supplementation	3 (13.6)	3 (7.5)	0.657	N/A
Admitted to intensive care unit	1 (4.5)	1 (2.5)	1.000	N/A
Comorbidities				
Hypertension	2 (9.1)	7 (17.5)	0.471	N/A
Chronic heart disease	0 (0)	2 (5.0)	0.535	N/A
Chronic lung disease	0 (0)	2 (5.0)	0.535	N/A
Chronic liver disease	0 (0)	3 (7.5)	0.546	N/A
Chronic kidney disease	0 (0)	0 (0)	N/A	N/A
Neurological disorders	2 (9.1)	2 (5.0)	0.610	N/A
Diabetes mellitus	4 (18.2)	2 (5.0)	0.174	N/A
Malignancy	2 (9.1)	1 (2.5)	0.285	N/A
Connective tissue disease	0 (0)	1 (2.5)	1.000	N/A
None	14 (63.6)	22 (55.0)	0.596	N/A
Vaccination type				
CoronaVac	19 (86.4)	11 (27.5)	<0.001	<0.001
BNT162b2	3 (13.6)	29 (72.5)		

***Table 2*: Factors associated with detectable neutralizing antibody activity against the Omicron variant among the 62 vaccinated individuals.**

N.A, not applicable

[a] Mann Whitney U test was used for continuous variables. Fisher's exact test was used for categorical variables.

geometric mean NAb titer between the ancestral virus and Beta or Delta variants for either BNT162b2 or CoronaVac recipients.

Comparison of neutralizing antibody activity against Omicron variant between one and two doses of vaccine

Among the 30 CoronaVac recipients, 23 received one dose while 7 received two doses. The geometric mean NAb titer was significantly higher among individuals with 2 doses than those with 1 dose (18.1 vs 6.8; $P = 0.0018$; Mann Whitney U test) (Figure 4a). The seropositive rate for Omicron NAb was significantly higher for patients who had received two doses compared to patients who had received one dose (85.7% [6/7] vs 21.7% [5/23], $P = 0.0045$; Fisher's exact test) (Figure 4b). For BNT162b2, 90.6% (29/32) recipients had detectable NAb against Omicron variant. However, due to the small number of patients who received two

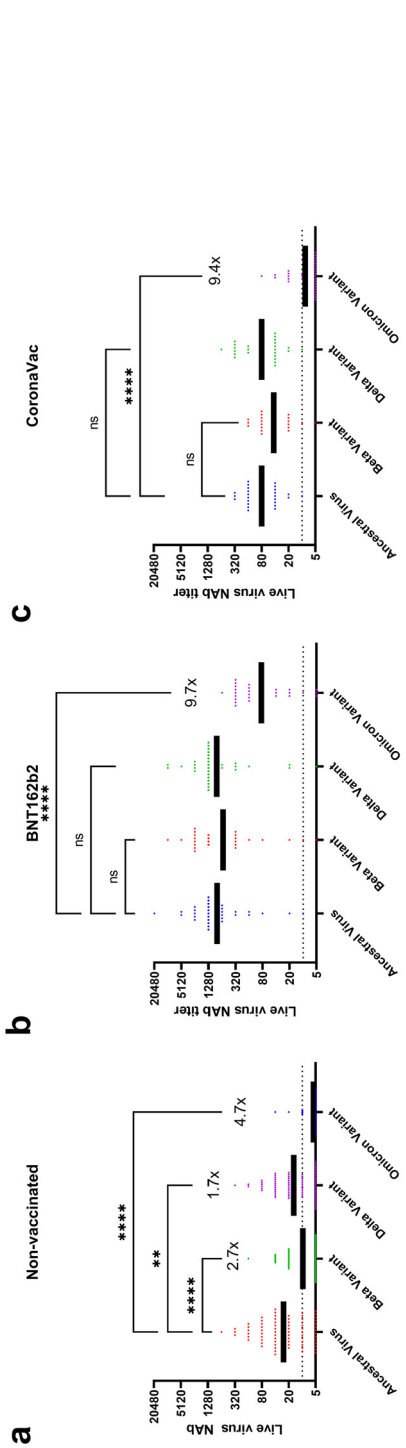

Figure 3. Comparison of live virus neutralizing antibody activity against ancestral virus and different variants. (a) Non-vaccinated (n = 73); (b) BNT162b2 recipients (n = 32); (c) CoronaVac recipients (n = 30). The serum specimens for all groups were collected at a median of 12 months post-symptom onset. For each variant, the fold reduction compared with ancestral virus is shown. Thick black horizontal bars indicate the geometric mean neutralizing antibody titer. Horizontal dotted line represents the limit of detection for the live virus neutralizing antibody assay. Statistical analysis was performed using Friedman's test.

doses of BNT162b2 vaccines (n = 2), we could not determine whether two doses of BNT162b2 vaccine was superior to one dose.

Correlation between surrogate neutralizing antibody and live virus neutralizing antibody assays

Surrogate NAb assay is a commonly used commercially available antibody assay for the determination of NAb levels since it has better correlation with live virus NAb titer than that for other binding antibody assays.[36] However, currently available commercial surrogate NAb assays were designed based on the ancestral SARS-CoV-2 RBD, and therefore may not be suitable for variants with RBD mutations. Here, we compared the surrogate NAb levels with the live virus NAb titers against the ancestral virus or the Omicron variant among the 135 recovered patients with or without COVID-19 vaccine. Surrogate NAb level positively correlated with live virus NAb titer against ancestral virus (Spearman rho=0.908; 95% confidence interval [95% CI], 0.871–0.934; $P < 0.0001$) (Figure 5a) or Omicron variant (Spearman rho=0.797 [95% CI, 0.724–0.853]; $P < 0.0001$) (Figure 5b). Using the surrogate NAb manufacturer's cutoff of 15 AU/ml, the sensitivity of surrogate NAb for live virus NAb assay was 86.0% (95% CI, 78.7–91.0) and 100% (95% CI, 92.7–100) for ancestral virus and Omicron variant, respectively; while the specificity was 92.9% (95% CI, 68.5–99.6) and 34.9% (95% CI, 25.7–45.4) for the corresponding viruses.

In the ROC curve analysis, the surrogate NAb had similar area under the ROC curve (AUC) for ancestral virus (0.959 [95% CI, 0.916–1.000]) and Omicron variant (0.961 [95% CI, 0.931–0.990]) (Figure 5c and d). For ancestral virus, a surrogate NAb of 11.73 AU/ml have a sensitivity of 92.9% (95% CI, 68.5–99.6) and a specificity of 93.4% (95% CI, 87.5–96.6), which is similar to the manufacturer's cutoff of 15 AU/ml. For Omicron variant, a surrogate NAb cutoff of 109.1 AU/ml, which is 7.3 times higher than the manufacturer's recommended cutoff, could achieve a sensitivity of 89.5% (95% CI, 81.3–94.4) and a specificity of 89.8% (95% CI, 78.2–95.6).

Discussion

In this study that included patients previously infected in 2020 or early 2021, only 12.3% of 73 non-vaccinated recovered COVID-19 patients had detectable NAb against the Omicron variant. In contrast, at a median of 33 days after just one dose of BNT162b2, Omicron NAb could be detected in 92.3% of recovered COVID-19 patients. For CoronaVac, Omicron NAb could be detected in 21.7% and 85.7% of individuals after 1 (at a median of 38 days after 1st dose) and 2 doses (median 55 days after 1st dose), respectively. As we have included patients from different adult age groups and disease

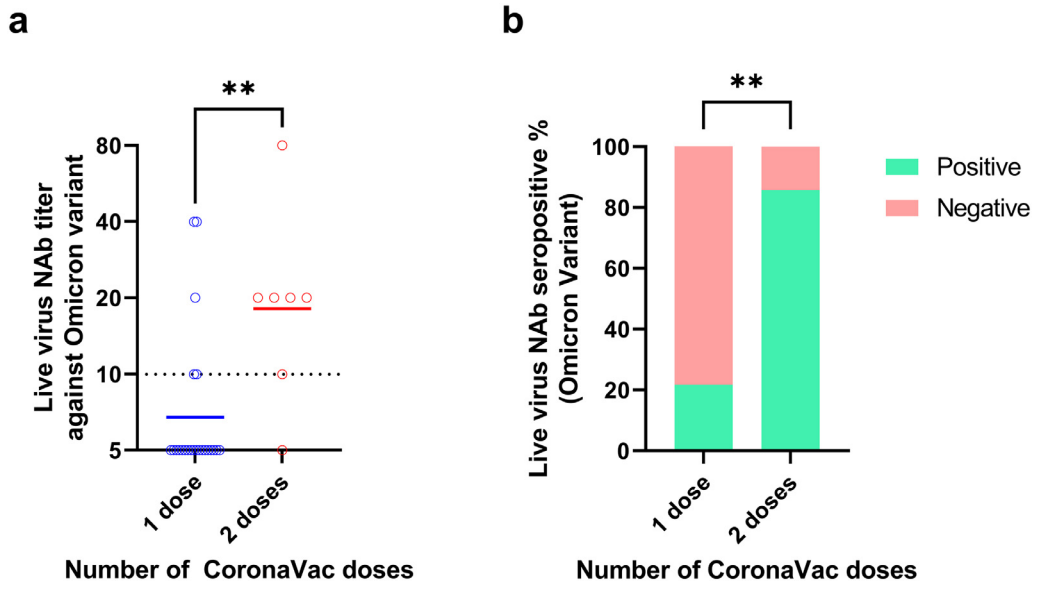

Figure 4. Comparison of live virus neutralizing antibody activity against the Omicron variant between one (n = 23) and two doses (n = 7) of CoronaVac. (a) Comparison of live virus neutralizing antibody titer against the Omicron variant. Horizontal bars indicate the geometric mean neutralizing antibody titer. Horizontal dotted line represents the limit of detection for the live virus neutralizing antibody assay. Mann Whitney U test was used for the statistical analysis. (b) Comparison of seropositive rate for Omicron variant. A neutralizing antibody titer of ≥10 was considered as seropositive. Fisher's exact test was used for the statistical analysis.

severity, our data are representative of the wider population. Our study concurs with previous studies which showed that boosting with vaccination greatly enhanced Omicron NAb titers among recovered COVID-19 patients.[23,25,37–40] However, these studies mainly assessed 2 doses of vaccines among the recover COVID-19 patients, and only few have assessed the NAb titer with CoronaVac.[39,40] Since NAb titers have a positive correlation with protection from reinfection or vaccine breakthrough infection in both human and animal studies,[41–44] vaccination in recovered COVID-19 patients will likely reduce the risk of reinfection by the Omicron variant or other variants.

BNT162b2 and CoronaVac are two of the most commonly administered COVID-19 vaccine worldwide.[45,46] We showed that recovered patients developed much better NAb response after boosting with BNT162b2 compared to boosting with CoronaVac. This is consistent with previous studies which showed a weaker NAb response among recipients of inactivated vaccines compared to mRNA vaccines.[19,24,32,39,40,47] However, we did not assess the T cell response, which may be important for the prevention of severe disease. Gilbert et al. has shown that COVID-19 vaccine efficacy of an mRNA vaccine was 51% even when NAb titer was undetectable, and estimated that NAb mediated only two-thirds of the vaccine efficacy.[41] Previous studies have shown that CoronaVac can induce a broad T cell response against both ancestral virus and VOCs, but there is conflicting data on whether CoronaVac or BNT162b2 can induce higher CD4+ and CD8+ T cell responses to structural proteins.[48,49,54] Despite the relatively lower NAb titers against the Omicron variant, the inactivated vaccines may still offer protection against the Omicron variant, especially against severe disease.

In the non-vaccinated cohort, there was a 2.7-fold and 1.7-fold reduction in NAb against Beta and Delta variants when compared with ancestral virus, respectively. However, in the vaccinated cohort, there was no statistically significant difference in the live virus NAb titers between ancestral virus and the Delta variant, and there was a <2-fold difference between the ancestral virus and the Beta variant. This suggest that vaccination, either by mRNA or inactivated whole-virion vaccine, can increase the breadth of antibody response against heterologous virus. This may be due to the somatic hypermutation and affinity maturation in the memory B cell population after natural infection. Dan et al. has shown that spike-specific memory B cells were more abundant at 6 months than at 1 month PSO.[34] Upon vaccination, high potency matured antibody targeting conserved regions of the RBD are rapidly generated, similar to the situation for COVID-19 naÿve subjects with 3 doses of vaccines.[50] However, it should be noted that there is still a large difference between the ancestral virus and the Omicron variant (11.6-fold for BNT162b2; 9.8-fold for CoronaVac), which suggests that the memory B cell elicited by prior infection may not cross react with the Omicron variant as well as for Beta or Delta variant. Unlike the Beta and Delta variant, the Omicron variant

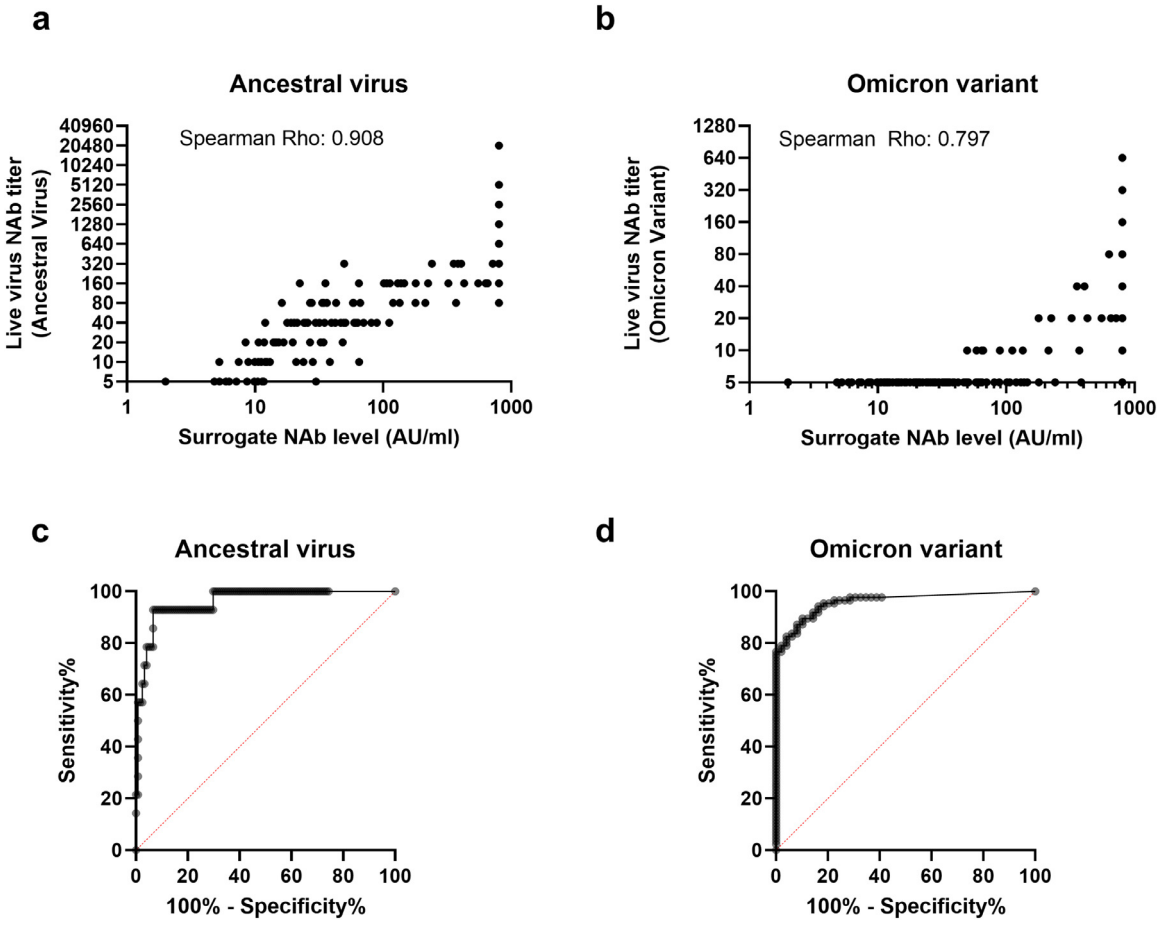

Figure 5. Correlation between surrogate neutralizing antibody level and live virus neutralizing antibody titer. (a, b) Correlation between surrogate neutralizing antibody titer and live virus neutralizing antibody titer against ancestral virus (a) and the Omicron variant (b). (c, d) Receiver operating characteristic curve analysis for ancestral virus (c) and the Omicron variant (d). The data points included the serum specimens collected at approximately 12 months post-symptom onset from the 135 recovered COVID-19 patients.

contains many more mutations at the RBD which can affect antibody binding.[51]

Since live virus NAb assay for SARS-CoV-2 can only be conducted in biosafety level 3 laboratories, most laboratories determine the antibody titer using commercial binding antibody assays or surrogate NAb assay. Surrogate NAb assays are based on antibody-mediated blockage of the interaction between the spike RBD and human ACE2 receptor.[36] Currently available commercial surrogate NAb assays are based on the ancestral virus spike RBD. Previous studies showed that surrogate NAb levels showed good correlation with live virus NAb titers against the homologous ancestral virus.[33,36] Here, we also showed a good correlation between the surrogate NAb with the Omicron variant. Furthermore, we demonstrated that the surrogate NAb assay can have a high sensitivity and specificity for the detection of NAb against the Omicron variant if we choose an appropriate cutoff.

RBD IgG has the highest seropositive rate at all time points, while all other antibody assays have poor sensitivity for determining past infection beyond 6 months. Our results agree with those presented by Peluso et al., who showed that RBD IgG sensitivity remains very high at 6 months post infection.[52] Therefore, anti-RBD IgG is a reliable assay to determine the burden of infection in non-vaccinated populations.

There are several limitations in this study. First, we included only adult patients in this study. Children and adolescents have a distinct humoral immune response from adults,[24,53] and the results obtained from adult patients may not be applicable to pediatric patients. Second, we have not assessed the waning of antibodies after vaccination. Peng et al. showed that there is waning of humoral and T cell immunity at three months after the second dose of vaccination for both BNT162b2 and CoronaVac among individuals without prior infection.[54] Further studies are required to assess waning of

immunity for vaccinees with prior infection. Third, we do not know the virus lineage causing the infection in these recovered individuals. However, they were unlikely infected with either the Beta or Delta variant, as these variants were first detected in Hong Kong after these patients were admitted. Fourth, since the NAb titer against the Omicron variant fell below the detection limit for many serum specimens, the fold reduction between the ancestral virus and the Omicron variant may be underestimated. Fifth, due to the small sample size, we could not perform subgroup analysis to determine the demographic or clinical factors associated with NAb titers. Finally, we were not able to perform a meaningful comparison between one and two doses of BNT162b2 among recovered COVID-19 patients, as there were only two patients in the BNT162b2 group who have received two doses.

COVID-19 vaccination is critical in preventing reinfection by the Omicron variant, which is now dominant in many parts of the world. Although high-income countries are already recommending 3 doses of COVID-19 vaccines, there is a shortage of COVID-19 vaccines especially among developing countries. At the time of writing, the percentage of population who received at least 1 dose of COVID-19 vaccine is still below 20% in most African countries.[55,56] One possible strategy to optimize vaccine usage in these countries is to use one dose instead of two or three doses among recovered patients. Our results suggest that although one dose of BNT162b2 is sufficient to induce neutralizing antibody against the Omicron variant, two doses of CoronaVac are required.

Contributors

LL and KKWT had roles in study design, data collection, data analysis, data interpretation, literature search and writing of the manuscript. OTYT, JMCC, ART, WSL, TSHC, DPLL, CYCC, IFNH had roles in patient recruitment, data collection and/or clinical managements. LL, LLC, RRQZ, CHYF, JPC, HWT, CYKC, XZ, SMUA, BPCC, KHC had roles in performing the experiments, data collection, data analysis, and/or data interpretation. LLC, OTYT, IFNH, KHC, and KYY had roles in study design. LL and KKWT verified the underlying data. LL, LLC, OTYT, SMUA, KYY, IFNH, KKWT had roles in reviewing and editing the final draft. LL and KKWT has directly accessed and verified the underlying data. All authors interpreted the data, revised the manuscript critically for important intellectual content and approved the final version of the manuscript.

Data sharing

Data are available upon reasonable request from the corresponding author.

Declaration of interests

KYY and KKWT report collaboration with SinoVac and Sinopharm. IFNH report collaboration with Sinovac, Sinopharm, Pfizer-BNT-Fosun, and MSD. Other authors declare no conflict of interest.

Acknowledgments

We would like to acknowledge Deborah Ho and Polly Pang for their help in patient recruitement and blood taking, and Ka-Yi Leung and Dan-Lei Liu for their technical support. This work was supported by Health and Medical Research Fund, the Food and Health Bureau, The Government of the Hong Kong Special Administrative Region (Ref no.: COVID190124 and COVID1903010 [Project 1]), and donations of Richard Yu and Carol Yu, Shaw Foundation Hong Kong, Michael Seak-Kan Tong, May Tam Mak Mei Yin, Lee Wan Keung Charity Foundation Limited, Hong Kong Sanatorium & Hospital, Respiratory Viral Research Foundation Limited, Hui Ming, Hui Hoy and Chow Sin Lan Charity Fund Limited, Chan Yin Chuen Memorial Charitable Foundation, Marina Man-Wai Lee, the Hong Kong Hainan Commercial Association South China Microbiology Research Fund, the Jessie & George Ho Charitable Foundation, Kai Chong Tong, Tse Kam Ming Laurence, Foo Oi Foundation Limited, Betty Hing-Chu Lee, and Ping Cham So.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ebiom.2022.103986.

References

1 Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet*. 2020;395:514–523.
2 Tregoning JS, Flight KE, Higham SL, Wang Z, Pierce BF. Progress of the COVID-19 vaccine effort: viruses, vaccines and variants versus efficacy, effectiveness and escape. *Nat Rev Immunol*. 2021;21:626–636.
3 To KK, Hung IF, Ip JD, et al. Coronavirus disease 2019 (COVID-19) Re-infection by a phylogenetically distinct severe acute respiratory syndrome coronavirus 2 strain confirmed by whole genome sequencing. *Clin Infect Dis*. 2021;73:e2946–e2951.
4 Hansen CH, Michlmayr D, Gubbels SM, Molbak K, Ethelberg S. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. *Lancet*. 2021;397:1204–1212.
5 Hall VJ, Foulkes S, Charlett A, et al. SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN). *Lancet*. 2021;397:1459–1469.
6 To KK, Hung IF, Chan KH, et al. Serum antibody profile of a patient with coronavirus disease 2019 reinfection. *Clin Infect Dis*. 2021;72:e659–ee62.
7 Lipsitch M, Krammer F, Regev-Yochay G, Lustig Y, Balicer RD. SARS-CoV-2 breakthrough infections in vaccinated individuals: measurement, causes and impact. *Nat Rev Immunol*. 2022;22:57–65.

8 Cevik M, Grubaugh ND, Iwasaki A, Openshaw P. COVID-19 vaccines: keeping pace with SARS-CoV-2 variants. *Cell*. 2021;184:5077–5081.
9 Twohig KA, Nyberg T, Zaidi A, et al. Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study. *Lancet Infect Dis*. 2022;22:35–42.
10 Davies NG, Abbott S, Barnard RC, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. *Science*. 2021;372:eabg3055.
11 Davies NG, Jarvis CI, Group CCW, et al. Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7. *Nature*. 2021;593:270–274.
12 Chen LL, Lu L, Choi CY, et al. Impact of SARS-CoV-2 variant-associated RBD mutations on the susceptibility to serum antibodies elicited by COVID-19 infection or vaccination. *Clin Infect Dis*. 2021: ciab656. https://doi.org/10.1093/cid/ciab656.
13 Chemaitelly H, Bertollini R, Abu-Raddad LJ. National study group for C-E. Efficacy of natural immunity against SARS-CoV-2 reinfection with the beta variant. *N Engl J Med*. 2021;385:2585–2586.
14 Ulrich L, Halwe NJ, Taddeo A, et al. Enhanced fitness of SARS-CoV-2 variant of concern Alpha but not Beta. *Nature*. 2022;602:307–313.
15 Bushman M, Kahn R, Taylor BP, Lipsitch M, Hanage WP. Population impact of SARS-CoV-2 variants with enhanced transmissibility and/or partial immune escape. *Cell*. 2021;184:6229–6242.e18.
16 Wong SC, Au AK, Chen H, et al. Transmission of Omicron (B.1.1.529) - SARS-CoV-2 variant of concern in a designated quarantine hotel for travelers: a challenge of elimination strategy of COVID-19. *Lancet Reg Health West Pac*. 2022;18:100360.
17 World Health Organization. Enhanced readiness for Omicron (B.1.1.529): technical brief and priority actions for member states; 2021. Available at https://www.who.int/publications/m/item/enhancing-readiness-for-omicron-(b.1.1.529)-technical-brief-and-priority-actions-for-member-states. Accessed 30 December 2021.
18 UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England. Technical Briefing 32. Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1042046/Technical_Briefing_32.pdf. Accessed 18 December 2021.
19 Lu L, Mok BW, Chen LL, et al. Neutralization of SARS-CoV-2 Omicron variant by sera from BNT162b2 or Coronavac vaccine recipients. *Clin Infect Dis*. 2021. https://doi.org/10.1093/cid/ciab1041.
20 Cele S, Jackson L, Khoury DS, et al. Omicron extensively but incompletely escapes Pfizer BNT162b2 neutralization. *Nature*. 2022;602:654–656.
21 Dejnirattisai W, Shaw RH, Supasa P, et al. Reduced neutralisation of SARS-CoV-2 omicron B.1.1.529 variant by post-immunisation serum. *Lancet*. 2022;399:234–236.
22 Hoffmann M, Kruger N, Schulz S, et al. The Omicron variant is highly resistant against antibody-mediated neutralization: implications for control of the COVID-19 pandemic. *Cell*. 2022;185:447–456.e11.
23 Garcia-Beltran WF, St Denis KJ, Hoelzemer A, et al. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 Omicron variant. *Cell*. 2022;185:457–466.e4.
24 Chen LL, Chua GT, Lu L, et al. Omicron variant susceptibility to neutralizing antibodies induced in children by natural SARS-CoV-2 infection or COVID-19 vaccine. *Emerg Microbes Infect*. 2022;11:543–547.
25 Schmidt F, Muecksch F, Weisblum Y, et al. Plasma neutralization of the SARS-CoV-2 Omicron variant. *N Engl J Med*. 2022;386:599–601.
26 UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England Technical briefing 33 (23 December 2021). Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1043680/technical-briefing-33.pdf. Accessed 24 December 2021.
27 Collie S, Champion J, Moultrie H, Bekker LG, Gray G. Effectiveness of BNT162b2 vaccine against Omicron variant in South Africa. *N Engl J Med*. 2022;386:494–496.
28 Pulliam JRC, van Schalkwyk C, Govender N, et al. Increased risk of SARS-CoV-2 reinfection associated with emergence of Omicron in South Africa. *Science*. 2022;2022:eabn4947. https://doi.org/10.1126/science.abn4947.
29 To KK, Cheng VC, Cai JP, et al. Seroprevalence of SARS-CoV-2 in Hong Kong Special Administrative Region and our returnees evacuated from Hubei province of China: a multi-cohort study. *Lancet Microbe*. 2020;1:e111–e118. https://doi.org/10.1016/S2666-5247(20)30053-7.
30 He Z, Ren L, Yang J, et al. Seroprevalence and humoral immune durability of anti-SARS-CoV-2 antibodies in Wuhan, China: a longitudinal, population-level, cross-sectional study. *Lancet*. 2021;397:1075–1084.
31 Kalish H, Klumpp-Thomas C, Hunsberger S, et al. Undiagnosed SARS-CoV-2 seropositivity during the first 6 months of the COVID-19 pandemic in the United States. *Sci Transl Med*. 2021;13: eabh3826.
32 Zhang R, Khong KW, Leung KY, et al. Antibody response of BNT162b2 and CoronaVac platforms in recovered individuals previously infected by COVID-19 against SARS-CoV-2 wild type and delta variant. *Vaccines*. 2021;9:1442. (Basel).
33 Chan KH, Leung KY, Zhang RR, et al. Performance of a surrogate SARS-CoV-2-neutralizing antibody assay in natural infection and vaccination samples. *Diagnostics (Basel)*. 2021;11:1757.
34 Dan JM, Mateus J, Kato Y, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. *Science*. 2021;371:eabf4063.
35 Habibzadeh F, Habibzadeh P, Yadollahie M. On determining the most appropriate test cut-off value: the case of tests with continuous results. *Biochem Med*. 2016;26:297–307. (Zagreb).
36 Tan CW, Chia WN, Qin X, et al. A SARS-CoV-2 surrogate virus neutralization test based on antibody-mediated blockage of ACE2-spike protein-protein interaction. *Nat Biotechnol*. 2020;38:1073–1078.
37 Rossler 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.
38 Carreno JM, Alshammary H, Tcheou J, et al. Activity of convalescent and vaccine serum against SARS-CoV-2 Omicron. *Nature*. 2022;602:682–688.
39 Cheng SMS, Mok CKP, Leung YWY, et al. Neutralizing antibodies against the SARS-CoV-2 Omicron variant BA.1 following homologous and heterologous CoronaVac or BNT162b2 vaccination. *Nat Med*. 2022. https://doi.org/10.1038/s41591-022-01704-7.
40 Perez-Then E, Lucas C, Monteiro VS, et al. Neutralizing antibodies against the SARS-CoV-2 Delta and Omicron variants following heterologous CoronaVac plus BNT162b2 booster vaccination. *Nat Med*. 2022;28:481–485. https://doi.org/10.1038/s41591-022-01705-6.
41 Gilbert PB, Montefiori DC, McDermott AB, et al. Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. *Science*. 2022;375:43–50.
42 Bergwerk M, Gonen T, Lustig Y, et al. Covid-19 breakthrough infections in vaccinated health care workers. *N Engl J Med*. 2021;385:1474–1484.
43 Corbett KS, Nason MC, Flach B, et al. Immune correlates of protection by mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates. *Science*. 2021;373:eabj0299.
44 Mercado NB, Zahn R, Wegmann F, et al. Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques. *Nature*. 2020;586:583–588.
45 Basta N.E. and Moodie E.M.M on behalf of the VIPER (Vaccines IdP, and Epidemiology Research) group COVID-19 vaccine development and approvals tracker team, COVID-19 vaccine development and approvals tracker. Available at https://covid19.trackvaccines.org/. Accessed 31 December 2021.
46 Mallapaty S. China's COVID vaccines have been crucial — now immunity is waning. *Nature*. 2021;598:398–399.
47 Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med*. 2021;27:1205–1211.
48 Melo-Gonzalez F, Soto JA, Gonzalez LA, et al. Recognition of Variants of concern by antibodies and T cells induced by a SARS-CoV-2 inactivated vaccine. *Front Immunol*. 2021;12:747830.
49 Mok CKP, Cohen CA, Cheng SMS, et al. Comparison of the immunogenicity of BNT162b2 and CoronaVac COVID-19 vaccines in Hong Kong. *Respirology*. 2021. https://doi.org/10.1111/resp.14191.
50 Tong P, Gautam A, Windsor IW, et al. Memory B cell repertoire for recognition of evolving SARS-CoV-2 spike. *Cell*. 2021;184:4969–4980.e15.
51 Liu L, Iketani S, Guo Y, et al. Striking antibody evasion manifested by the Omicron variant of SARS-CoV-2. *Nature*. 2022;602:676–681.

52 Peluso MJ, Takahashi S, Hakim J, et al. SARS-CoV-2 antibody magnitude and detectability are driven by disease severity, timing, and assay. *Sci Adv*. 2021;7:eabh3409.
53 Weisberg SP, Connors TJ, Zhu Y, et al. Distinct antibody responses to SARS-CoV-2 in children and adults across the COVID-19 clinical spectrum. *Nat Immunol*. 2021;22:25–31.
54 Peng Q, Zhou R, Wang Y, et al. Waning immune responses against SARS-CoV-2 variants of concern among vaccinees in Hong Kong. *EBioMedicine*. 2022;77:103904.
55 Holder J. Tracking coronavirus vaccinations around the world. Available at https://www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html. Accessed 6 February 2022.
56 Multilateral leaders task force on COVID-19. Data. Available at https://www.covid19taskforce.com/en/programs/task-force-on-covid-19-vaccines/data. Accessed 6 February 2022.