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Dynamics of neutralizing antibody and T-cell responses to SARS-CoV-2 and variants of concern after primary immunization with CoronaVac and booster with BNT162b2 or ChAdOx1 in health care workers

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Abstract:

Inactivated SARS-CoV-2 vaccine (CoronaVac) is commonly used in national immunization programs. However, the immune response significantly declined within a few months. Our study assessed the immune response against SARS-CoV-2 after receiving booster shots of BNT162b2 or ChAdOx1 among health care workers who previously received CoronaVac as their primary immunization. Fifty-six participants received ChAdOx1 and forty-two participants received BNT162b2 were enrolled into this study which evaluated the immune responses including anti-SARS-CoV-2 spike total antibodies (Elecsys®), surrogated viral neutralization test (sVNT) to ancestral strain (cPass™; GenScript) and five variants of concern (Alpha, Beta, Gamma, Delta, and Omicron) (Luminex; multiplex sVNT) and the ELISpot with spike (S1 and S2) peptide pool against the ancestral SARS-CoV-2 strain. The samples were analyzed at baseline, 4, and 12 weeks after primary immunization as well as 4 and 12 weeks after receiving the booster. This study showed a significantly higher B-cell response among the BNT162b2 than the ChAdOx1 booster group, particularly against the Omicron variant, as well

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as a trend of good T-cell immune response in the BNT162b2 group. Moreover, the immune response rapidly declined at 12 weeks after the booster. A fourth dose or a second booster should be recommended, especially for reducing Omicron severity.

Keywords: COVID-19; SARS-CoV-2; Vaccines; anti-SARS-CoV-2 spike total antibodies; Surrogate viral neutralizing antibody; T-cell immune response, CoronaVac, ChAdOx1, BNT162b2, booster

Introduction

In 2020, there are many coronavirus diseases 2019 (COVID-19) vaccines that have been used to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and decrease the severity of the diseases. CoronaVac (an inactivated SARS-CoV-2 vaccine, Sinovac Life Science) is widely used as the primary vaccination. The waning immunity of the primary vaccination (2 doses of CoronaVac) over time is observed after 12 weeks which indicated that a booster dose is needed [1]. Moreover, the new emergence of variants of concern (VOCs) raises a concern about the vaccine's effectiveness which varies against each VOCs. The five major VOCs recognized by the World Health Organization (WHO) are Alpha, Beta, Delta, Gamma, and Omicron [2]. In several studies, the vaccine efficacy is particularly lower against Delta and Omicron variants [3-5].

Homologous or heterologous COVID-19 prime-boost vaccinations are introduced and reported to improve the humoral and cellular immune responses [6, 7]. Homologous third dose of CoronaVac demonstrated increased immune responses against SARS-CoV-2; however, the immunogenicity was lower when compared to heterologous prime-boost with BNT162b2 [8-12]. Heterologous prime-boost vaccination with mRNA vaccine or viral vector vaccine is widely used as a booster dose because it can induce a high immune response and higher antibody levels which are likely to have greater protection against the infection as well as overcome the new VOCs when there is a lack of specific VOCs COVID-19 vaccines [11, 13]. However, the data of

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dynamic immune response after ChAdOx1 booster or BNT162b2 booster in CoronaVac based regimen to each VOCs are limited.

The neutralizing antibodies (NAbs) titer against the SARS-CoV-2 is a highly predictive indicator of protective immunity after vaccination or infection and several of the surrogate virus neutralization tests (sVNT) are widely used. The neutralizing antibody levels from sVNT are well correlated to the conventional live virus-neutralizing test or pseudovirus-mediated viral neutralization test [14]. However, sVNT needs to have a specific target to the viral spike protein receptor-binding domain (RBD) of each VOCs, therefore, a multiplex sVNT platform was developed and reported a high correlation with live virus-neutralizing test. Additionally, the binding antibody against the SARS-CoV-2 can be used to monitor the immune response.

Herein, this study described the dynamics of the immune response (both B-cell and T-cell) against SARS-CoV-2 ancestral type and VOCs in healthy adults who had received a primary immunization with inactivated SARS-CoV-2 (CoronaVac) and a booster with either ChAdOx1 or BNT162b2 at 4 and 12 weeks after receiving the booster.

Materials and Methods

Study design and the participants

A prospective cohort study was conducted among health care workers (HCWs) aged 18 years or older who received CoronaVac (3-4 weeks apart) as their primary vaccination (2 doses of CoronaVac) at a tertiary care center in Bangkok, Thailand, during March-April 2021 and have results of their immune responses at 4 and 12 weeks after primary vaccination [1]. At 3 months after primary vaccination, the participants were non-randomized to voluntarily receive their booster dose of either ChAdOx1 or BNT162b2.

The exclusion criteria at enrollment were ongoing immunosuppressive medication, any vaccination within 1 month, and having received any blood components or intravenous immunoglobulin within 3 months. The termination criteria were either SARS-CoV-2 infection or received prophylaxis or investigational treatment against COVID-19.

Study procedures

Demographics and Clinical Data

Baseline demographics and clinical data such as the medical history, current medications used, a history of exposure to COVID-19 patients, and history of SARS-CoV-2 infection were

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collected. All HCWs were highly aware of their infection risk. Moreover, they had to follow the surveillance protocol such as completing a daily questionnaire to screen for COVID-19 symptoms and exposure risk. Any HCWs who had any symptoms or risk factors were tested for SARS-CoV-2 infection using the RT-PCR technique.

Sample Collections and Study Protocol

For the B-cell response assessment, 4 ml of clotted blood was collected at 4 (+/- 1 week) and 12 weeks (+/-2 weeks) after primary vaccination as well as 4 (+/- 1 week) and 12 weeks (+/-2 weeks) after the booster dose with either ChAdOx1 or BNT162b2. For the T-cell response assessment, peripheral blood mononuclear cells *(PBMCs) from whole blood were isolated by* density gradient centrifugation using Lymphoprep™ *(STEMCELL Technologies,* Canada) at 1,500 rpm for 30 min at room temperature. Isolated PBMCs were washed with RPMI 1640 Medium (Gibco, Life Technologies Corporation, NY, USA) which was ***supplemented with 10% fetal bovine serum (FBS). The cells were then*** cryopreserved in 10% dimethyl sulfoxide (DMSO) in FBS for ***further experiments.***

B-cell response against SARS-CoV-2 assessment

The antibody titers against SARS-CoV-2 were determined by anti-SARS-CoV-2 spike total antibodies using the ELISA technique (Elecsys®), the surrogate neutralizing antibody to ancestral type (GenScript, cPass^{TM}) and Multiplex sVNT (Luminex) against five VOCs (alpha, delta, beta, gamma, and omicron).

1. *Anti-SARS-CoV-2 spike total antibodies*

The anti-SARS-CoV-2 spike total antibodies were detected by the Elecsys® Anti-SARS-CoV-2 S using Cobas e411 immunoassay analyzers (Roche Diagnostics, Rotkreuz, Switzerland), which is also used by the US Food and Drug Administration (FDA) under the emergency use authorization (EUAs) act. The Elecsys® is the immunoassay to detect total SARS-CoV-2 antibodies against the RBD of the S antigen, and the antibody level is reported as U/ml. This assay has a measuring range of 0.40-250 U/ml. Two hundred microliter of 100-fold diluted samples were used following the manufacturer's protocol (measuring range is 40-25,000 U/ml). For the participants who had anti-SARS-CoV-2 spike total antibodies over the maximum measuring range (>25,000 U/ml), the samples were further diluted to 1000-fold and re-evaluated

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using the Elecsys® Diluent Universal kit [15]. Of note, the assigned U/mL is equivalent to Binding Antibody Units (BAU)/mL as defined by the WHO International Standard for anti-SARS-CoV-2 immunoglobulin (NIBSC code 20/136) guideline. Results reported in U/mL do not need to be converted to another unit and can directly be compared to other studies or results using BAU/mL [16].

2. SARS-CoV-2 neutralizing antibodies to ancestral type

The cPass™ SARS-CoV-2 Neutralization Antibody Detection Kit (GenScript) measures SARS-CoV-2 neutralizing antibodies that block recombinant SARS-CoV-2 RBD conjugated with Horseradish peroxidase (HRP-RBD) from binding to the human ACE2 receptor protein (hACE2). The neutralizing antibody level was detected according to the manufacturer's instructions. Serum samples and controls were diluted 1:10 and pre-incubated with HRP-RBD for 30 minutes at 37ºC, allowing SARS-CoV-2 neutralizing antibodies to bind to HRP-RBD. The mixture was then added to the microplate pre-coated with hACE2 where the unbound HRP-RBD and HRP-RBD bound non-neutralizing antibodies were captured, while HRP-RBD complexed with neutralizing antibodies were subsequently removed during the washing steps. After washing, 3,3',5,5'-tetramethylbenzidine (TMB) substrate was added, followed by the stop solution to terminate the reaction and the optical density (OD) of the reaction was measured at 450 nm. The antibody level was reported as the percentage inhibition by using the equation from the manufacturer with the cut-off level for SARS-CoV-2 neutralizing antibody detection of ≥30% inhibition. The seroconversion rate was defined as sVNT ≥68% which was adopted from the US FDA's guideline for a high titer of the COVID-19 convalescent plasma [17].

3. Multiplex sVNT to ancestral type SARS-CoV-2 and VOCs

The sVNT was adapted using the Luminex platform to perform multiplex sVNT as previously described [18]. His-Avi-Tag, biotin-labeled receptor-binding domain (RBD) from SARS-CoV-2 ancestral strain and 5 VOCs (alpha, delta, beta, gamma, and omicron) were coupled to paramagnetic MagPlex-Avidin microspheres from Luminex. Diluted RBD-coated microsphere mixture containing approximately 600 beads per RBD protein was incubated with 1:10 diluted sera in a 1:1 ratio in a 96-well plate for 1 hour at 37ºC while shaking at 800 rpm. Human ACE2 receptor protein phycoerythrin (PE)-conjugated (1 ug/ml, GenScript) was then added to the plate and incubated for 30 minutes at 37ºC with shaking at 800 rpm. After incubation, the mixture was washed two times with assay buffer (PBS + 1% bovine serum albumin) followed by resuspension in assay buffer. The plate was then read using the Bioplex MAGPIX system (Luminex) to acquire the data.

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T-cell response against SARS-CoV-2 assessment

SARS-CoV-2-specific T-cell responses were investigated by Enzyme-linked immunospot assay (ELISpot assay). ELISpot plates (Millipore) were coated with human IFNγ antibody (1-D1K, Mabtech; 5 µg/ml) overnight at 4 °C. Then, 2.5×10^5 PBMCs were stimulated with overlapping spike (S1 and S2) peptide pool (Genscript, USA) of SARS-CoV-2 in AIM-V medium (Gibco) at a final concentration of 2 ug/ml for 16 hours. Negative control and positive control, CMV lysates (Meridian Bioscience, USA), and Phytohemagglutinin (Sigma) were also included. The spots were quantified using ImmunoSpot. Spot counts of negative control wells were subtracted from the peptide-stimulated wells to generate normalized results. These are reported as spot forming units (SFU) per million PBMCs. The responses higher than mean SFU counts plus 3 standard deviations (SD) of unstimulated wells, which is higher than 19 SFU per million PBMCs, were considered to be positive [19].

Statistical analysis

Descriptive statistics were used to present demographic data, and clinical and laboratory parameters. Continuous variables were presented as the median and interquartile range (IQR). The Wilcoxon rank-sum test was used to compare the continuous variables between the two groups. The Chi-square test or Fisher exact test were used to compare the proportion between groups. Paired t-test was used to compare the change in immunogenicity at week 12 from week 4 (reference) after the vaccine booster dose within group and was reported as geometric mean (GM) and geometric mean ratio (GMR) with 95% confidence interval (CI). The correlation between anti-SARS-CoV-2 spike total antibodies and other immune responses was determined by the Spearman rank test. Statistical significance was considered when the p-value was <0.05. STATA version 15.1 (Stata Corp., College Station, Texas) was used for statistical analysis.

Results

Characteristics of the participants

From July-August 2021, 56 participants had ChAdOx1 booster and 42 participants had the BNT162b2 booster. The blood was collected after 4- and 12-week post booster. The median age of the participants that had CoronaVac was 41 (31-52) years and most of them were female. (Table 1) The median (IQR) interval after the second CoronaVac and ChAdOx1 booster was 88 (74-92) days and 113 (112-115) days for the BNT162b2 booster. Fourteen participants had a

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history of contact with COVID-19 patients without appropriate personal preventive equipment and/or had symptoms suspected to be of COVID-19, and one participant was diagnosed with COVID-19 3 days after receiving the booster; the latter participant was excluded from the analysis. This infected participant had mild severity of the disease with upper respiratory tract symptoms and no pneumonia.

Immune response

1. Anti-SARS-CoV-2 spike total antibodies

Anti-SARS-CoV-2 spike total antibodies after primary immunization and booster dose are shown in Table 2. Anti-SARS-CoV-2 spike total antibodies at 12 weeks after primary vaccination (2 doses of CoronaVac) were lower than 4 weeks in both groups. After the the participants received the ChAdOx1 booster, the anti-SARS-CoV-2 spike total antibodies at 4 and 12 weeks post booster was significantly lower than the BNT162b2 booster group, $p < 0.001$. The Anti-SARS-CoV-2 spike total antibodies rapidly decreased in the BNT162b2 booster group at 12 weeks after booster (79% in the BNT162b2 group vs 59% in the ChAdOx1 group) but were still higher than post-primary vaccination.

2. *Surrogated viral neutralizing antibody to* ancestral *type by GenScript and VOCs by Luminex*

The sVNT to ancestral type at 12 weeks after primary vaccination (2 doses of CoronaVac) was lower than at 4 weeks in both groups. The median (IQR) of sVNT to ancestral type after the booster with ChAdOx1 was significantly lower than the BNT162b2 booster group at 4 weeks after the booster. (Table 2 and Figure 1) sVNT to each VOCs were different. Overall, the median sVNT to each VOCs in the BNT162b2 booster group was higher than the ChAdOx1 booster group. In addition, the median of sVNT to wild type, Alpha, and Delta had similar patterns whereas the Beta had similar patterns as that of the Gamma variant. However, sVNT to Omicron is significantly lower than other VOCs. (Figure 2 and Supplement table 1) The median (IQR) of sVNT to Omicron after the booster with ChAdOx1 at 12 weeks was 26.6% (12.4-37.7%) which was significantly lower than the booster with BNT162b2 (median 50.7 (IQR 34.6-71.9%), $p < 0.001$. The decline rate of sVNT to omicron from week 4 to week 12 was 45% among BNT162b2 and 62% among ChAdOx1 participants; however, the decline rate of sVNT to other VOC was only 6-20%. (Tables 2 and 3)

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According to the US FDA guideline for a high titer of the COVID-19 convalescent plasma, the % inhibition using the cPass^{TM} SARS-CoV-2 Neutralization Antibody Detection Kit should be $\geq$ 68% [17]. None of the participants had sVNT > 68% to omicron after the primary CoronaVac immunization; however, the seroconversion rate increased to 83% and 35% after 4 weeks of BNT 162b2 and ChAdOx1 boosters, respectively. The seroconversion rate of other VOCs except omicron was 94-100% in the BNT162b2 group and 80-100% in the ChAdOx1 group.

3. T-cell response assessment by ELISpot

The result of IFN-g secreting T cell by Pool S1 and Pool S2 are shown in Figure 3 and Supplement Table 2. The responses had a similar pattern which showed that there was a reduction of the immune response 12 weeks after primary immunization, increased immune response at 4 weeks after the booster dose, and a reduction of the immune response 12 weeks after the booster. Percent positive responses after the booster at week 4 and week 12 are 100% and 90% with BNT162b2, and 80% and 80% with ChAdOx1, respectively. Although there was no significant difference between the BNT162b2 and ChAdOx1 booster groups, however, the median SFU after BNT162b2 was higher than ChAdOx1 at 4 and 12 weeks post booster.

Discussion

This prospective observational cohort study reported the dynamic of antibodies against ancestral type and five VOCs as well as T-cell responses in participants who received a primary immunization with CoronaVac and booster with BNT162b2 or ChAdOx1. The results showed that there was a decrease in the immune response at 12 weeks after primary immunization. Since November 2021, the variant has changed to omicron and a booster dose is recommended. At 4 weeks post booster, both BNT162b2 and ChAdOx1 had a significant boost of anti-RBD level. BNT162b is approximately 4 times higher than ChAdOx1 which correlates with higher sVNT against omicron strain (median 80.9% versus 54.5%). At 12 weeks post booster, the anti-RBD rapidly declined which may reduce the effectiveness of the vaccines in preventing infection. Cell-mediated immune response, measured by ELISPOT assay, showed that there was a similar T-cell immune response after booster in the ChAdOx1 group and BNT162b2 booster group. Cell-mediated immunity has been reported as an immune response to reduce the severity of the disease [20].

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Among the ChAdOx1 booster group, the anti-SARS-CoV-2 spike total antibodies to ancestral type SARS-CoV-2 and sVNT to ancestral type, alpha, beta, and delta at 4 weeks post booster in this study were similar to other studies [13, 21]. However, the median of sVNT to omicron was 61.2% at 4 weeks post booster and at 12 weeks post booster, this declined to 26.6% which indicated that one booster may not be able to prevent infection and hence, an additional booster is needed. Among the BNT162b2 booster group, the immune response by neutralizing antibody to ancestral type SARS-CoV-2, delta, and omicron at 4 weeks post booster was similar to other studies [10, 22, 23]. However, there was a significant decline of sVNT to omicron at 12 weeks after booster [median (IQR) sVNT to omicron 50.7% (IQR 34.6-71.9%)]. The immune response in the BNT162b2 booster group was higher than the ChAdOx1 booster group 4 weeks post booster which is in line with data from a previous study conducted in Brazil [11]. The mRNA vaccines have demonstrated a high neutralizing antibody response when compared to other vaccine platforms including viral vector vaccine or inactivated virus vaccine used in the primary immunization [24].

T-cell responses to the spike protein increased substantially after the booster dose with either ChAdOx1 or BNT162b2. The response rate and the magnitude of T cell response seem to be higher in the BNT162b2 booster group compared to ChAdOx1 which supports the findings from a previous study [25]. It should be noted that there were some positive T-cell responses at baseline similar to a previous report [26]. However, after the primary vaccination (2 doses of CoronaVac), the magnitude of T-cell responses is higher in every case supporting the need for immunization. There was a correlation between specific T-cells and antibody responses to the spike protein (Supplement correlation graph) which is similar to the immune response seen in patients with primary infection [27].

The difference in the humoral immune response to each VOC is because the vaccines were designed to recognize the ancestral type's spike protein of SARS-CoV-2. Delta has 9 mutations and Omicron has at least 46 high prevalent mutations which are more than any previously emerged variant belonging to the S protein; therefore, it is not surprising to see a decrease in the humoral immune response towards other variants [4, 28]. While neutralizing antibodies target the spike protein and block cellular entry, the cytotoxic T-cell plays an important role in eliminating virus-infected cells. The heterologous prime-boost strategy with different platforms has been shown to effectively improve immunogenicity [29]. The mRNA vaccine seems to induce a stronger immune response than the viral vector vaccine, however, the immune response to Omicron rapidly declines which indicates that an additional booster dose is

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needed, especially for health care workers who are the frontline in this pandemic and then to all populations. A second booster should be mRNA vaccine or protein-based vaccine with adjuvant. For example, a protein-based vaccine with an adjuvant from Novavax shows promising results; it has a high anti-RBD at the primary vaccination or after a booster [30, 31].

This study has several strengths. First, this study is a longitudinal cohort. Second, this study has B cell and T cell responses data from baseline to primary immunization and post booster. Moreover, this study has the immune response data to all of the VOCs, especially the delta and omicron variants which are predominantly circulating around the world at the time when this study was conducted. There were some limitations in this study. First, the study was non-randomized. Second, the sample size was small so there was not enough power to study the clinical efficacy of the vaccine regimens. Last, the T-cell responses were only performed in a subset of the sample, and this study did not test the T-cell responses to the spikes from different variants. However, a recent study showed that the T-cell responses were still detectable to the spikes of various variants among vaccinated individuals [32].

Conclusions

The heterologous prime-boost regimen with CoronaVac followed with a booster with BNT162b2 or ChAdOx1 induced a significant increase in anti-RBD and neutralizing antibodies. However, the BNT162b2 has a higher anti-RBD level and neutralizing antibodies against omicron strains, which is the predominant strain in the year 2022. The humoral immune response tends to decrease rapidly after 12 weeks post booster, therefore, health care workers who are at high risk of virus acquisition may need an additional booster dose (i.e., second booster) after 3 months of the first booster dose. Future studies should assess the long-term immune response to determine the appropriate time to administer the second booster.

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Informed Consent Statement: Informed consent was obtained from all participants involved in the study.

Data Availability Statement: The supporting data for the findings of this study are available from the corresponding author upon reasonable request.

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Table 1: Baseline characteristics of the participants who received primary immunization with CoronaVac and booster with ChAdOx1 or BNT162b2.

Characteristics	**ChAdOx1 booster** N =56	**BNT 162b2 booster** N42	**P-value**
Age, years, median (IQR)	47 (34-53)	32 (30-45)	0.001
Age group, n (%)			<0.001
20-30 years	7 (12.5)	15 (35.7)	
31-50 years	25 (44.6)	19 (45.2)	
51-70 years	24 (42.9)	8 (19.1)	
Female, n (%)	44 (78.6)	34 (81)	0.005
BMI (kg/m^2), median (IQR)	22.6 (20.3-25.9)	21.5 (20-25.8)	0.45

IQR; interquartile rang, BMI; body mass index

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Table 2. Comparison of anti-SARS-CoV-2 spike total antibodies (U/mL) by Elecsys and surrogate viral neutralizing antibody to ancestral strain by GenScript in participants who received primary immunization with CoronaVac and booster with the ChAdOx1 or BNT 162b2.

Median (IQR)	**Anti-SARS-CoV-2 spike total antibodies (U/mL)**			**Surrogate viral neutralizing antibody to ancestral type, (%inhibition) by GenScript**		
Primary immunization	**(N=56)**	**(N=42)**	**P-value**	**(N=56)**	**(N=42)**	**P-value**
Week 4	179 (92-301)	242 (163-462)	0.04	66.8 (47.4-86.1)	83.4 (66.8-91)	0.04
Week 12	56 (41-126)	117 (61-198)	0.001	39.4 (18.6-57.8)	41.3 (31.7-59.2)	0.26
Booster	**ChAdOx1**	**BNT162b2**	**P-value**	**ChAdOx1**	**BNT162b2**	**P-value**
Week 4	7768 (5349-11142)	25129 (17531-39434)	<0.001	98.1 (97.9-98.2)	98.5 (98.5-98.6)	<0.001
Week 12	3139 (2185-4660)	6558 (3836-8885)	<0.001	97.9 (95.8-98.1)	97.9 (97.8-98.2)	0.03

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Table 3. Comparison of the changes of surrogate viral neutralizing antibody (sVNT) by Multiplex sVNT between week 4 and week 12 after the booster dose.

	Primary immunization with CoronaVac and booster with ChAdOx1			Primary immunization with CoronaVac and booster with BNT162b2		
Post Booster	GM	GMR	% Decrease	GM	GMR	% Decrease
Ancestral type						
week 4	92.8 (90.3-95.3)	ref		99.5 (99.4-99.7)	ref	
week 12	79.2 (74.1-84.6)	0.85 (0.81-0.89)	15%	93.8 (91.7-96.0)	0.94 (0.92-0.96)	6%
Alpha						
week 4	90.3 (87-93.8)	ref		90.3 (87-93.8)	ref	
week 12	74.8 (69.4-80.6)	0.83 (0.79-0.87)	17%	74.8 (69.4-80.6)	0.83 (0.79-0.87)	17%
Beta						
week 4	79.7 (75-84.8)	ref		96.4 (95.7-97.2)	ref	
week 12	58.1 (52.3-64.4)	0.73 (0.68-0.78)	27%	85.2 (81.5-89)	0.88 (0.85-0.92)	12%
Gamma						
week 4	81.9 (77.4-86.7)	ref		97.1 (96.4-97.8)	ref	
week 12	59.8 (53.8-66.4)	0.73 (0.68-0.78)	27%	86.7 (83.3-90.3)	0.89 (0.86-0.93)	11%
Delta						
week 4	89.6 (86.3-93.1)	ref		99.1 (98.9-99.3)	ref	
week 12	71.4 (65.6-77.7)	0.8 (0.75-0.84)	20%	91.1 (88.3-94)	0.92 (0.89-0.95)	8%
Omicron						
week 4	54.5 (48.6-61.3)	ref		80.9 (75.1-87.1)	ref	
week 12	20.8 (15.3-28.2)	0.38 (0.29-0.49)	62%	44.4 (35.3-55.7)	0.55 (0.43-0.69)	45%

GM; Geometric mean, GMR; Geometric mean ratio

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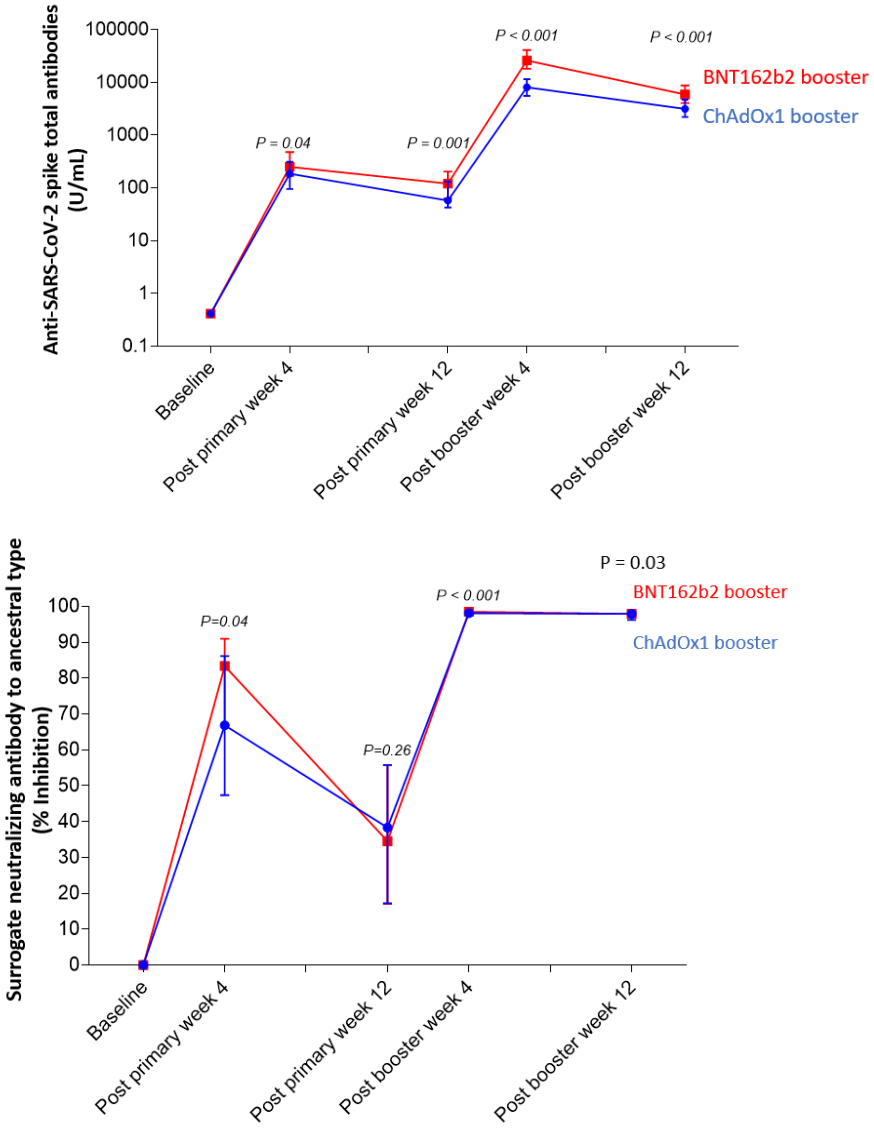

Figure 1. Dynamic of immune response of participants who received primary CoronaVac vaccination and boosted with BNT162b2 or ChAdOx1 at week 12 for (A) anti-SARS-CoV-2 spike total antibodies (U/mL) by Elecsys, and (B) surrogate neutralizing antibody to ancestral type (% inhibition) by GenScript at 4 and 12 weeks post booster.

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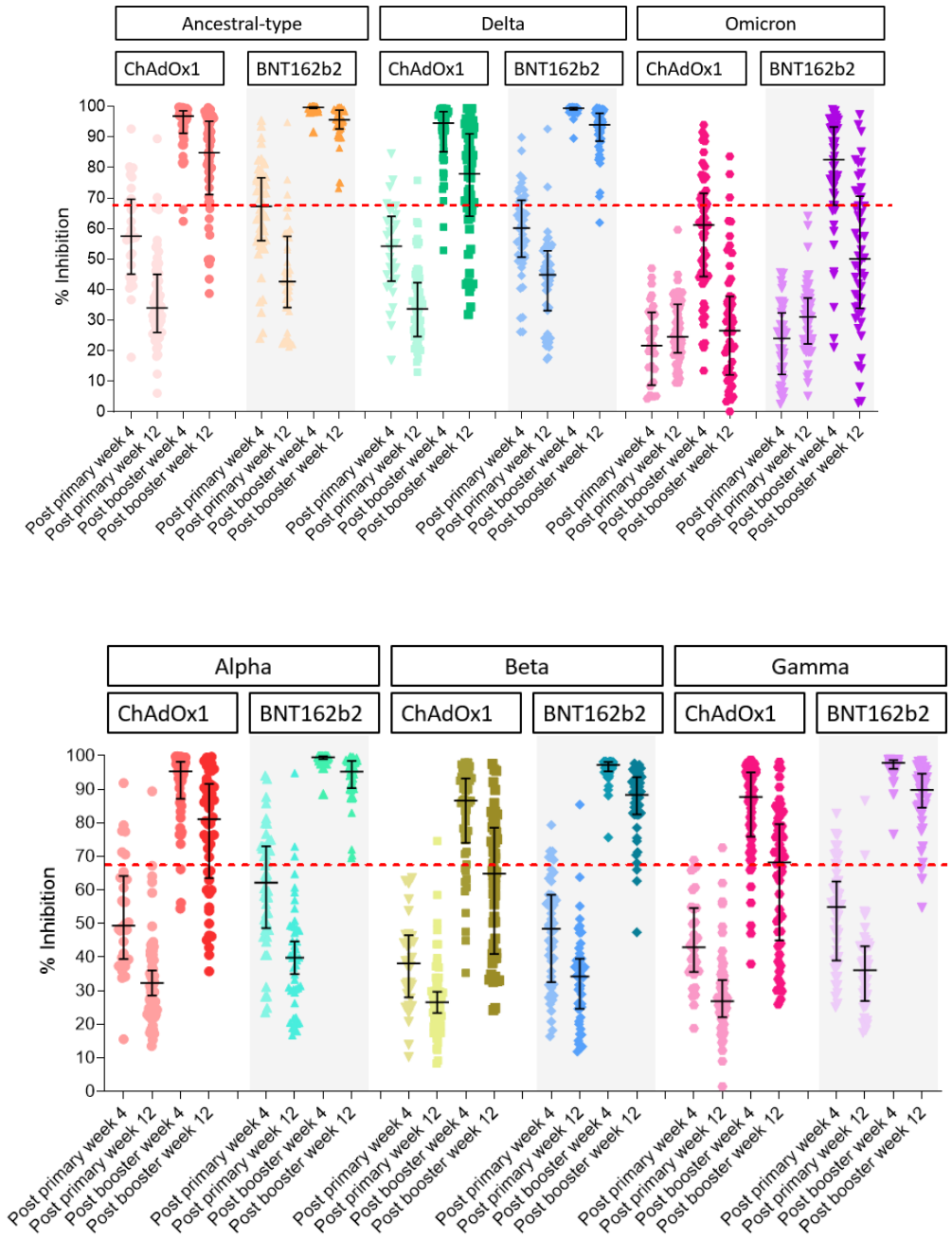

Figure 2. Dynamic of immune response surrogate neutralizing antibody (sVNT) to ancestral type, Delta, Omicron, Alpha, Beta, and Gamma in participants who received primary CoronaVac vaccination and boosted with BNT162b2 or ChAdOx1 by multiplex sVNT.

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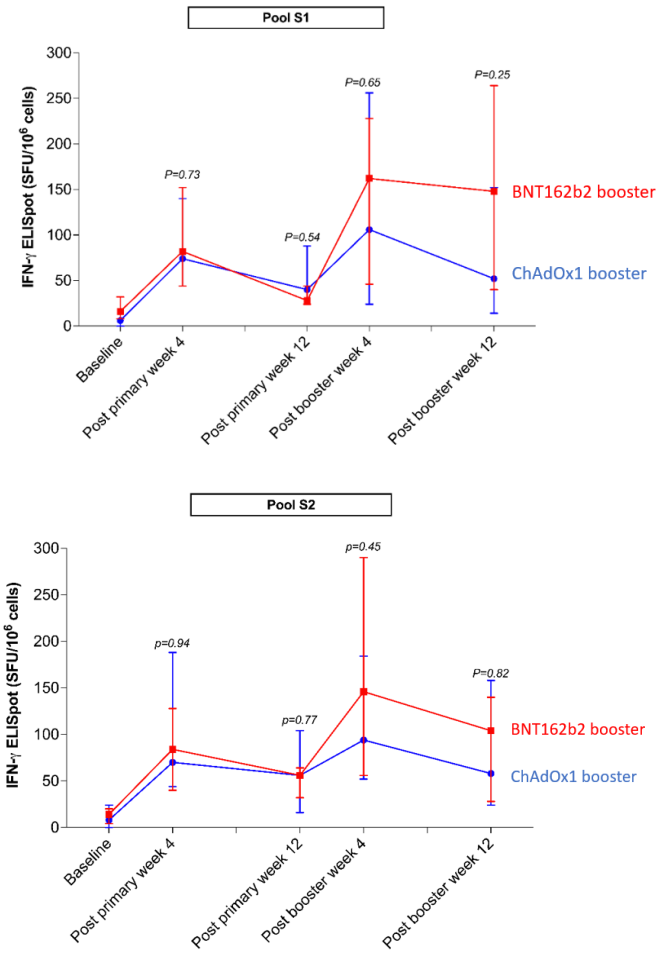

Figure 3. Dynamic of T-cell response by ELISpot (A) Pool S1, and (B) Pool S2 in participants who received primary CoronaVac vaccination and boosted with BNT162b2 or ChAdOx1.

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Supplement Table 1: Comparison of SARS-CoV2 surrogate viral neutralizing antibody (sVNT) (%inhibition) and seroconversion rate of sVNT ≥68% to wild type and VOC by multiplex sVNT in participants who received primary immunization with CoronaVac and booster with ChAdOx1 or BNT 162b2.

	ChAdOx1 booster Median (IQR)	BNT162b2 booster Median (IQR)	P	ChAdOx1 booster N (%)	BNT162b2 booster N%	P
Ancestral						
Post primary immunization week 4	57.5 (46.1-69.4)	67.3 (56.1-76.6)	0.07	8 (14.6)	23 (54.8)	0.02
Post primary immunization week 12	34 (26-44.9)	42.7 (34.1-57.4)	0.01	2 (3.6)	3 (7.1)	0.44
Post booster week 4	96.8 (91.5-98.5)	99.7 (99.4-99.8)	<0.001	52 (96.3)	42 (100)	0.21
Post booster week 12	84.8 (71.9-95)	95.6 (92.8-98.8)	<0.001	42/52 (80.8)	42 (100)	0.003
Alpha						
Post primary immunization week 4	49.4 (39.6-64)	62.2 (49.1-73)	0.03	6	19 (45.2)	0.03
Post primary immunization week 12	29.8 (23-39.1)	39.8 (29.5-49)	0.01	1 (1.8)	3 (7.1)	0.19
Post booster week 4	95.4 (87.2-98.2)	99.6 (99-99.8)	<0.001	93 (96.9)	51 (94.4)	0.25
Post booster week 12	81.1 (64.2-91.5)	95.2 (90.5-98.4)	<0.001	79 (84)	37 (71.2)	<0.001
Beta						
Post primary immunization week 4	38.2 (28.4-46.5)	48.5 (33.1-58.6)	0.01	0 (0)	6 (14.3)	0.08
Post primary immunization week 12	25.4 (19.4-29.9)	34.2 (24.6-39.5)	0.005	1 (1.8)	1 (2.4)	0.85

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Post booster week 4	86.6 (75-93.2)	97.3 (95.7-98.1)	<0.001	43 (79.6)	42 (100)	0.002
Post booster week 12	64.9 (41.1-78.4)	88.3 (82.5-93.7)	<0.001	22 (42.3)	39 (92.9)	<0.001
Delta						
Post primary immunization week 4	54.2 (43.1-63.5)	60.2 (50.8-69.1)	0.07	3 (10.3)	13 (31)	0.05
Post primary immunization week 12	33.7 (24.7-42.2)	44.9 (33.2-52.7)	0.003	1 (1.8)	2 (4.8)	0.58
Post booster week 4	94.6 (85.5-98.3)	99.4 (98.9-99.6)	<0.001	52 (96.3)	42 (100)	0.50
Post booster week 12	77.9 (64.5-91)	94 (88.7-97.7)	<0.001	35 (67.3)	41 (97.6)	<0.001
Gamma						
Post primary immunization week 4	42.9 (35.7-54.5)	54.9 (39.1-62.4)	0.02	1 (3.5)	8 (19.1)	0.07
Post primary immunization week 12	26.9 (22.2-32.9)	36.1 (27-43.3)	0.001	1 (1.8)	2 (4.8)	0.58
Post booster week 4	87.7 (76.1-95)	97.9 (96.3-98.7)	<0.001	47 (87)	42 (100)	0.02
Post booster week 12	68.3 (45.8-79.5)	89.9 (84.7-94.7)	<0.001	26 (50)	39 (92.9)	<0.001
Omicron						
Post primary immunization week 4	21.6 (9.1-32.4)	24.1 (12.5-32.2)	0.72	0	0	NA
Post primary immunization week 12	24.6 (19.6-35.2)	31.5 (22-38.6)	0.03	0	0	NA
Post booster week 4	61.2 (44.3-71.3)	86.3 (73.8-93.6)	<0.001	19 (35.2)	35 (83.3)	<0.001
Post booster week 12	26.6 (12.4-37.7)	50.7 (34.6-71.9)	<0.001	3 (5.8)	12 (28.6)	0.004

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Supplement Table 2 Comparison of T cell response by ELISpot to Pool S1 and S2 in participants who received primary immunization with CoronaVac and booster with ChAdOx1 or BNT 162b2.

	ChAdOx1 booster N=10 Median (IQR)	BNT162b2 booster N=10 Median (IQR)	P-value
Pool S1			
Pre immunization	6 (0-32)	16 (8-32)	0.42
Post primary immunization week 4	74 (44-140)	82 (44-152)	0.73
Post primary immunization week 12	40 (24-88)	28 (24-44)	0.54
Post booster week 4	106 (24-256)	162 (46-228)	0.65
Post booster week 12	52 (14-152)	148 (40-264)	0.25
Pool S2			
Pre immunization	8 (0-24)	14 (4-20)	0.51
Post primary immunization week 4	70 (44-188)	84 (40-128)	0.94
Post primary immunization week 12	56 (16-104)	56 (32-64)	0.77
Post booster week 4	94 (52-184)	146 (56-290)	0.45
Post booster week 12	58 (24-158)	104 (28-140)	0.82

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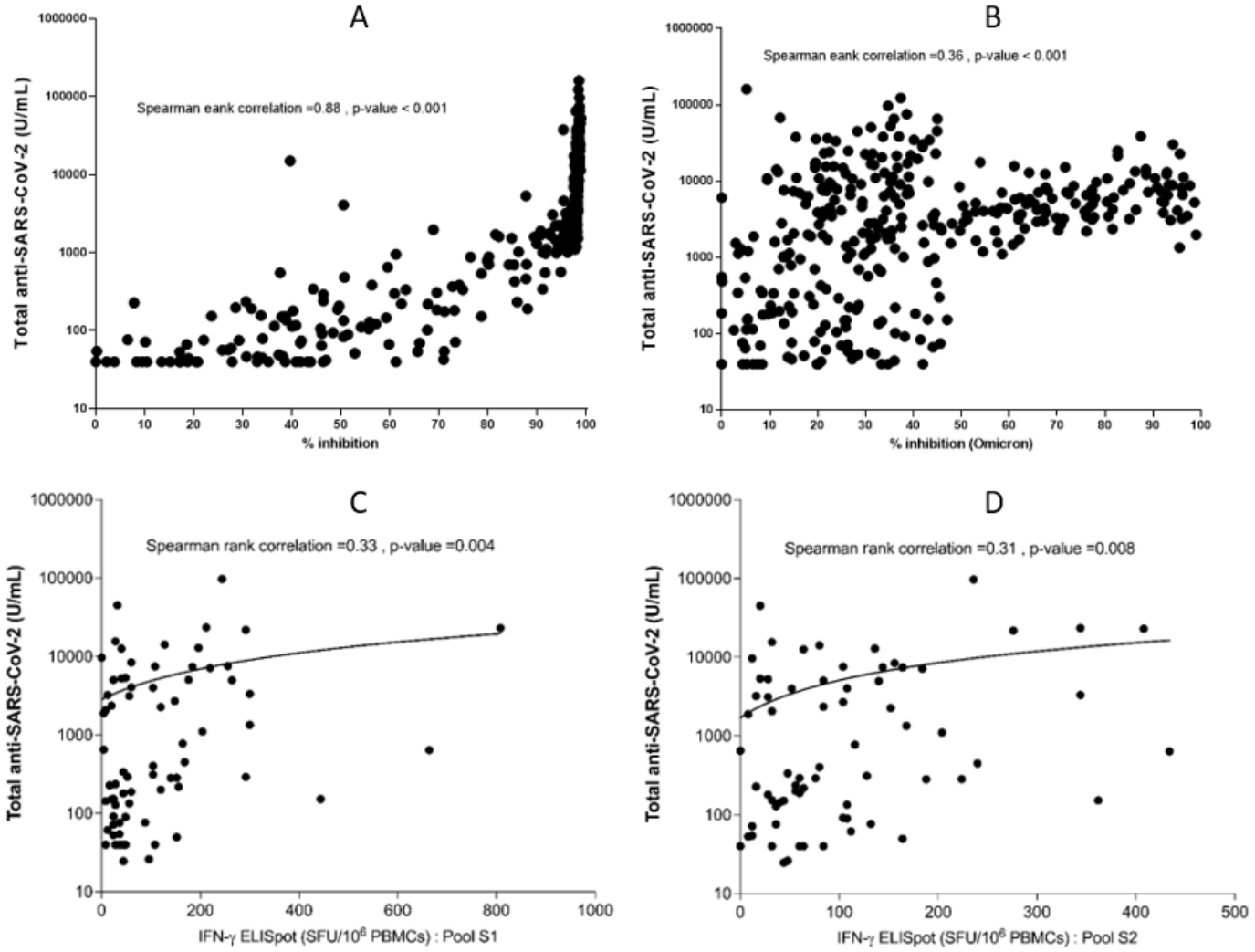

Supplement Figure 1. Correlation between total anti-SARS-CoV-2 and other immune response including a) sVNT to ancestral type b) sVNT to Omicron c) the ELISpot of Pool S1 and d) the ELISpot of S2.

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