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The immunogenicity and reactogenicity of four COVID-19 booster vaccinations against SARS-CoV-2 variants following CoronaVac or ChAdOx1 nCoV-19 primary series

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Abstract

Background: The appropriate COVID-19 booster vaccine following inactivated or adenoviral vector COVID-19 vaccination is unclear.

Objective: To investigate the immunogenicity of four COVID-19 booster vaccines.

Methods: We prospectively enrolled healthy adults who received a two-dose CoronaVac or ChAdOx1 8–12 weeks earlier and allocated them to receive one of the following booster vaccine: inactivated (BBIBP-CorV), ChAdOx1 or mRNA (BNT162b2 at full [30 µg] and half [15 µg] dose) vaccines. We determined the reactogenicity and the humoral (anti-receptor binding domain IgG (anti-RBD-IgG), neutralizing antibodies (nAb) against Delta, Beta and Omicron variants) and cellular immunity measuring by interferon gamma (IFN-γ) responses post-booster.

Results: Among the 352 participants (179 CoronaVac and 173 ChAdOx1 participants), 285 (81%) were female, and median age was 39 (IQR: 31–47) years. Two weeks post-booster, both 30 µg- and 15 µg- BNT162b2 induced the highest anti-RBD IgG concentration (BAU/mL); Coronavac-prime: 30 µg-BNT162b2, 5152.2 (95%CI 4491.7–5909.8); 15 µg-BNT162b2, 3981.1 (3397.2–4665.4); ChAdOx1, 1358.0 (1141.8–1615.1); BBIBP-CorV, 154.6 (92.11–259.47); ChAdOx1-prime: 30 µg-BNT162b2, 2363.8 (2005.6–2786.1; 15 µg-BNT162b2, 1961.9 (1624.6–2369.1); ChAdOx1, 246.4 (199.6–304.2); BBIBP-CorV, 128.1 (93.5–175.4). Similarly, both 30 µg- and 15 µg- BNT162b2 boosting induced the highest nAb titers against Beta, Delta and Omicron BA.1 variants and highest T-cell response at 2 weeks after boosting. While all BNT162b2 or heterologous ChAdOx1-boosted participants had nAb against Omicron, these were < 50% for BBIBP-CorV and 75% for homologous ChAdOx1-boosted participants. There was significant decrease in nAb (> 4-fold) at 16–20 weeks post booster for all groups.

Conclusion: Heterologous boosting with BNT162b2 following CoronaVac or ChAdOx1 primary series is most immunogenic. Additional studies are needed to verify the clinical efficacy and persistence of immunity following half-dose BNT162b2.

Key words: Booster, COVID-19, CoronaVac, ChAdOx1, vaccine

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Introduction

Both CoronaVac (an inactivated whole-virion SARS-CoV-2 vaccine, Sinovac Life Science) and ChAdOx1 (a chimpanzee adenovirus-vectored vaccine expressing the SARS-CoV-2 spike protein, Oxford, AstraZeneca) are safe and effective vaccines against symptomatic COVID-19 caused by the ancestral Wuhan strain.[1-4] These two vaccines are widely used vaccines globally, particularly in low- and middle-income countries.[5]

Breakthrough infections following COVID-19 vaccination, which are likely due to a combination of waning immunity and the emergence of SARS-CoV-2 variants (i.e. Omicron) that evade vaccine-induced responses, have led to the need for booster vaccination.[6-9]

Several studies have demonstrated improved humoral responses with heterologous COVID-19 3rd dose vaccination, primarily on ChAdOx1 and mRNA vaccines.[10-13] However, other combinations of COVID-19 vaccination involving inactivated COVID-19 vaccines as booster and fractional doses have not been evaluated. A recent study of reduced dosage of mRNA-1273 vaccine as a booster was found to be highly immunogenic, suggesting that a lower dosage vaccine may be equally immunogenic as a standard dosage, particularly for mRNA vaccines.[14]

In this study, we examined the safety and immunogenicity of four booster vaccines in healthy adults who previously received a 2-dose primary series of CoronaVac or ChAdOx1 vaccine 8-12 weeks earlier.

Methods

Study design and participants

This single-center prospective, non-randomized, open-labeled cohort study enrolled healthy adults, aged 18 years or older at Siriraj Hospital, Bangkok, Thailand, from July 2021 to September 2021. The eligible participants were those who have received either 2 doses of CoronaVac (4 weeks apart) (CoronaVac-prime) or ChAdOx1 (8–10 weeks apart) (ChAdOx1-prime) primary series vaccination 8–12 weeks prior to recruitment. The exclusion criteria were history of SARS-CoV-2 infection; prior received prophylactic or investigational treatment against COVID-19 within 90 days; had an unstable underlying disease; history of vaccine anaphylaxis; being pregnant; immunocompromised or currently receiving immunosuppressive agents. Written informed consent was obtained from all study participants. The study protocol was approved by the Siriraj Institutional Review Board (COA no. Si 537/2021). The study was registered in thaichinicaltrials.org (TCTR20210719006) on 12/07/2021. All methods were performed in accordance with relevant guidelines and regulations.

Study Procedures

Eligible participants were openly assigned to receive one of the four intramuscular booster vaccinations: BBIBP-CorV (Sinopharm), ChAdOx1 (AstraZeneca), full dose [30 μg] or half dose [15 μg] BNT162b2 (Pfizer). We performed open assignment in this study by using the electronic registration system for each participant to rank the four study arms from the most to the least preferred arm. After all participants had registered, the study team then assigned the vaccine to each participant by their most preference and by the order of registration into the system. When the number of participants achieved the target, that arm will be closed, and the participants will be assigned to the next preferred arm from their ranking. Participants were observed for at least 30 min following vaccination for any immediate adverse events (AE) and were instructed to record self-assessment signs or symptoms in an electronic diary (eDiary) for seven days after vaccination. An AE were defined as described in the previous study.[4]

Blood samples were collected at baseline (pre-booster), two weeks, and 16–20 weeks after booster vaccination to determine the anti-SARS-CoV-2 RBD IgG antibody levels. A subset of samples at two weeks and 16–20 weeks post-booster were randomly picked from each group for testing of neutralizing antibodies against the SARS-CoV-2 Delta and Beta variants using the 50% plaque reduction neutralization test (PRNT50) and against Delta and Omicron variants using the pseudovirus neutralization test (PVNT). Cellular immunity was measured using the *QuantiFERON* SARS-CoV-2 interferon gamma release assay (IGRA).

Laboratory Assays

Chemiluminescent microparticle assay (CMIA) for anti-SARS-CoV-2 RBD IgG

The anti-RBD IgG was measured by CMIA against ancestral strain using the SARS-CoV-2 IgG II Quant (Abbott, List No. 06S60) on the ARCHITECT I System as described in previous study.[4] Samples with a value > 11,360 BAU/mL were reported as 11,360 BAU/mL.

50% plaque reduction neutralization test (PRNT)

The standard live virus 50% plaque reduction neutralization test ($PRNT_{50}$) against Delta variant (B.1.617.2) and Beta variant (B.1.351) were performed as described in the previous study.[4] The $PRNT_{50}$ titer is defined as the highest test serum dilution for which the virus infectivity is reduced by 50% when compared with the average plaque counts of the virus control (no serum). The $PRNT_{50}$ titer of 5 was used for all samples that were below the detectable level (1:10).

Pseudovirus neutralization assay (PVNT)

Codon-optimized gene encoding the spike of Omicron (B.1.1.529/BA.1) and Delta (B.1.617.2) were generated by gene synthesis (Genscript) and cloned into the pCAGGS expressing plasmid by In-Fusion assembly (Clontech). Pseudovirus was generated and concentrated as previously described.[15] Pseudotype-based neutralization assays were carried out as described previously.[15] The 50% pseudovirion neutralizing antibody titer ($PVNT_{50}$) was calculated by interpolating the point at which infectivity was reduced to 50% of the value for the control samples (no serum).

QuantiFERON SARS-CoV-2 interferon gamma release assay (IGRA)

SARS-CoV-2 specific T cell responses were assessed by whole blood IGRA using QIAGEN's *QuantiFERON* according to the manufacturer's instruction. Briefly, whole blood samples were stimulated with SARS-CoV-2 S peptide pools, CD4+ T cell (Ag1), CD8+ T cells (Ag2), along with positive and negative controls, and incubated at 37°C for 16–24 hr. Interferon-gamma (IFN-γ) concentration was measured in plasma using an automated *QuantiFERON* SARS-CoV-2 ELISA instrument and reported in International Units per mL (IU/mL).[16,17] The cut-off for positivity was determined as the level above the mean plus three standard deviations of the negative control. The cut-offs for Ag1 (> 0.12 IU/mL) and Ag2 (> 0.17 IU/mL) were determined based on 61 SARS-CoV-2 negative control samples. A positive response to either of the two peptide pools was considered positive.

Statistical Analysis

The sample size was calculated using the lower bounds of anti-RBD IgG geometric mean concentration (GMC) from previous study.[4] A sample size of 50 participants in each group would provide us 80% power to detect any difference between groups.

The AEs endpoints were presented as frequencies and Chi-square test was used to test for statistical difference. The anti-SARS-CoV-2 RBD IgG concentration and neutralization antibodies were reported as GMC and geometric mean titers (GMT) with 95% confidence interval (CI), respectively. Anti-RBD IgG GMC and $PRNT_{50}$ GMTs at two weeks after the primary series (post-primary series) from our previous study was used for comparison.[4] Paired *t* test, unpaired *t* test, and analysis of variance (ANOVA) were used to compare GMC and GMT within group, between groups, and across groups using GraphPad Prism 9 version 9.2.0 (283) (GraphPad Software, CA, USA), respectively. Other statistical analyses were conducted using STATA version 17 (Stata Corp, LP, College Station, TX, USA).

Results

Among 352 participants enrolled (179 and 173 participants in CoronaVac- and ChAdOx1-prime group), 285 (81%) were female, and the median age was 39 (interquartile range, IQR: 31–47) years. The demographic of the study participants receiving different booster vaccine was shown in **Table 1**. The recruitment for BBIBP-CorV booster groups was stopped after 37 participants, 14 in CoronaVac-prime and 23 in ChAdOx1-prime when the preliminary analysis found low anti-SARS-CoV-2 RBD IgG concentration.

Table 1. Baseline characteristics of participants.

Type of booster vaccinations					
CoronaVac-prime (n = 179)	**BBIBP-CorV n = 14**	**ChAdOx1 n = 65**	**30 μg BNT162b2 n = 50**	**15 μg BNT162b2 n = 50**	***p*-value**
Age (years), median (IQR)	31 (27, 41.5)	36.6 (29.5, 44)	32 (28, 41.8)	40 (31.5, 45.3)	0.018
Female, n (%)	12 (85.7)	51 (78.5)	40 (80.0)	33 (66.0)	0.249
BMI (kg/m^2), median (IQR)	25.2 (21.1, 31.6)	23.4 (20.9, 27.1)	22.1 (19.5, 25.5)	23.9 (20.9, 26.0)	0.325
Interval between second dose and booster dose (weeks), median (IQR)	10.3 (10.3, 11.0)	10.3 (10.0, 11.1)	13.9 (13.4, 14.6)	11.4 (9.6, 14.0.)	0.003

Table 1. (Continued)

Type of booster vaccinations					
ChAdOx1-prime (n = 173)	**BBIBP-CorV n = 23**	**ChAdOx1 n = 50**	**30 µg BNT162b2 n = 50**	**15 µg BNT162b2 n = 50**	***p*-value**
Age (years), median (IQR)	51 (42, 59)	45.5 (36, 57)	34 (30, 43)	41.5 (34, 49.5)	0.001
Female, n (%)	21 (91.3)	47 (94.0)	37 (74.0)	44 (88.0)	0.001
BMI (kg/m^2), median (IQR)	24.8 (22.4, 27.6)	23.8 (21.3, 26.7)	21.4 (19.3, 24.7)	23.3 (20.4, 26.5)	0.001
Interval between second dose and booster dose (weeks), median (IQR)	10.3 (9.9, 10.4)	10.0 (9.9, 10.1)	9.7 (9.6, 10.0)	9.7 (9.7, 10.0)	0.001

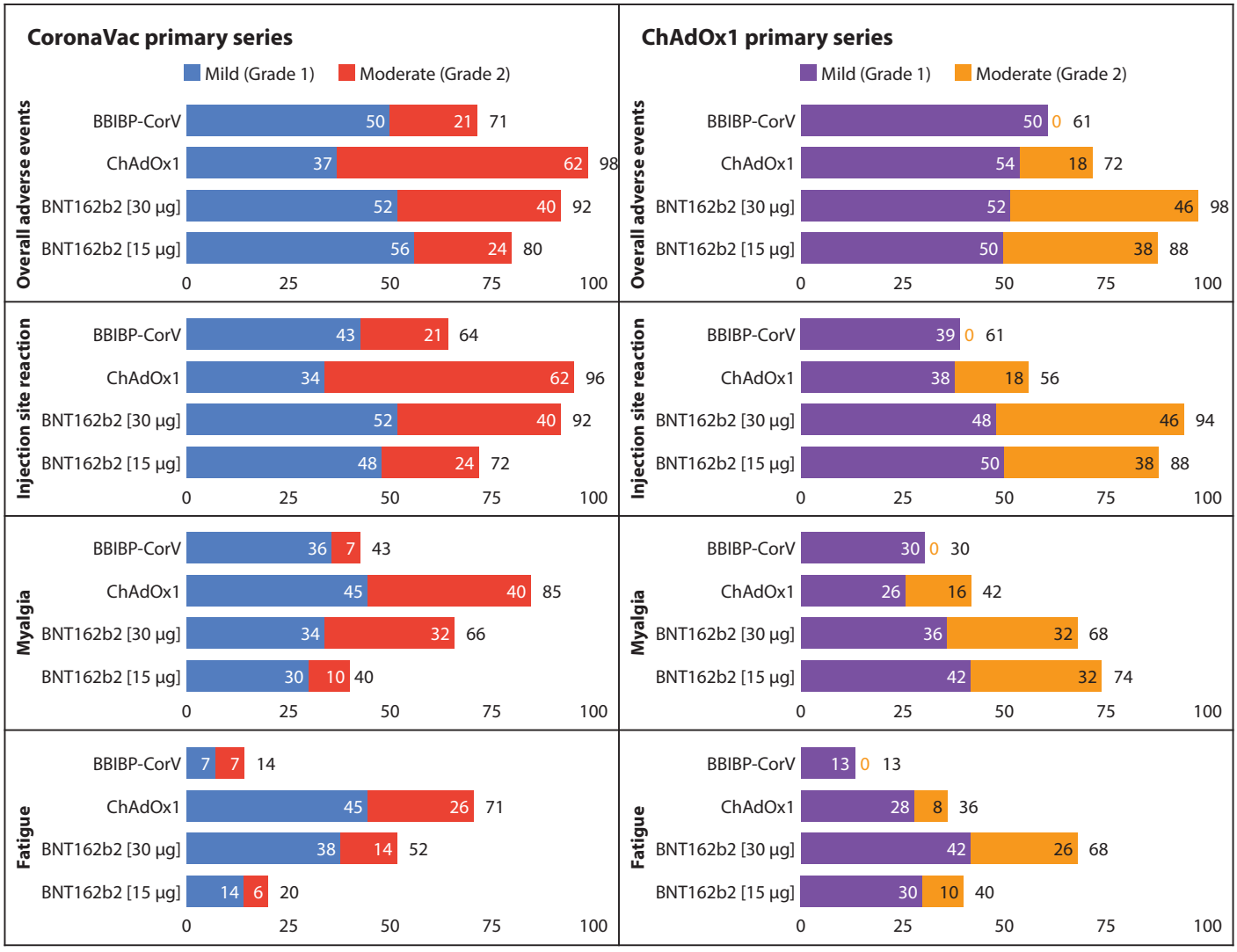

Figure 1. Adverse events following four different booster vaccinations. The stacked bars represent the percentage of participants who reported mild and moderate adverse events after the booster vaccinations in the subjects who had received 2-dose (A) CoronaVac-primary series and (B) ChAdOx1-primary series vaccination. Chi-square was used for statistical analyses.

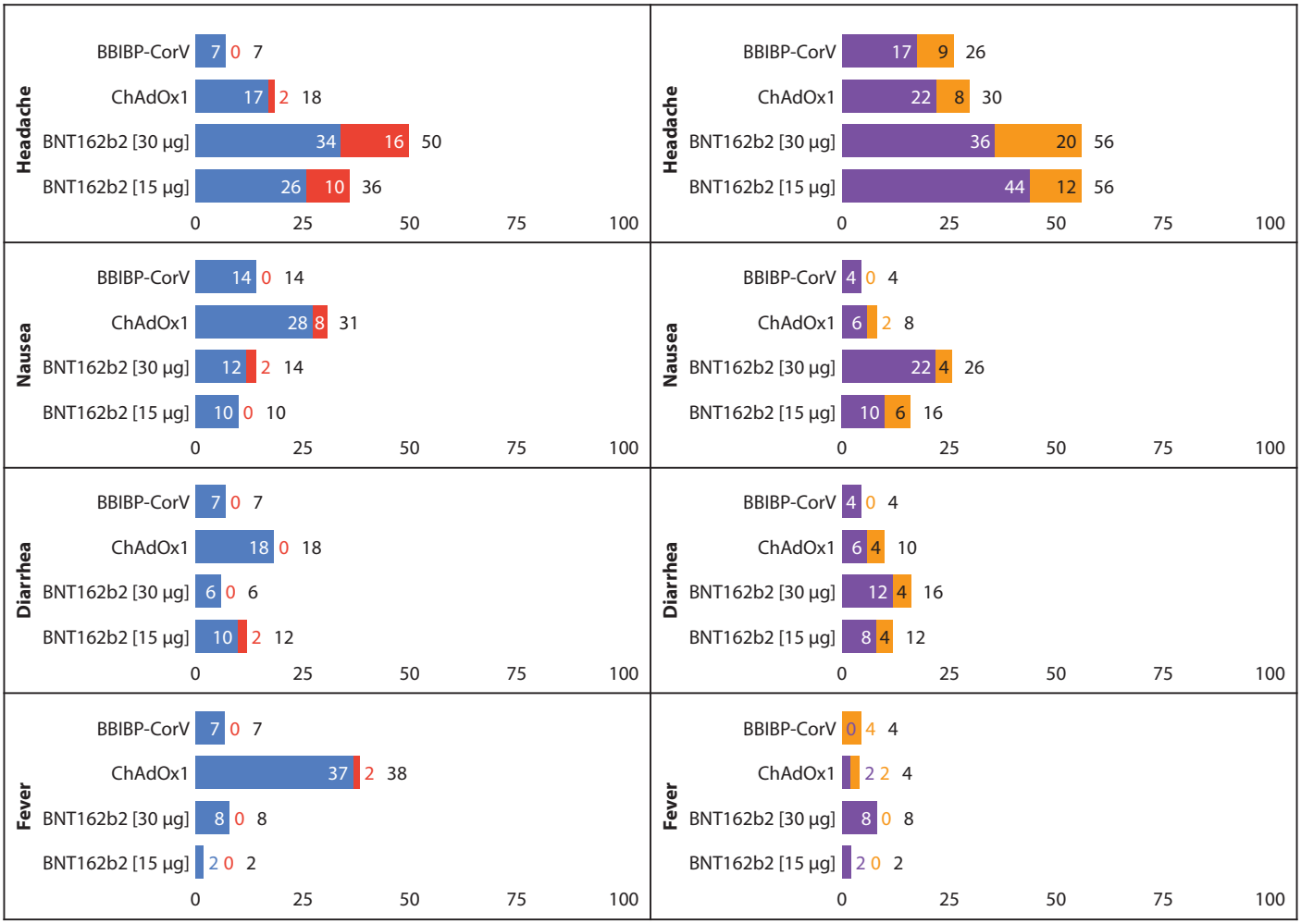

Figure 1. (Continued)

Adverse events (AEs)

Among the CoronaVac-prime groups, the overall AEs was most frequent after boosting with ChAdOx1 (98%), followed by 30 µg-BNT162b2 (92%), 15 µg-BNT162b2 (80%), and BBIBP-CorV (70%); whereas in ChAdOx1-prime group, the overall AEs was most frequent after boosting with 30 µg-BNT162b2 (98%), followed by 15 µg-BNT162b2 (88%), ChAdOx1 (72%), and BBIBP-CorV (61%) (**Figure 1**). Systemic AEs were in the same trend as local AEs. All AEs were mild (grade 1) to moderate (grade 2) in severity and recovered within 2–3 days. No serious AE was found in this study.

Anti-SARS-CoV-2 RBD IgG responses

At baseline (8–12 weeks post-primary series), 175/179 (97.8%) participants in CoronaVac-prime and 172/173 (99.4%) in ChAdOx1-prime remained seropositive. The anti-RBD IgG GMC at baseline were lower in the CoronaVac-prime groups than in the ChAdOx1-prime group (36.31 vs. 98.27 BAU/mL). For the CoronaVac-prime groups, the anti-RBD IgG GMC in the 30 µg-BNT162b2 group (5152.2 BAU/mL, 95%CI 4491.7–5909.8) was significantly higher than other vaccine booster groups: 15 µg-BNT162b2 (3981.1 BAU/mL, 95%CI 3397.2–4665.4), ChAdOx1 (1358 BAU/mL, 95%CI 1141.8–1615.1), and BBIBP-CorV (154 BAU/mL, 95%CI 92.11, 259.47) (**Figure 2A**). The geometric mean ratio (GMR) of anti-RBD IgG between post-booster and post-primary series of CoronaVac-prime participants for BBIBP-CorV, ChAdOx1, 30 µg-BNT162b2 and 15 µg-BNT162b2 were 0.94, 8.26, 31.34, and 24.22, respectively.

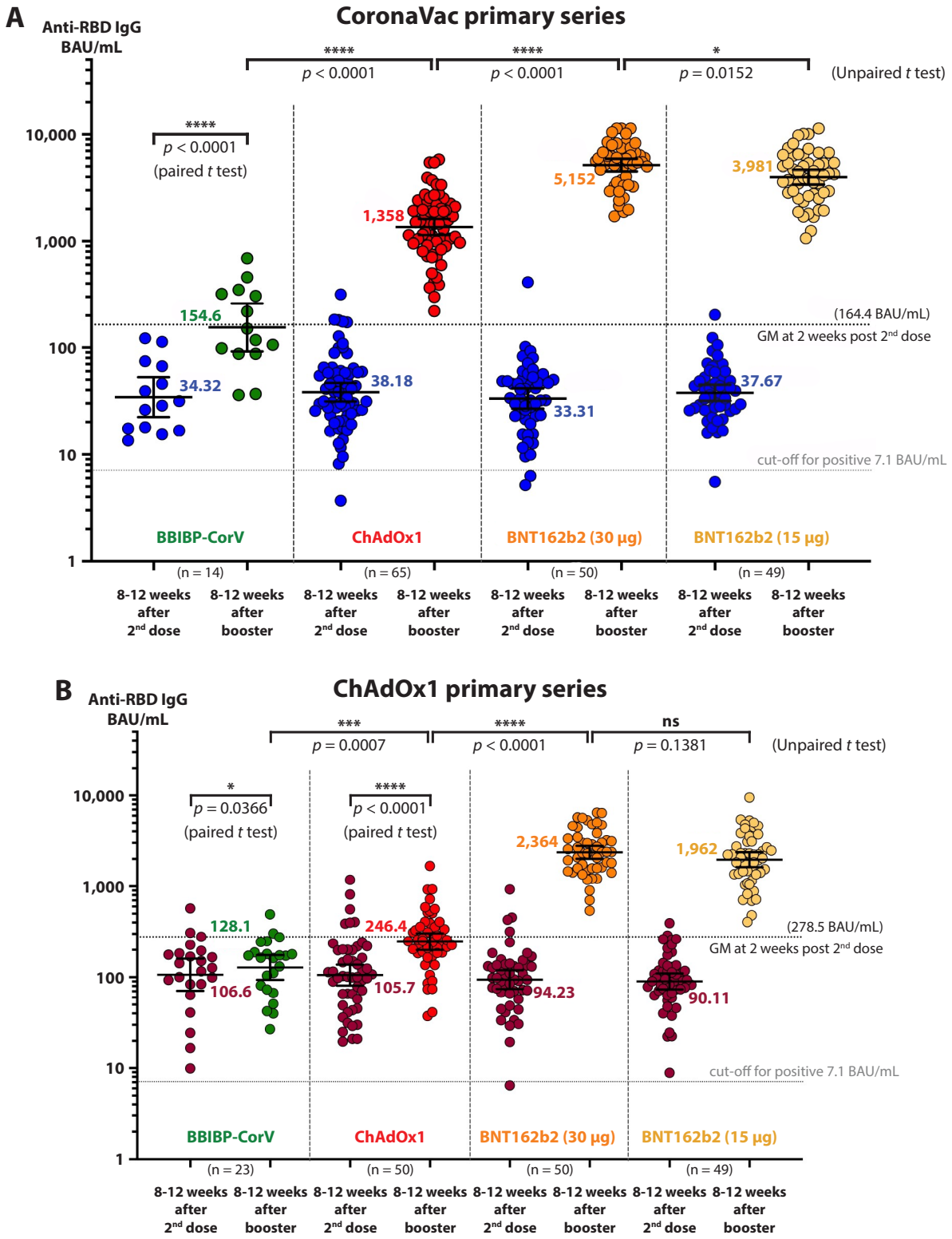

Figure 2. SARS-CoV-2 RBD IgG 2 weeks after booster vaccination. The scatter dot plot represents the SARS-CoV-2 RBD IgG concentration before and 2 weeks after different booster vaccination in participants who received 2-dose (A) CoronaVac primary series or (B) ChAdOx1-primary series. (C) Comparison of SARS-CoV-2 RBD IgG levels at 2 weeks after booster vaccination between participants who received CoronaVac primary series (blue) or ChAdOx1 primary series (red). Error bars represent geometric mean and 95% confidence interval. The upper dotted line represents the geometric mean concentration (GMC) of SARS-CoV-2 RBD IgG at 2 weeks after the 2-dose primary series of CoronaVac or ChAdOx1.[4] The lower dotted line represents the cut-off level for seropositivity.

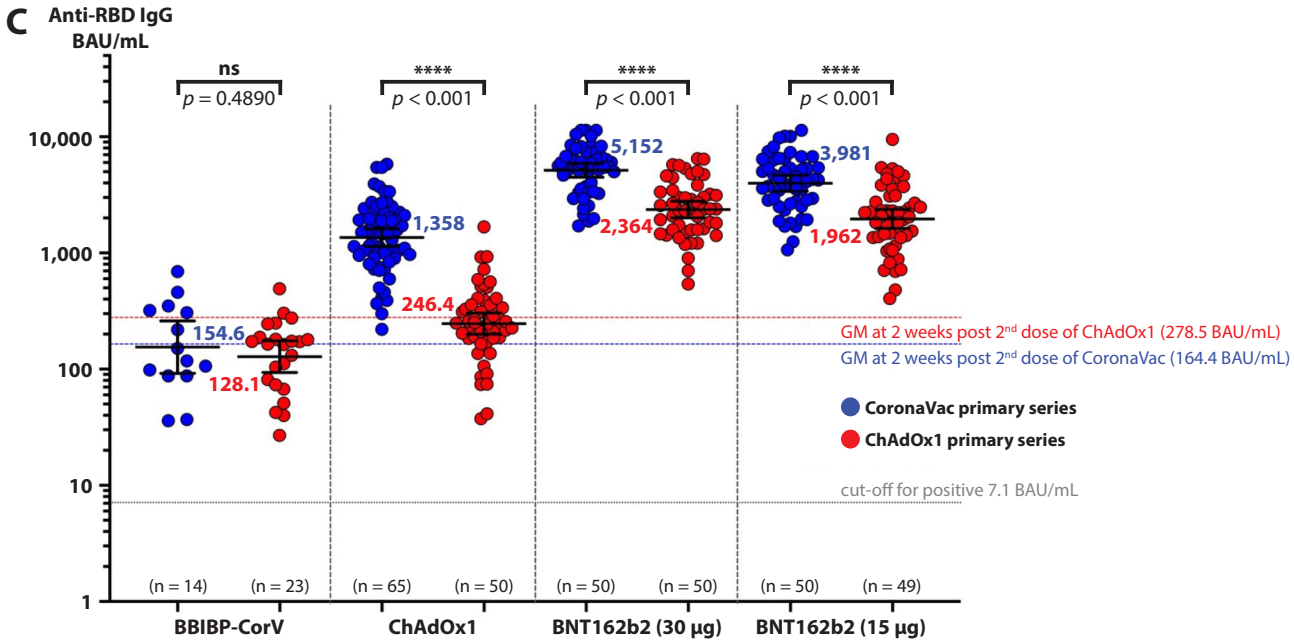

Figure 2. (Continued)

For the ChAdOx1-prime group, the anti-RBD IgG GMC post-booster was significantly higher in participants who received 30 µg-BNT162b2 (2363.8 BAU/mL, 95%CI 2005.6–2786.1) or 15 µg-BNT162b2 (1961.9 BAU/mL, 95%CI 1624.6–2369.1) compared to those who received ChAdOx1 (246.4 BAU/mL, 95%CI 199.6–304.2); or BBIBP-CorV (128.1 BAU/mL, 95%CI 93.5–175.4) (**Figure 2B**). The anti-RBD IgG GMR between post-booster and post-primary series of ChAdOx1-prime participants were 0.46, 0.88, 8.49, and 7.04 for BBIBP-CorV, ChAdOx1, 30 µg-BNT162b2 and 15 µg-BNT162b2, respectively. The post-boost GMC levels in ChAdOx1-prime were generally lower than that in the CoronaVac-prime group for all booster vaccines (**Figure 2C**).

Neutralizing antibody responses against the SARS-CoV-2 variants

For both the CoronaVac-prime and ChAdOx1-prime groups, the neutralizing antibodies (PRNT50) against the Delta (**Figure 3A**) and Beta (**Figure 3B**) variant were significantly higher among those who received a booster dose of BNT162b2 (30 µg or 15 µg) compared to those who received ChAdOx1 or BBIBP-CorV. There was no statistical difference in $PRNT_{50}$ between boosting with 30 µg and 15 µg- BNT162b2 regardless of the primary series vaccine and the type of variants. However, the $PRNT_{50}$ against the Beta variant was around 1.5-fold lower than $PRNT_{50}$ against the Delta variant for both CoronaVac-prime and ChAdOx1-prime groups. The GMRs of the $PRNT_{50}$ between post-booster and post-primary series were highest among the participants who received BNT162b2 booster in both CoronaVac-prime and ChAdOx1-prime groups (**Table 2**). The SARS-CoV-2 RBD IgG levels and the $PRNT_{50}$ against Delta variant or Beta variant were strongly correlated (r = 0.49–0.89).

A pseudovirion neutralization test (PVNT) assay was used to measure neutralizing antibodies against Delta and Omicron. At 2 weeks post booster dose, both CoronaVac- and ChAdOx1-prime groups that received ChAdOx1 booster had significantly lower $PVNT_{50}$ against Delta and Omicron variants than the groups that received 15 µg- or 30 µg BNT162b2 (**Figure 4A–B**). Almost all participants had neutralizing antibodies ($PRNT_{50}$) against Delta, except for 4 participants in the CoronaVac-BBIBP-CorV (2/14, 14%) and ChAdOx1-BBIBP-CorV (2/20, 10%) groups (**Figure 4A**). In contrast, while all participants who received 15 µg and 30 µg BNT162b2 had $PRNT_{50}$ against Omicron, ≤ 50% of participants in the CoronaVac-BBIBP-CorV and ChAdOx1-BBIBP-CorV groups, and 75% (15/20) in the ChAdOx1- ChAdOx1 had $PRNT_{50}$ against Omicron (**Figure 4B**). There was no difference in $PRNT_{50}$ against Delta and Omicron between those who received 15 µg BNT162b2 and 30 µg BNT162, except for the ChAdOx1-prime groups that 30 µg BNT162 had higher $PRNT_{50}$ against Omicron than 15 µg BNT162b2. Notably, among the groups that received ChAdOx1 booster, CoronaVac-prime group had significantly higher $PVNT_{50}$ against Delta and Omicron variants than the ChAdOx1-prime group (**Figure 4A–B** and **Table 2**). The $PVNT_{50}$ GMT against Omicron was 2- to 37-folds lower than that against Delta.

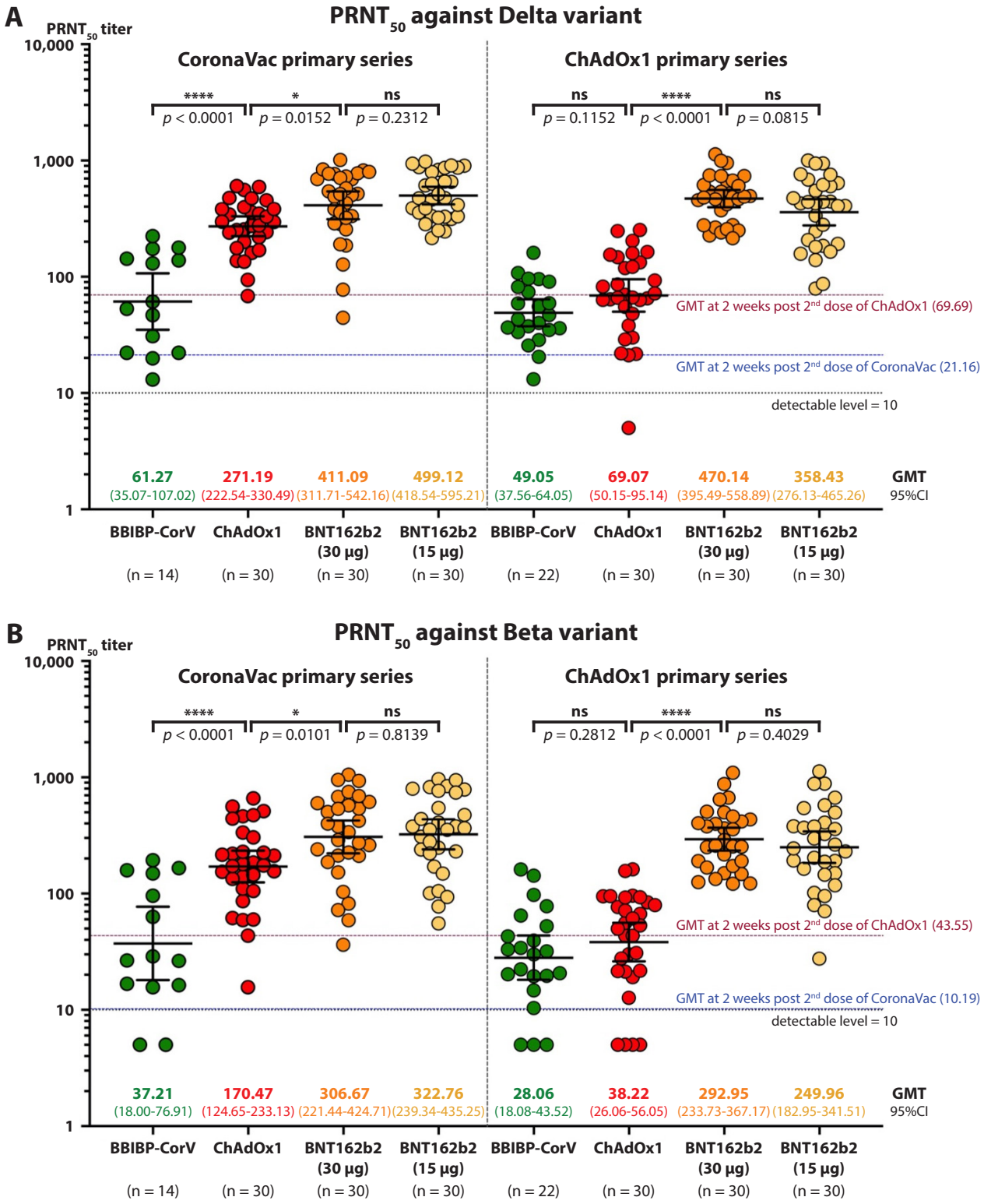

Figure 3. Plaque reduction neutralization titers ($PRNT_{50}$) for SARS-CoV-2 Delta and Beta variants. Scatter dot plots represent $PRNT_{50}$ titer against the (A) Delta or (B) Beta variant at 2 weeks after different booster vaccines in participants who received two doses of Coronavac or ChAdOx1 8–12 weeks earlier. Error bars represent geometric mean titer (GMT) and 95% confidence interval (CI). The upper dotted line represents the geometric mean values of anti-SARS-CoV-2 RBD IgG at 2 weeks after the the 2-dose primary series of CoronaVac or ChAdOx1.[4] Lower dot line represents the cut-off level for seropositivity.

Table 2. The 50% plaque reduction neutralization ($PRNT_{50}$) and 50% pseudovirus neutralization ($PVNT_{50}$) geometric mean antibody titers (GMT) against variant

Type of booster vaccinations					
CoronaVac-prime (n = 104)	**BBIBP-CorV n = 14**	**ChAdOx1 n = 30**	**30 µg BNT162b2 n = 30**	**15 µg BNT162b2 n = 30**	***p*-value**
$PRNT_{50}$ at 2 weeks after boosting					
GMT (95%CI) against Delta variant	61.3 (35.07, 107.02)	271.2 (222.54, 330.49)	411.1 (311.71, 542.16)	499.12 (418.54, 595.21)	< 0.0001
GMR (95%CI) between post-boosting and post-primary series* against Delta variant	2.89 (1.52, 5.50)	12.79 (9.06, 18.06)	19.39 (13.04, 28.84)	23.54 (16.89, 32.82)	< 0.0001
GMT (95%CI) against Beta variant	37.2 (18.00, 76.91)	170.5 (124.65, 233.13)	306.7 (221.44, 424.71)	322.8 (239.34, 435.25)	< 0.0001
GMR (95% CI) between post-boosting and post-primary series* against Beta variant	3.65 (1.65, 8.08)	16.72 (11.11, 25.15)	30.07 (19.79, 45.69)	31.65 (21.27, 47.09)	< 0.0001
$PVNT_{50}$ at 2 weeks after boosting	**n = 14**	**n = 20**	**n = 20**	**n = 20**	
GMT (95%CI) against Delta variant	24.31 (3.42, 172.56)	586.65 (437.72, 786.25)	1,584.8 (1,192.1, 2,106.9)	1,512.7 (1,061.6, 2,155.5)	< 0.0001
GMT (95%CI) against Omicron variant	0.70 (0.55, 8.96)	169.59 (111.80, 257.26)	542.6 (317.52, 927.25)	551.29 (384.25, 790.96)	< 0.0001
$PVNT_{50}$ at 16–20 weeks after boosting		**n = 20**	**n = 20**	**n = 20**	
GMT (95%CI) against Delta variant	NA	93.22 (65.18, 133.33)	212.46 (143.96, 313.54)	164.86 (121.38, 223.91)	0.0012
GMT (95%CI) against Omicron variant	NA	1.39 (0.21, 9.10)	54.34 (17.76, 166.25)	22.33 (4.68, 106.44)	0.001
ChAdOx1-prime (n = 112)	**BBIBP-CorV n = 22**	**ChAdOx1 n = 30**	**30 µg BNT162b2 n = 30**	**15 µg BNT162b2 n = 30**	***p*-value**
$PRNT_{50}$ at 2 weeks after boosting					
GMT (95%CI) against Delta variant	49.0 (37.56, 64.05)	69.1 (50.14, 95.14)	470.1 (395.49, 558.89)	358.4 (276.13, 465.26)	< 0.0001
GMR (95%CI) between post-boosting and post-primary series* against Delta variant	0.70 (0.44, 1.12)	0.99 (0.60, 1.63)	6.74 (4.45, 10.23)	5.14 (3.24, 8.16)	< 0.0001
GMT (95%CI) against Beta variant	28.1 (18.08, 43.53)	38.2 (26.06, 56.05)	292.9 (233.73, 367.17)	250.0 (182.95, 341.51)	< 0.0001
GMR (95%CI) between post-boosting and post-primary series* against Beta variant	0.65 (0.36, 1.15)	0.88 (0.52, 1.49)	6.73 (4.42, 10.26)	5.75 (3.57, 9.24)	< 0.0001
$PVNT_{50}$ at 2 weeks after boosting	**n = 20**	**n = 20**	**n = 20**	**n = 20**	
GMT (95%CI) against Delta variant	17.15 (4.80, 61.29)	120.6 (77.63, 187.36)	1,081.2 (797.92, 1,465.1)	720.66 (505.26, 1,027.9)	< 0.0001
GMT (95%CI) against Omicron variant	0.10 (0.02, 0.52)	3.25 (0.60, 17.53)	521.16 (396.91, 684.30)	232.31 (155.20, 347.72)	< 0.0001
$PVNT_{50}$ at 16–20 weeks after boosting			**n = 20**	**n = 20**	
GMT (95%CI) against Delta variant	NA	NA	207.1 (158.57, 270.47)	178.63 (120.49, 264.83)	0.0012
GMT (95%CI) against Omicron variant	NA	NA	116.88 (76.94, 177.54)	14.04 (3.138, 62.83)	0.001

*The geometric mean ratio (GMR) of $PRNT_{50}$ between post-booster and post-primary series. The post primary series GMC was derived from the study in the same setting as the current study.[4] The post primary series GMT (95%CI) at 2 weeks after the second dose of the 2-dose homologous CoronaVac, 4 weeks apart, were 21.2 (16.07, 27.87) and 10.2 (7.92, 13.12) against Delta and Beta variants, respectively; and after 2-dose homologous ChAdOx1, 10 weeks apart, were 69.7 (48.08, 101.00) and 43.5 (30.73, 61.72) against Delta and Beta variants, respectively.
CI: confidence interval; IQR: interquartile range

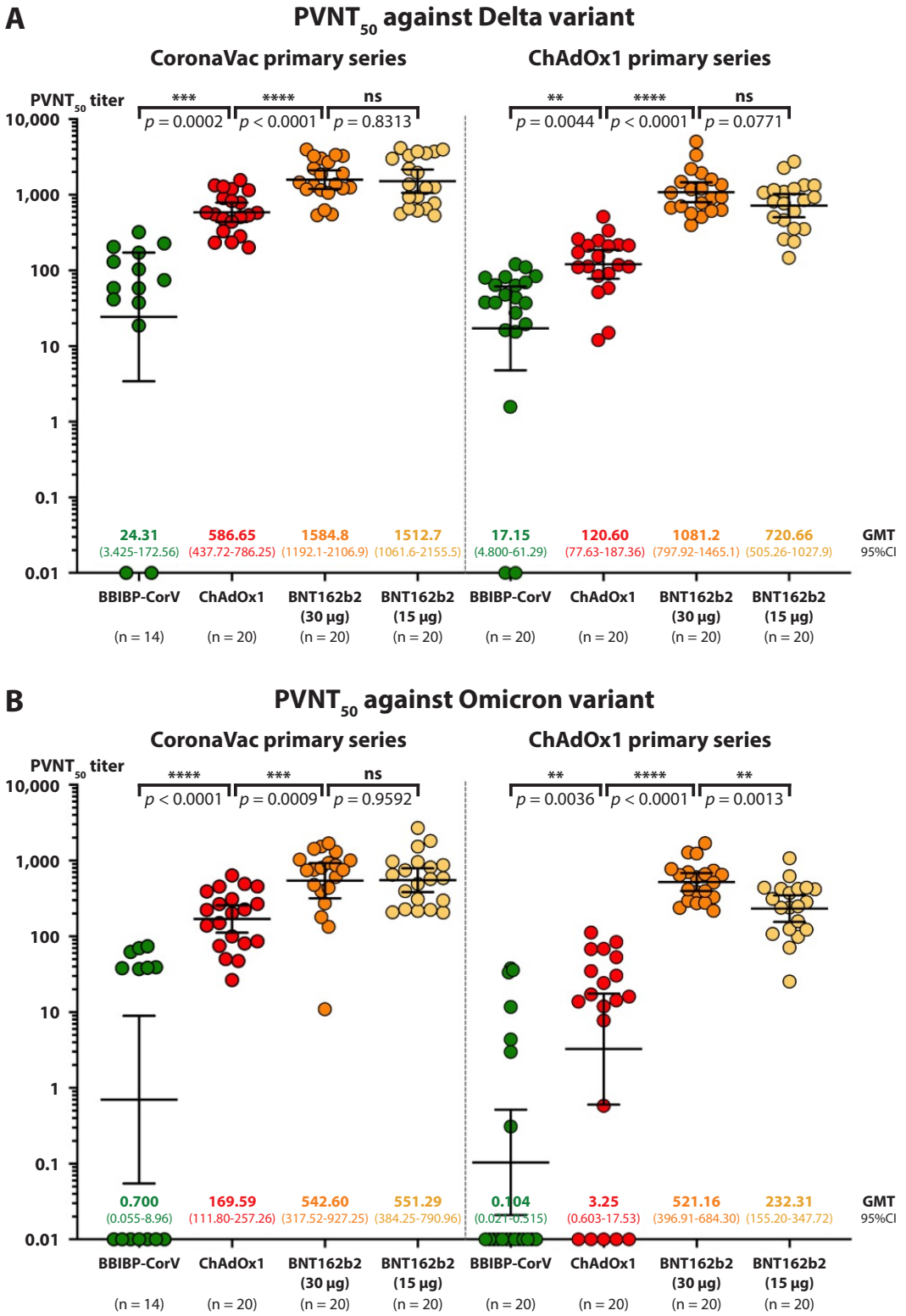

Figure 4. Pseudovirion neutralization titers ($PVNT_{50}$) for SARS-CoV-2 Delta and Omicron variants. Aligned dot plots represent $PVNT_{50}$ against the (A) Delta or (B) Omicron variant at 2 weeks after different booster vaccines in participants who received two doses of Coronavac or ChAdOx1 8–12 weeks earlier. Error bars represent geometric mean titer (GMT) and 95% confidence interval (CI). The $PVNT_{50}$ titer against the (D) Delta or (E) Omicron variant at 2 weeks and 16–20 weeks of the same participants after different booster vaccines. Paired t test is used for statistical analysis and the *p* values are indicated.

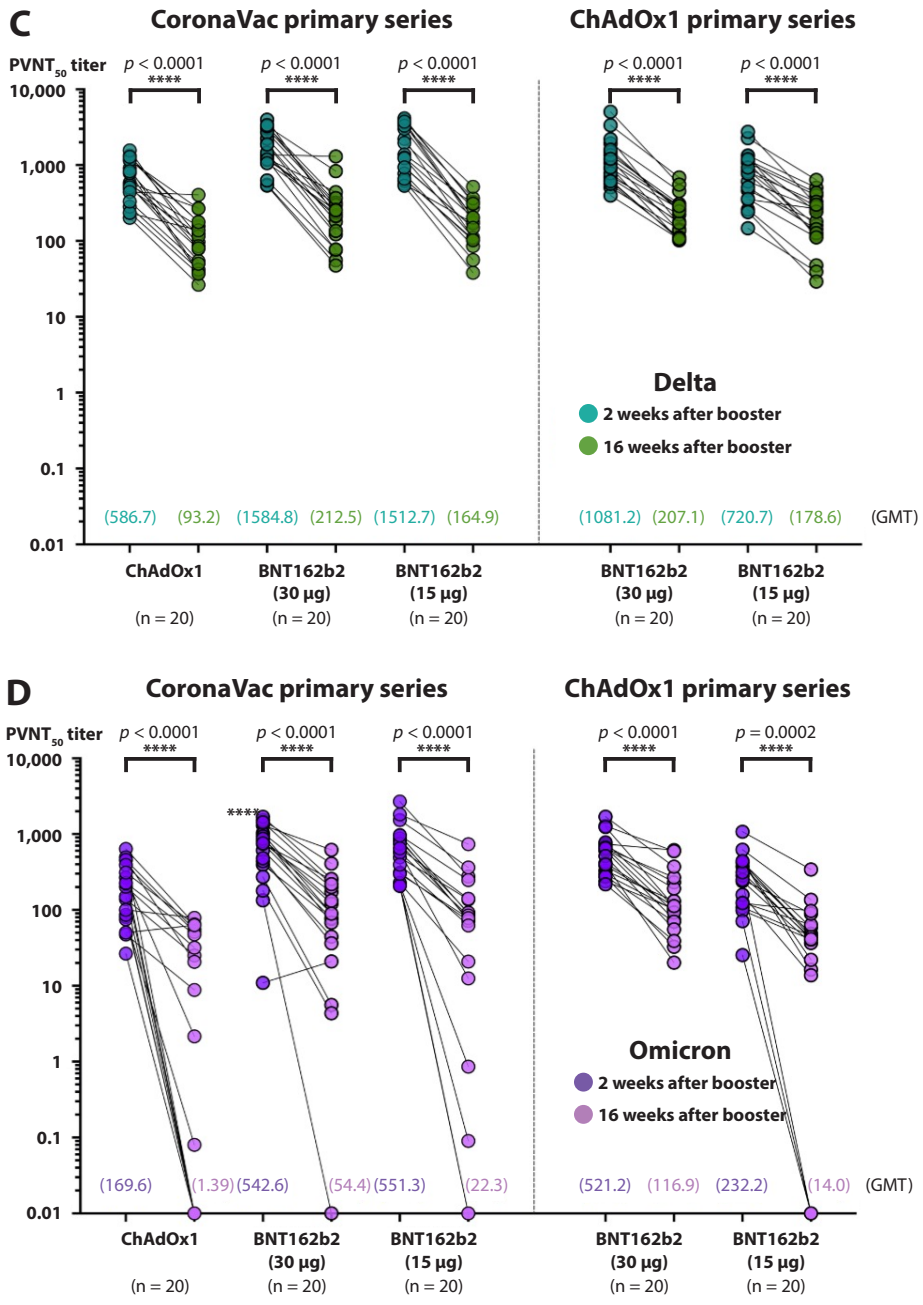

Figure 4. (Continued)

Only the groups that received BNT162b2 booster and CoronaVac-ChAdOx1 groups were followed up as participants in the other groups have received additional booster vaccination outside of this study due to their low SARS-CoV-2 IgG levels. There was a significant decline (at least 4-fold) in $PVNT_{50}$ against Delta and Omicron at 16–20 weeks following the booster. More significant decline in $PVNT_{50}$ against Omicron (4.5 to 122 folds) was observed compared to the Delta variant (4 to 9-fold) (**Figure 4C–D**, **Table 2**). However, 100% and > 90% of each group remained seropositive against Delta and Omicron. Notably, $PVNT_{50}$ GMT against Delta and Omicron were highest in 30 µg BNT162 group for both the CoronaVac-prime and ChAdOx1-prime groups at this timepoint (**Figure 4C–D**, **Table 2**).

QuantiFERON SARS-CoV-2 interferon gamma release assay (IGRA)

Cellular immunity was measured at baseline using the *QuantiFERON* SARS-CoV-2 interferon gamma release assay (IGRA). Participants with a negative IGRA response at baseline were tested again at two weeks post-booster. At baseline, 35.8% (62/173) of participants in ChAdOx1-prime group and 25% (45/179) of CoronaVac-prime group had positive IGRA (p = 0.029). Among those with negative IGRA at baseline, IGRA conversion was the highest after a booster dose of 30 µg-BNT162b2, followed by 15 µg-BNT162b2, ChAdOx1, and BBIBP-CorV. None of the study participants who were IGRA-negative at baseline in the ChAdOx1-prime group had a positive IGRA response following boosting with BBIBP-CorV or ChAdOx1.

Discussion

This study is one of the few studies that have evaluated the reactogenicity and immunogenicity of BBIBP-CorV and half dose BNT162b2. There were a number of major findings from this study. First, BBIBP-CorV, ChAdOx1, BNT162b2 (standard and reduced dosage) given as booster dose to individuals who previously received either CoronaVac or ChAdOx1 primary series were found to be safe and well tolerated. Second, BNT162b2 given as a booster induced the highest humoral and cellular immune responses compared to BBIBP-CorV or ChAdOx1. Third, both 15 μg and 30 μg-BNT162b2 given as booster in general induced similar humoral responses against all the SARS-CoV-2 variants regardless of their primary series. Fourth, despite lower anti-RBD IgG at baseline, higher humoral response was observed in the CoronaVac-prime group following the booster dose compared to the ChAdOx1-prime group. Fifth, a high proportion of individuals still have antibodies against Delta and Omicron at 16–20 weeks following BNT162b2 booster and those who were prime with CoronaVac and boosted with ChAdOx1. Lastly, ChAdOx1-prime-30 μg-BNT162b2 boost had the highest antibodies against Omicron at 16–20 weeks.

Heterologous boosting vaccination in our study were generally well tolerated, and the AEs rates observed in this study were in line with those reported in COVID-19 vaccine primary series and booster studies.[14,18] Heterologous boosting regimen were also found to be more immunogenic than homologous ChAdOx1 boosting regimen or homologous inactivated vaccines regimen (CoronaVac prime-BBIBP-CorV boost) in our study, which was consistent with recent studies.[19-23] An important finding from our study is that heterologous boosting with BBIBP-CorV vaccine and homologous ChAdOx1 prime and boost was poorly immunogenic. This finding is supported by a previous study that revealed poor immunogenicity of heterologous ChAdOx1 prime-VLA2001 (inactivated vaccine by Valvena) boost and homologous ChAdOx1 prime and boosting.[19] Our findings suggest that inactivated whole virus vaccine as a booster vaccine and homologous ChAdOx1 boosting may not be effective at generating high levels of neutralizing antibodies, particularly against the Omicron BA.1 variant. Taken together, our data support the use of BNT162b2 as a 1st booster, although other vaccines such as mRNA-1273 and Novavax were not tested in this study.

The persistence of immunity following COVID-19 booster is unknown. Our findings suggest possible protection for at least 16–20 weeks despite rapid waning antibody levels. It is important to note that the antibody threshold of protection against infection and severe disease has not been identified, and immune memory cells which are thought to be important for long-term protection were not measured in our study. Furthermore, a recent study reported breakthrough infections two months after receiving a mRNA booster dose.[24] It is increasing clear that the current approved COVID-19 vaccines do not adequately protect against SARS-CoV-2 infection, particularly against the Omicron subvariants which are able to evade immunity generated against previous variants and vaccination. However, the vaccine appears to still provide protection against severe disease in healthy adults although the duration is unclear. Several studies have found that a fourth dose (2nd booster vaccination) is highly immunogenic and efficacious, and several countries including Australia has recommended a 4th dose vaccination for older adults and to those who are immunocompromised.[25,26] Whether a fourth dose is needed against the rapidly changing SARS-CoV-2 variants are being closely monitored.

Virus-specific memory T cells are important for protection against SARS-CoV-2, particularly against severe disease. Only a third of ChAdOx1-prime and a quarter of CoronaVac-prime participants in our study remained positive for IGRA as a marker for T cell response at 8–12 weeks post primary series. Previous studies evaluating 2-dose ChAdOx1 primary series have reported the generation of robust T cell response following the first dose, with no significant increase in T cell responses following the second dose,[27,28] and following a homologous ChAdOx1 booster.[19] On the other hand, the study of 2-dose CoronaVac primary series revealed poor inducer of T-cell response.[29] The discrepancy in T cell responses after primary series from our study could be due to waning immunity, population differences and the different assays used to measure IFN-γ response (Quantiferon vs. IFN-γ ELISPOT). We found BBIBP-CorV boosting induced poor IGRA response against the spike protein; however, it is important to note that inactivated vaccine (i.e. BBIBP-CorV) may have other antigens (i.e., M or N proteins) that induce T cell responses,[30] which was not measured in our study. While IGRA have been used as a surrogate marker for T cell response against SARS-CoV-2,[31,32] other measurement of T cell responses including the number of T cells and other cytokine responses (TNFα, IL-2 and IL-10) may provide more in-depth analysis of the SARS-CoV-2 vaccine-induced T cell responses. The low T cell boosting responses following homologous boosting regimen of ChAdOx1 is consistent with the low neutralizing antibody boosting responses observed in our study. This could be explained by the anti-vector interference, and possibly due to a short interval (8–12 weeks) between the third and second dose.

Our finding that half-dose BNT162b2 was equally immunogenic as the standard dosage, but with less reactogenicity, suggesting that less amount of antigen may be sufficient for boosting immune responses against SARS-CoV-2. This finding is in concordance with previous study on mRNA1273 vaccine where half dose of the mRNA1273 (50 μg) was able to induce significantly higher neutralizing antibodies than the level induced after primary series against the SARS-CoV-2 variants of concerns.[14] Additional studies are needed to verify the clinical efficacy and persistence of immunity of half-dose mRNA vaccines. The use of fractional dose will be relevant in the context of vaccine shortages that may be applicable for future epidemics.

There are some limitations in this study. First, our study was conducted in a non-randomized open label manner which was due to the availability of each vaccine which may lead to selection bias. Second, our sample size is small, particularly those who received BBIBP-CorV as booster; therefore, the data need to be interpreted with caution. Third, the participants in this study were healthy adults, and may not be generalized to other populations such as immunocompromised individuals. Furthermore participants in our study were predominantly female, which might have limited generalizability of the findings to male, although a recent systematic review did not find any difference in vaccine efficacy between male and female.[33] Lastly, we did not measure neutralizing antibodies titers against ancestral strain and were not able to directly compare the neutralizing titers to other SARS-CoV-2 variants.

Conclusion

Our study found that a booster dose of standard or half dose BNT162b2 given to individuals previously vaccinated with CoronaVac or ChAdOx1 is highly immunogenic, while BBIBP-CorV and homologous ChAdOx1 are not effective booster vaccines. Our study findings have important implications on the choice of booster dose for countries that have introduced CoronaVac or ChAdOx1 as primary series to date.

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Conflict of Interest Declaration

All authors declare no personal or professional conflicts of interest, and no financial support from the companies that produce and/or distribute the drugs, devices, or materials described in this report.

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Author Contributions

- N.A. and S.N. equally contributed to the research work.
- Conceptualization and Methodology: N.A., S.N., J.S., K.R., Y.J., K.S.
- Formal analysis and data curation: N.A., J.S., S.N., Z.Q.T.
- Project administration: N.A, J.S., S.N.
- Supervision: K.C.
- Resources and Funding: K.C.
- All authors involved with investigation, and writing-review and editing.

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