

1 **The immunogenicity and reactogenicity of four COVID-19 booster vaccinations against**
2 **SARS-CoV-2 variants of concerns (Delta, Beta, and Omicron) following CoronaVac or**
3 **ChAdOx1 nCoV-19 primary series**

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46 **Abstract**

47 The CoronaVac (Sinovac Biotech) and ChAdOx1(Oxford-AstraZeneca) are two widely used
48 COVID-19 vaccines. We examined the immunogenicity of four COVID-19 booster vaccine:
49 BBIBP-CorV (Sinopharm Biotech), ChAdOx1, 30µg-BNT162b2 and 15µg-BNT162b2 (Pfizer-
50 BioNTech), in healthy adults who received a two-dose CoronaVac or ChAdOx1 8-12 weeks
51 earlier. Among the 352 participants (179 CoronaVac and 173 ChAdOx1 participants), 285 (81%)
52 were female, and median age was 39(IQR: 31-47) years. 98%(175/179) and 99%(172/173) of
53 Coronavac and ChAdOx1 participants remained seropositive at baseline. Two weeks post-
54 booster, both 30µg- and 15µg- BNT162b2 induced the highest anti-RBD IgG concentration
55 (BAU/mL); Coronavac-prime: 30µg-BNT162b2, 5152.2(95%CI 4491.7-5909.8); 15µg-
56 BNT162b2, 3981.1(3397.2-4665.4); ChAdOx1, 1358.0(1141.8-1615.1); BBIBP-CorV,
57 154.6(92.11-259.47); ChAdOx1-prime: 30µg-BNT162b2, 2363.8(2005.6-2786.1); 15µg-
58 BNT162b2, 1961.9(1624.6-2369.1); ChAdOx1, 246.4(199.6-304.2); BBIBP-CorV, 128.1(93.5-
59 175.4). Similarly, both 30µg- and 15µg- BNT162b2 boosting induced the highest neutralizing
60 antibodies (nAb) titres against all variants and highest T-cell response evaluated by interferon
61 gamma released assays. While all BNT162b2 or heterologous ChAdOx1-boosted participants
62 had nAb against Omicron, these were <50% for BBIBP-CorV and 75% for homologous
63 ChAdOx1-boosted participants. There was significant decrease in nAb (>4-fold) 16-20 weeks
64 post booster. Heterologous boosting with BNT162b2 following CoronaVac or ChAdOx1
65 primary series is most immunogenic. A lower dose BNT162b2 may be considered as booster in
66 settings with limited vaccine supply.

67

68 **Keywords:** Booster; COVID-19; CoronaVac; ChAdOx1; vaccine.

69 **Introduction**

70 Both CoronaVac (an inactivated whole-virion SARS-CoV-2 vaccine, Sinovac Life Science)
71 and ChAdOx1 (a chimpanzee adenovirus-vectored vaccine expressing the SARS-CoV-2 spike
72 protein, Oxford, AstraZeneca) are safe and effective vaccines against symptomatic COVID-19
73 caused by the ancestral Wuhan strain, and to a lower extent against the Delta variant, and even
74 lower efficacy against Omicron [1-7]. These two vaccines are widely used vaccines globally,
75 particularly in low- and middle-income countries [8].

76 Breakthrough infections following COVID-19 vaccination, which are likely due to a
77 combination of waning immunity and the emergence of SARS-CoV-2 variants, have led to the
78 need for booster vaccination [9-13]. While the antibody threshold of protection has not been
79 identified, higher antibody levels are likely to be associated with greater protection⁷. Cell
80 mediated immune responses generated following vaccination also plays an important role in
81 protection against SARS-CoV-2.

82 Several studies have demonstrated improved humoral responses with heterologous COVID-
83 19 prime-boost vaccination, primarily on ChAdOx1 and mRNA vaccines [14-18]. However,
84 other combinations of prime-boost COVID-19 vaccination involving inactivated COVID-19
85 vaccines have not been evaluated. Furthermore, the persistence of immunity following a booster
86 (3rd) dose of COVID-19 vaccine is unknown. A recent study of reduced dosage of mRNA-1273
87 vaccine as a booster was found to be highly immunogenic, suggesting that a lower dosage
88 vaccine may be equally immunogenic as a standard dosage, particularly for mRNA vaccines
89 [19].

90 In this study, we examined the safety and immunogenicity of four booster vaccinations at 2
91 weeks and up to 16-20 weeks in healthy adults who previously received a 2-dose primary series
92 of CoronaVac or ChAdOx1 vaccine 8-12 weeks earlier.

93

94 **Results**

95 Among 352 participants enrolled (179 and 173 participants in CoronaVac- and
96 ChAdOx1-prime group), 285 (81%) were female, and the median age was 39 (interquartile
97 range, IQR: 31-47) years. The demographic of the study participants receiving different booster
98 vaccine was shown in Table 1. The recruitment for BBIBP-CorV booster groups were stopped
99 after 36 participants, 14 in CoronaVac-prime and 22 in ChAdOx1-prime, after the preliminary
100 analysis found low anti-SARS-CoV-2 RBD IgG concentration.

101

102 **Adverse events (AEs)**

103 Among the CoronaVac-prime groups, the overall AEs was most frequent after boosting
104 with ChAdOx1 (98%), followed by 30 μ g-BNT162b2 (92%), 15 μ g-BNT162b2 (80%), and
105 BBIBP-CorV (70%); whereas in ChAdOx1-prime group, the overall AEs was most frequent
106 after boosting with 30 μ g-BNT162b2 (98%), followed by 15 μ g-BNT162b2 (88%), ChAdOx1
107 (72%), and BBIBP-CorV (61%) (Fig. 1, Supplementary Table 1). Systemic AEs were in the
108 same trend as local AEs (Fig. 1 and Supplementary Table 1). All AEs were mild (grade 1) to
109 moderate (grade 2) in severity and recovered within 2-3 days. No serious AEs was found in this
110 study.

111

112 **Anti-SARS-CoV-2 RBD IgG responses**

113 At baseline (8-12 weeks post-primary series), 175/179 (97.8%) participants in
114 CoronaVac-prime and 172/173 (99.4%) in ChAdOx1-prime remained seropositive. The anti-
115 RBD IgG GMC at baseline were lower in the CoronaVac-prime groups than in the ChAdOx1-
116 prime group (36.31 vs. 98.27 BAU/mL) (Fig. 2A-B). For the CoronaVac-prime groups, the anti-
117 RBD IgG geometric mean concentrations (GMC) post-booster in the 30 μ g-BNT162b2 group
118 (5152.2 BAU/mL, 95%CI 4491.7-5909.8) was significantly higher than other vaccine booster
119 groups: 15 μ g-BNT162b2 (3981.1 BAU/mL, 95% CI 3397.2-4665.4), ChAdOx1 (1,358
120 BAU/mL, 95%CI 1141.8, 1615.1), and BBIBP-CorV (154 BAU/mL, 95%CI 92.11, 259.47)
121 (Fig. 2A and Supplementary Table 2). The geometric mean ratio (GMR) between post-boost and
122 post-primary series of CoronaVac for BBIBP-CorV, ChAdOx1, 30 μ g-BNT162b2 and 15 μ g-
123 BNT162b2 were 0.94, 8.26, 31.34, and 24.22, respectively (Supplementary Table 2).

124 For the ChAdOx1-prime group, the anti-RBD IgG GMC post-booster was significantly
125 higher in participants who received 30 μ g-BNT162b2 (2363.8, 95%CI 2005.6-2786.1) or 15 μ g-
126 BNT162b2 (1961.9 BAU/mL, 95% CI 1624.6-2369.1) compared to those who received
127 ChAdOx1 (246.4 BAU/mL, 95%CI 199.6-304.2); and BBIBP-CorV (128.1 BAU/mL, 95%CI
128 93.5-175.4) (Fig. 2B). The GMR between post-boost and post-primary series of ChAdOx1 were
129 0.46, 0.88, 8.49, and 7.04 for BBIBP-CorV, ChAdOx1, 30 μ g-BNT162b2 and 15 μ g-BNT162b2,
130 respectively (Supplementary Table 2). The post-boost GMC levels in ChAdOx1-prime were
131 generally lower than that in the CoronaVac-prime group for all booster vaccines (Fig. 2C).

132

133 **Neutralizing antibody responses against the SARS-CoV-2 variants**

134 At 2 weeks post booster dose, almost all participants had (50% plaque reduction
135 neutralization titre) PRNT₅₀ against Delta and Beta; 1/30 (3%) participant in the ChAdOx1-

136 ChAdOx1 group was negative against Delta and nine participants among the CoronaVac-
137 BBIBP-CorV (2/14, 14%), ChAdOx1-BBIBP-CorV (3/22, 14%) and ChAdOx1-ChAdOx1 (4/30,
138 13%) were negative against Beta. For both the CoronaVac-prime and ChAdOx1-prime groups,
139 the PRNT₅₀ GMT against the Delta (Fig. 3A) and Beta (Fig. 3B) variant were significantly
140 higher among those who received a booster dose of BNT162b2 (30µg or 15µg) compared to
141 those who received ChAdOx1 or BBIBP-CorV. There was no statistical difference in PRNT₅₀
142 between boosting with 30µg and 15µg- BNT162b2 regardless of the primary series vaccine and
143 the type of variants. However, the PRNT₅₀ against the Beta variant was in general around 1.5-
144 fold lower than the Delta variants for both CoronaVac-prime and ChAdOx1-prime groups (Fig.
145 3C). The GMRs of the PRNT₅₀ between post-boost and post-primary series were highest among
146 the participants who received BNT162b2 boosting vaccination in both CoronaVac-prime and
147 ChAdOx1-prime groups (Table 2). The SARS-CoV-2 RBD IgG levels and the PRNT₅₀ against
148 Delta variant (Supplementary Fig. S1A and B) or Beta variant (Supplementary Fig. S1C and D)
149 were strongly correlated ($r = 0.49-0.89$).

150 In order to compare the neutralising titers between Delta and Omicron, we performed the
151 pseudovirion neutralization test (PVNT) assay on both variants. At 2 weeks post booster dose,
152 almost all participants had 50% pseudovirus neutralization antibody titres (PRNT₅₀) against
153 Delta, except for 4 participants in the CoronaVac-BBIBP-CorV (2/14, 14%) and ChAdOx1-
154 BBIBP-CorV (2/20, 10%). In contrast, PRNT₅₀ against Omicron was only present in $\leq 50\%$ in
155 CoronaVac-BBIBP-CorV and ChAdOx1-BBIBP-CorV groups, and 75% (15/20) in the
156 ChAdOx1- ChAdOx1. Among the CoronaVac-prime groups, 15µg and 30µg-BNT162b2 booster
157 induced similar PVNT₅₀ against Omicron (Fig 4A), whereas in the ChAdOx1-prime groups, the
158 group that received 15µg-BNT162b2 induced significantly lower PVNT₅₀ against Omicron

159 compared to the 30 μ g-BNT162b2 group (Fig. 4B). Notably, both CoronaVac- and ChAdOx1-
160 prime groups that received ChAdOx1 booster had significantly lower PVNT₅₀ against Delta and
161 Omicron variants than the groups that received 15 μ g- or 30 μ g BNT162b2 (Fig. 4A and 4B).
162 Between the CoronaVac- and ChAdOx1-prime groups that received ChAdOx1 booster,
163 CoronaVac prime-ChAdOx1 boost group had significantly higher PVNT₅₀ against Delta and
164 Omicron variants than the ChAdOx1 prime-ChAdOx1 boost group (Fig. 4A-B and Table 2). The
165 PVNT₅₀ GMT against Omicron was 2- to 37-folds lower than that against Delta (Fig. 4C and
166 Table 2).

167 The groups that received BBIPB-CorV as booster or ChAdOx1 as priming and booster
168 (3-dose ChAdOx1) were not followed up for the 16-20 weeks as they have received additional
169 booster vaccination outside of this study after revealing the low antibody results. For the rest of
170 the groups, there was a significant decline (at least 4-fold) in PVNT₅₀ against Delta and Omicron
171 at 16-20 weeks after boosting in both the CoronaVac-prime and ChAdOx1-prime groups (Fig.
172 4D-E and Table 2). However, 100% and >90% of each group remained seropositive against
173 Delta and Omicron. No significant difference in PVNT₅₀ against Delta and Omicron was
174 observed between the CoronaVac-prime and ChAdOx1-prime groups at this timepoint (Table 2).
175 However, a more significant drop in PVNT₅₀ against Omicron (4.5 to 122 folds) was observed
176 compared to the Delta variant (4 to 9-fold) (Fig 4D-E, Table 2).

177

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

179 Cellular immunity was measured at baseline using the QuantiFERON SARS-CoV-2
180 interferon gamma release assay (IGRA). Participants with a negative IGRA response at baseline
181 were tested again at two weeks post-booster. At baseline, a higher proportion of 35.8% (62/173)

182 of participants in ChAdOx1-prime group and 25% (45/179) of CoronaVac-prime group had
183 positive IGRA ($P=0.029$). Among those with negative IGRA at baseline, IGRA conversion was
184 the highest after a booster dose of 30 μ g-BNT162b2, followed by 15 μ g-BNT162b2, ChAdOx1,
185 and BBIBP-CorV (Supplementary Table 2). None of the study participants who were IGRA-
186 negative at baseline in the ChAdOx1-prime group had a positive IGRA response following
187 boosting with BBIBP-CorV or ChAdOx1 (Supplementary Table 2 and Supplementary Fig. S2).

188

189 **Discussion**

190 In this study, BBIBP-CorV, ChAdOx1, BNT162b2 (standard and reduced dosage) given
191 as booster dose to individuals who previously received either CoronaVac or ChAdOx1 primary
192 series were found to be safe and well tolerated. BNT162b2 given as a booster induced the
193 highest humoral and cellular immune responses compared to BBIBP-CorV or ChAdOx1.
194 Furthermore, both 15 μ g and 30 μ g-BNT162b2 induced similar humoral responses against the
195 SARS-CoV-2 all variants tested for both CoronaVac- and ChAdOx1- prime groups, except for
196 the neutralising antibody titers against the Omicron variant in the ChAdOx1-prime group.
197 Notably, higher humoral response was observed in the CoronaVac-prime group following the
198 booster dose compared to the ChAdOx1-prime group while having the lower circulating
199 antibodies at baseline. Despite a rapid decline in neutralising antibodies against Delta and
200 Omicron 16-20 weeks following heterologous ChAdOx1 or BNT162b2 booster, a high
201 proportion of individuals still have antibodies against Delta and Omicron.

202 Heterologous boosting vaccination in our study were generally well tolerated, and the
203 AEs rates observed in this study were in line with those reported in COVID-19 vaccine primary
204 series and booster studies [19,20]. Heterologous boosting regimen were also found to be more

205 immunogenic than homologous ChAdOx1 boosting regimen or homologous inactivated vaccines
206 regimen (CoronaVac prime-BBIBP-CorV boost) in our study, which was consistent with recent
207 studies [21-25]. However, heterologous boosting with BBIBP-CorV vaccine was poorly
208 immunogenic, which was in line with previous studies, including a study that revealed poor
209 immunogenicity of heterologous ChAdOx1 prime-VLA2001 (inactivated vaccine by Valvena)
210 boost [24]. Our findings suggest that inactivated whole virus vaccine as a booster vaccine may
211 not be effective at generating high levels of neutralising antibodies.

212 The SARS-CoV-2 Omicron variant, recently identified in November 2021 has been
213 reported to evade immunity induced from past infection or two vaccine doses [26-28]. Our
214 results suggest that a third dose of BNT162b2 can overcome this immune evasion through the
215 induction of neutralising antibodies. A recent study also reported high antibodies against
216 Omicron following a third dose of mRNA vaccines (mRNA-1273 or BNT162b2) [29].
217 Heterologous boost with ChAdOx1 was immunogenic in CoronaVac-prime participants but was
218 poorly immunogenic in ChAdOx1-prime recipients. Taken together, these data support the use of
219 BNT162b2 as a booster regardless of the primary series against the Delta and Omicron variants
220 that are widely circulating globally. Consequently, ChAdOx1 may also be use as a booster for
221 CoronaVac-prime participants.

222 The persistence of immunity following COVID-19 booster is unknown. Our findings
223 suggest possible protection against Delta and Omicron infection for at least 16-20 weeks despite
224 rapid waning antibody levels. It is important to note that the antibody threshold of protection
225 against infection and severe disease has not been identified, and immune memory cells which are
226 thought to be important for long-term protection was not measured in our study. Furthermore, a
227 recent study reported breakthrough infections two months after receiving a mRNA booster dose

228 (received mRNA primar series) [30]. Larger studies with longer duration are needed to confirm
229 our findings and also determine the persistence of immunity against SARS-CoV-2 infection and
230 severe disease. A fourth booster dose study has been studied in high-risk groups [31] and is
231 currently under investigation in Israel [32].

232 Virus-specific memory T cells are important for protection against SARS-CoV-2,
233 particularly against severe disease. Only a third of ChAdOx1-prime and a quarter of CoronaVac-
234 prime participants in our study remained positive for IGRA as a marker for T cell response at
235 baseline; i.e. 8-12 weeks post primary series. Previous studies evaluating 2-dose ChAdOx1
236 primary series have reported the generation of robust T cell response following the first dose,
237 with no significant increase in T cell responses following the second dose [33,34], and following
238 a homologous ChAdOx1 booster [21]. On the other hand, the study of 2-dose CoronaVac
239 primary series revealed poor inducer of T-cell response [35]. The discrepancy in T cell responses
240 after primary series from our study could be due to waning immunity, population differences and
241 the different assays used to measure IFN- γ response (Quantiferon vs. IFN- γ ELISPOT). We
242 found BBIBP-CorV boosting poorly induced IGRA response; however, it is important to note
243 that inactivated vaccine (i.e. BBIBP-CorV) may have other antigens (i.e., M or N proteins) that
244 induce T cell responses [36], whereas in our study, we only examined T cell responses to S
245 protein, and thus may have underestimated the cellular responses. The low T cell boosting
246 responses following homologous boosting regimen of ChAdOx1 is in line with the low
247 neutralizing antibody boosting responses observed in this study. This could be explained by the
248 anti-vector interference, and possibly due to a short interval (8-12 weeks) between the third and
249 second dose.

250 Our finding that half-dose BNT162b2 was equally immunogenic as the standard dosage,
251 but with less reactogenicity, suggesting that less amount of antigen may be sufficient for
252 boosting immune responses against SARS-CoV-2. This finding is in concordance with previous
253 study on mRNA1273 vaccine where half dose of the mRNA1273 (50 µg) was able to induce
254 significantly higher neutralizing antibodies than the level induced after primary series against the
255 SARS-CoV-2 variants of concerns [19]. A lower mRNA vaccine dose may be considered for
256 COVID-19 booster vaccination, given that the limited vaccine supply globally.

257 There are some limitations in this study. First, our study was conducted in a non-
258 randomized open label manner which was due to the availability of each vaccine at a different
259 timing may lead to selection bias. Second, our sample size is small, particularly those who
260 received BBIBP-CorV as booster; therefore, the data need to interpret with caution. Third, the
261 participants in this study were healthy adults, and may not be generalized to other populations
262 such as immunocompromised individuals. Lastly, how our findings translate to disease
263 protection warrant further investigation.

264
265 In conclusion, our study found that a booster dose of BNT162b2 given to individuals
266 previously vaccinated with CoronaVac or ChAdOx1 is the most immunogenic and induced high
267 cross protective antibodies against Delta, Beta, and Omicron variants, and T-cell response.
268 BBIBP-CorV and homologous ChAdOx1 are not effective booster vaccines. The rapid decline of
269 antibodies after 16-20 weeks of receiving the booster warrants further investigation into the
270 efficacy and persistence of immunity following the booster dose. Our study findings have
271 important implications on the choice of booster dose for countries that have introduced
272 CoronaVac or ChAdOx1 as primary series to date. Our study also suggests that reduced dosage

273 of BNT162b2 may be used as a booster dose that may be highly relevant for countries with
274 limited vaccine supply particularly if CoronaVac was used in the primary series.

275

276 **Methods**

277 *Study design and participants*

278 This single-center prospective, non-randomized, open-labeled cohort study enrolled 352
279 healthy adults, aged 18 years or older at Siriraj Hospital, a university-based referral center in
280 Bangkok, Thailand, from July to September 2021. The eligible participants were those who have
281 received either 2 doses of CoronaVac (4 weeks apart) (CoronaVac-prime) or ChAdOx1 (8-10
282 weeks apart) (ChAdOx1-prime) primary series vaccination 8-12 weeks prior to recruitment. The
283 exclusion criteria were history of SARS-CoV-2 infection; prior received prophylactic or
284 investigational treatment against COVID-19 within 90 days; had an unstable underlying disease;
285 history of vaccine anaphylaxis; being pregnant; immunocompromised or currently receiving
286 immunosuppressive agents. Written informed consent was obtained from all study participants.
287 The study protocol was approved by the Siriraj Institutional Review Board (COA no. Si
288 537/2021). The study was registered in thaichinicaltrials.org (TCTR20210719006).

289

290 **Study Procedures**

291 Eligible participants were openly assigned to receive one of the four intramuscular
292 booster vaccinations: BBIBP-CorV (Sinopharm), ChAdOx1 (AstraZeneca), full dose [30 µg] or
293 half dose [15 µg] BNT162b2 (Pfizer). Due to the shortage of study vaccines during the peak of
294 the outbreak when the enrollment started, the study vaccine was assigned to the participant by
295 order of confirmation to participate in the study and the type of vaccine available on that day.

296 After about 4 weeks of enrollment, the BBIBP-CorV booster group was terminated after the
297 preliminary analysis that found low anti-SARS-CoV-2 RBD concentration.

298 The participants were observed for at least 30 min following vaccination for any
299 immediate adverse events (AE) and were instructed to record self-assessment signs or symptoms
300 in an electronic diary (eDiary) for seven days after vaccination. An AE were defined as described
301 in the previous study [7].

302 Blood samples were collected at baseline (pre-booster), two weeks, and 16-20 weeks
303 after booster vaccination to determine the anti-SARS-CoV-2 RBD IgG antibody levels. A subset
304 of samples at two weeks and 16-20 weeks post-booster were tested for neutralizing antibodies
305 against the SARS-CoV-2 Delta and Beta variants using the 50% plaque reduction neutralization
306 test (PRNT₅₀) and against Delta and Omicron variants using the pseudovirus neutralization test
307 (PVNT). The groups that received BBIBP-CorV as booster or ChAdOx1 as priming and booster
308 (3-dose ChAdOx1) were not followed up for the 16-20 weeks analysis; the participants have
309 received additional booster vaccination outside of this study at approximately 4 weeks after
310 receiving the study vaccination due to the low antibody response. Cellular immunity was
311 measured at baseline using the QuantiFERON SARS-CoV-2 interferon gamma release assay
312 (IGRA). Participants with a negative IGRA response at baseline were tested again at two weeks
313 post-booster.

314

315 **Laboratory Assays**

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

317 The anti-RBD IgG was measured by CMIA using the SARS-CoV-2 IgG II Quant
318 (Abbott, List No. 06S60) on the ARCHITECT I System as described in previous study⁷. Samples
319 with a value >11,360 BAU/mL were reported as 11,360 BAU/mL.

320

321 *50% plaque reduction neutralization test (PRNT)*

322 The standard live virus 50% plaque reduction neutralization test (PRNT₅₀) against Delta
323 variant (B.1.617.2) and Beta variant (B.1.351) were performed as described in the previous
324 study⁷. The PRNT₅₀ titer is defined as the the highest test serum dilution for which the virus
325 infectivity is reduced by 50% when compared with the average plaque counts of the virus control
326 (no serum). The PRNT₅₀ titer of 5 was used for all samples that were below the detectable level
327 (1:10).

328

329 *Pseudovirus neutralization assay (PVNT)*

330 Codon-optimized gene encoding the spike of Omicron (B.1.1.529/ BA.1) and Delta
331 (B.1.617.2) were generated by gene synthesis (Genscript) and cloned into the pCAGGS
332 expressing plasmid by In-Fusion assembly (Clontech). Pseudovirus was generated and
333 concentrated as previously described [37]. Pseudotype-based neutralization assays were carried
334 out as described previously [37]. The 50% pseudovirion neutralizing antibody titer (PVNT₅₀)
335 was calculated by interpolating the point at which infectivity was reduced to 50% of the value for
336 the control samples (no serum).

337

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

339 SARS-CoV-2 specific T cell responses were assessed by whole blood IGRA using
340 QIAGEN's proprietary mixes of SARS-CoV-2 S protein designed for CD4+ T cell (Ag1), CD8+
341 T cells (Ag2) according to the manufacturer's instruction. Interferon-gamma (IFN- γ)
342 concentration was measured with an automated QuantiFERON SARS-CoV-2 ELISA instrument
343 and reported in International Units per mL (IU/mL) [38,39]. The cut-off for positivity was
344 determined as the level above the mean plus three standard deviations of the negative control.
345 The cut-offs for Ag1 (>0.12 IU/mL) and Ag2 (>0.17 IU/mL) were determined based on 61
346 SARS-CoV-2 negative control samples. A positive response to either of the two peptides pools
347 was considered positive.

348 **Statistical Analysis**

349 The sample size was calculated using the lower bounds of anti-RBD IgG geometric mean
350 concentration (GMC) from previous study[7]. A sample size of 50 participants in each group
351 would provide us 80% power to detect any difference between groups.

352 The AEs endpoints were presented as frequencies and Chi-square test was used to test for
353 statistical difference. The anti-SARS-CoV-2 RBD IgG concentration and neutralization
354 antibodies were reported as GMC and geometric mean titers (GMT) with 95% confidence
355 interval (CI), respectively. Anti-RBD IgG GMC and PRNT₅₀ GMTs at two weeks after the
356 primary series (post-primary series) from our previous study was used for comparison [7]: the
357 anti-RBD IgG GMC for CoronaVac and ChAdOx1 was 164.4 BAU/mL and 278.5 BAU/mL,
358 respectively and the PRNT₅₀ GMT was 21.2 and 69.7 for Delta variant and 10.2 and 43.5 for
359 Beta variant, respectively [7]. The geometric mean ratio (GMR) with 95% CI was analyzed
360 between the post-boosting levels or titers and post-primary series levels or titers references.
361 Paired *t* test, unpaired *t* test, and analysis of variance (ANOVA) were used to compare GMC and

362 GMT within group, between groups, and across groups using GraphPad Prism 9 version 9.2.0
363 (283) (GraphPad Software, CA, USA), respectively. Other statistical analyses were conducted
364 using STATA version 17 (Stata Corp, LP, College Station, TX, USA).

365

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372

373 **Author Contributions**

374 N.A. and S.N. equally contributed to the research work. Conceptualization and Methodology:
375 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.;
376 Project administration, N.A, J.S., S.N.; Supervision, K.C.; Resources and Funding, K.C. All
377 authors involved with investigation, and writing-review and editing.

378

379 **Data availability statement**

380 Data are available upon reasonable request.

381

382 **Conflict of Interest Declaration**

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

386

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517 **Figure Legends**

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

522

523 **Figure 2.** SARS-CoV-2 RBD IgG 2 weeks after booster vaccination. The scatter dot plot
524 represents the SARS-CoV-2 RBD IgG concentration before and 2 weeks after different booster
525 vaccination in participants who received 2-dose CoronaVac primary series (A) or ChAdOx1-
526 primary series (B) 8-12 weeks prior. (C) Comparison of SARS-CoV-2 RBD IgG levels at 2
527 weeks after booster vaccination between participants who received CoronaVac primary series
528 (blue) or ChAdOx1 primary series (red). Error bars represent geometric mean and 95%
529 confidence interval. The upper dotted line represents the geometric mean concentration (GMC)
530 of SARS-CoV-2 RBD IgG at 2 weeks after the second dose of the 2-dose primary series of
531 CoronaVac or ChAdOx1[7]. The lower dotted line represents the cut-off level for seropositivity.

532

533 **Figure 3.** Plaque reduction neutralization titers (PRNT₅₀) for SARS-CoV-2 Delta and Beta
534 variants. Scatter dot plots represent PRNT₅₀ titer against the (A) Delta or (B) Beta variant at 2
535 weeks after different booster vaccines in participants who received two doses of Coronavac or
536 ChAdOx1 8-12 weeks earlier. (C) Comparison of PRNT₅₀ between SARS-CoV-2 Delta (green)
537 and Beta (pink) variants 2 weeks after booster vaccination. Error bars represent geometric mean
538 titer (GMT) and 95% confidence interval (CI). The upper dotted line represents the geometric
539 mean values of anti-SARS-CoV-2 RBD IgG at 2 weeks after the second dose of the 2-dose

540 primary series of CoronaVac or ChAdOx1 [7]. Lower dot line represents the cut-off level for
541 seropositivity.

542

543 **Figure 4.** Pseudovirion neutralization titers (PVNT₅₀) for SARS-CoV-2 Delta and Omicron
544 variants. Aligned dot plots represent PVNT₅₀ against the (A) Delta or (B) Omicron variant at 2
545 weeks after different booster vaccines in participants who received two doses of Coronavac or
546 ChAdOx1 8-12 weeks earlier. (C) Comparison of PRNT₅₀ between SARS-CoV-2 Delta (green)
547 and Omicron (purple) variants 2 weeks after booster vaccination. PVNT₅₀ titer against the Delta
548 (D) or (E) Omicron variant at 2 weeks and 16-20 weeks of the same participants after different
549 booster vaccines. Error bars represent geometric mean titer (GMT) and 95% confidence interval
550 (CI).

551

552 **Supplementary Figure S1.** Correlation between the level of anti-SARS-CoV-2 RBD IgG
553 and plaque reduction neutralization test (PRNT₅₀) titers for the SARS-CoV-2 Delta and Beta
554 variants. Dot plots show the correlation between the level of anti-SARS-CoV-2 RBD IgG and
555 PRNT₅₀ titer against the Delta participants who have previously received two doses of
556 CoronaVac (A) or ChAdOx1 (B) or Beta variant in participants who had completed two doses of
557 CoronaVac (C) or ChAdOx1 (D) 2 weeks after booster with BBIBP-CorV (green), ChAdOX1
558 (red), 30 µg BNT162b2 (orange) and 15 µg BNT162b2 (yellow). Pearson's correlation
559 coefficient (r) with *p* value for each booster vaccine indicated.

560

561 **Supplementary Figure S2.** Cellular immune responses by interferon-gamma (IFN γ) releasing
562 assay (IGRA). (A) Scatter dot plots represent the level of IFN γ following stimulation with either

563 Ag1 or Ag2 at 8-12 weeks after two doses of CoronaVac or ChAdOx1 (before booster
564 vaccination). Aligned dot plots show the level of IFN γ following stimulation with stimulated
565 with either **(B)** Ag1 or **(C)** Ag2 in samples collected before (teal) and 2 weeks after (pink)
566 booster with BBIBP-CorV, ChAdOX1, 30 μ g BNT162b2 and 15 μ g BNT162b2. Median and
567 interquartile range (IQR) of each group are indicated. IU/mL: international units per mL.

Table 1. Baseline characteristics of participants

	Type of booster vaccinations				<i>p</i> -value
	BBIBP-CorV n=14	ChAdOx1 n=65	30 µg BNT162b2 n=50	15 µg BNT162b2 n=50	
Corona Vac-prime (n=179)					
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
ChAdOx1-prime (n=173)					
	BBIBP-CorV n=23	ChAdOx1 n=50	30 µg BNT162b2 n=50	15 µg BNT162b2 n=50	<i>p</i> -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

Table 2. The 50% plaque reduction neutralization (PRNT₅₀) and 50% pseudovirus neutralization (PVNT₅₀) geometric mean antibody titers (GMT) against variant.

Corona Vac-prime (n=104)	Type of booster vaccinations				p-value
	BBIBP-CorV n=14	ChAdOx1 n=30	30 µg BNT162b2 n=30	15 µg BNT162b2 n=30	
PRNT₅₀ 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
PVNT₅₀ at 2 weeks after boosting					
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
PVNT₅₀ at 16-20 weeks after boosting					
GMT (95% CI) against Delta variant	NA	n=20 93.22 (65.18, 133.33)	n=20 212.46 (143.96, 313.54)	n=20 164.86 (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)					
PRNT₅₀ 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
PVNT₅₀ at 2 weeks after boosting					
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
PVNT₅₀ at 16-20 weeks after boosting					
GMT (95% CI) against Delta variant	NA	NA	n=20 207.1 (158.57, 270.47)	n=20 178.63 (120.49, 264.83)	0.0012
GMT (95% CI) against Omicron variant	NA	NA	116.88	14.04	0.001

(76.94, 177.54) (3.138, 62.83)

* The geometric mean ratio (GMR) of PRNT50 between post-boosting and post-primary series. The post primary series GMC was derived from the study in the same setting as the current study [7]. 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

Supplementary Table 1. Adverse events of following booster vaccination

Adverse events (AEs)	BBIBP-CorV	ChAdOx1	30 µg BNT162b2	15 µg BNT162b2	<i>p</i> -value
CoronaVac-prime (n=179)	n=14	n=65	n=50	n=50	
Overall AEs (%)	10 (71.43)	64 (98.46)	46 (92.0)	40 (80.0)	0.002
Injection site reaction (%)	9 (64.29)	62 (95.38)	46 (92.00)	36 (72.00)	<0.001
Fatigue (%)	2 (14.29)	46 (70.77)	26 (52.0)	10 (20.00)	<0.001
Headache (%)	1 (7.14)	12 (18.46)	25 (50.0)	18 (36.0)	<0.001
Myalgia (%)	6 (42.86)	54 (83.08)	2 (4.0)	1 (2.0)	<0.001
Malaise (%)	0	1 (1.54)	31 (62.0)	20 (40.0)	<0.001
Nausea (%)	2 (14.29)	20 (30.77)	7 (14.0)	5 (10.0)	0.119
Diarrhea (%)	1 (7.14)	12 (18.46)	3 (6.0)	6 (12.0)	0.284
Fever (%)	1 (7.14)	25 (38.46)	4 (8.0)	1 (2.0)	<0.001
Rash (%)	2 (14.29)	9 (13.85)	7 (14.0)	2 (4.0)	0.341
Somnolence (%)	0	0	2 (4.0)	2 (4.0)	0.357
Flu-like symptoms (%)	0	4 (6.15)	1 (2.0)	1 (2.0)	0.453
Arthralgia (%)	0	2 (3.08)	1 (2.0)	1 (2.0)	0.906
Dizziness (%)	0	1 (1.54)	1 (2.0)	0	0.758
Paresthesia (%)	2 (14.29)	1 (1.54)	1 (2.0)	0	0.014
Vomiting (%)	0	4 (6.15)	0	1 (2.0)	0.199
ChAdOx1-prime (n=173)	n=23	n=50	n=50	n=50	
Overall AEs (%)	14 (60.87)	36 (72.0)	49 (958.0)	44 (89.0)	<0.001
Injection site reaction (%)	9 (39.13)	28 (56.0)	47 (94.00)	44 (88.00)	<0.001
Fatigue (%)	3 (13.04)	18 (36.0)	34 (68.0)	20 (40.00)	<0.001
Headache (%)	6 (26.09)	15 (30.0)	28 (56.0)	28 (56.0)	0.024
Myalgia (%)	6 (42.86)	54 (83.08)	2 (4.0)	1 (2.0)	<0.001
Malaise (%)	7 (30.43)	21 (42.0)	34 (68.0)	37 (74)	0.001
Nausea (%)	1 (4.35)	20 (30.77)	7 (14.0)	5 (10.0)	0.102
Diarrhea (%)	1 (4.35)	5 (10.0)	8 (16.0)	6 (10.0)	0.834
Fever (%)	1 (4.35)	2 (4.0)	4 (8.0)	1 (2.0)	0.240
Rash (%)	0	1 (2.0)	1 (2.0)	0	0.688
Somnolence (%)	0	1 (2.0)	2 (4.0)	0	0.421
Flu like symptoms (%)	0	1 (2.0)	2 (4.0)	2 (4.0)	0.738
Arthralgia (%)	0	0	0	1 (2.0)	0.480
Dizziness (%)	2 (8.70)	1 (2.0)	0	0	0.118
Paresthesia (%)	0	0	0	0	-
Vomiting (%)	0	3 (6.0)	0	0	0.057

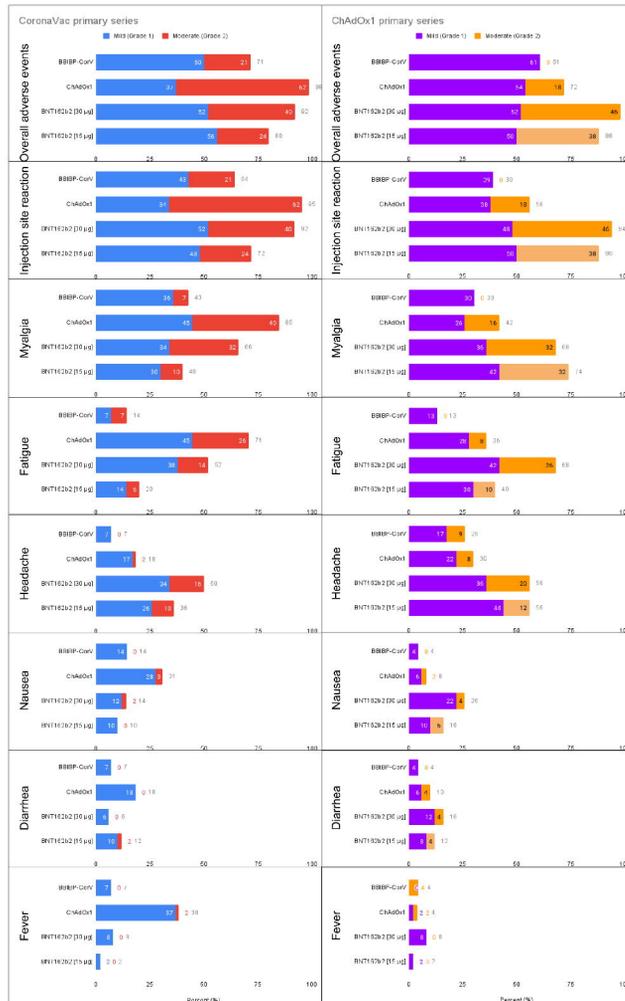
Supplementary Table 2. Anti-RBD IgG geometric mean concentration (GMC) and the geometric mean ratio (GMR) between post boosting and pre-boosting (baseline) or post primary series* and IGRA positive rate

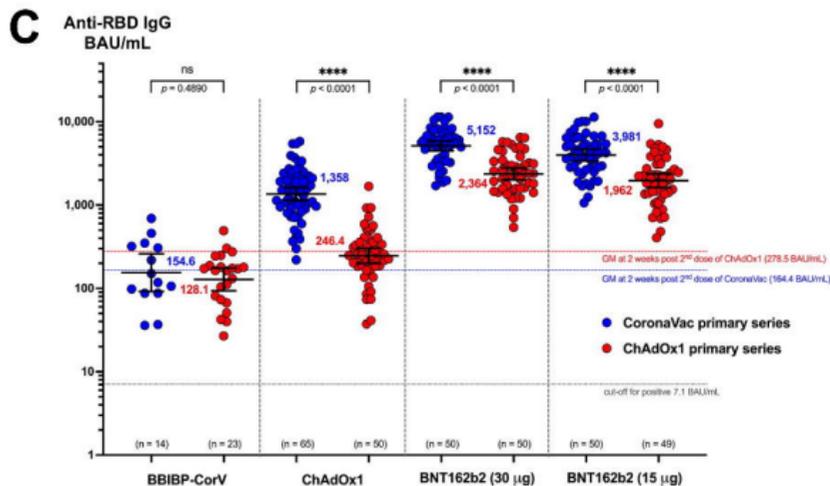
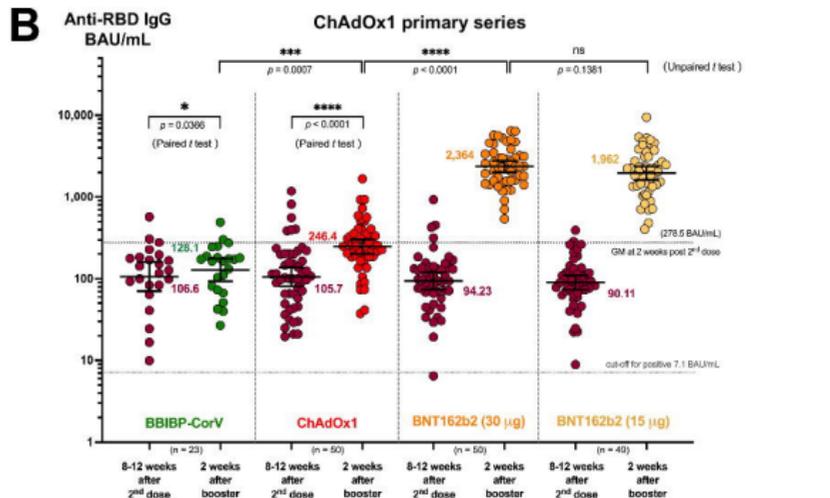
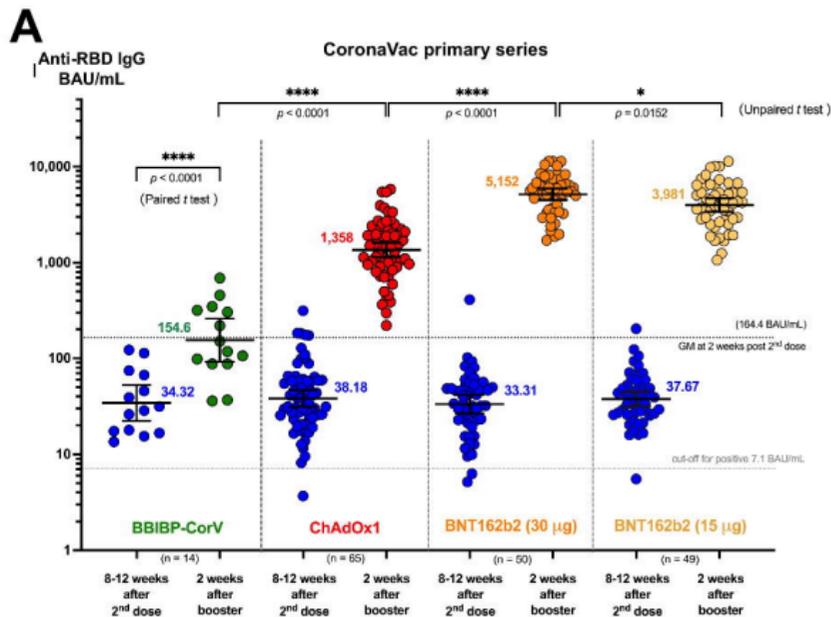
Anti-RBD IgG geometric mean concentration (GMC), BAU/mL	Type of booster vaccinations				
	BBIBP-CorV n=14	ChAdOx1 n=65	30 µg BNT162b2 n=50	15 µg BNT162b2 n=50	p-value between groups
Corona Vac-prime (n=179)					
GMC (95%CI) at baseline	34.32 (22.33, 52.77)	38.18 (31.21, 46.71)	33.31 (26.72, 41.53)	37.67 (31.65, 44.84)	0.7616
GMC (95%CI) at 2 weeks after boosting	154.6 (92.11, 259.47)	1358.0 (1141.84, 1615.07)	5152.2 (4491.65, 5909.83)	3981.1 (3397.15, 4665.42)	<0.0001
GMR (95% CI) between 2 weeks after boosting and baseline	4.5 (2.98, 6.80)	35.6 (29.18, 43.34)	154.7 (124.30, 192.50)	105.7 (90.31, 123.68)	<0.0001
GMR (95% CI) between 2 weeks after boosting and 2 weeks after primary series of CoronaVac*	0.94 (0.53, 1.67)	8.26 (6.29, 10.85)	31.34 (24.37, 40.30)	24.22 (18.60, 31.54)	<0.0001
GMC (95%CI) at 16-20 weeks after boosting	NA	291.32 (247.92, 342.33)	774.85 (653.33, 918.98)	525.31 (428.37, 644.18)	<0.0001
Baseline SARS-CoV-2 IGRA positive, n (%)	5 (35.7)	12 (18.5)	16 (32)	12 (24)	0.301
Post-boosting IGRA positive among baseline negative participants, n (%)	1/9 (11.1)	26/53 (49.1)	28/34 (82.4)	30/38 (79.0)	<0.0001
ChAdOx1-prime (n=173)					
	BBIBP-CorV n=23	ChAdOx1 n=50	30 µg BNT162b2 n=49	15 µg BNT162b2 n=50	p-value between groups
GMC (95%CI) at baseline	106.6 (70.89, 160.29)	105.7 (80.97, 137.97)	95.98 (75.84, 121.45)	90.11 (73.62, 110.30)	0.7661
GMC (95%CI) 2 weeks after boosting	128.1 (93.52, 175.37)	246.4 (199.59, 304.20)	2363.8 (2005.58, 2786.06)	1961.9 (1624.61, 2369.10)	<0.0001
GMR (95% CI) between 2 weeks after boosting and baseline	1.2 (1.01, 1.43)	2.3 (1.92, 2.83)	25.1 (20.30, 31.01)	21.8 (18.28, 25.92)	<0.0001
GMR (95% CI) between 2 weeks after boosting and 2 weeks after primary series of ChAdOx1*	0.46 (0.28, 0.65)	0.88 (0.58, 1.13)	8.49 (5.71, 10.44)	7.04 (4.69, 8.84)	<0.0001
GMC (95%CI) at 16-20 weeks after boosting	NA	NA	431.11 (367.59, 505.60)	314.43 (267.01, 370.27)	0.0066
Baseline SARS-CoV-2 IGRA positive, n (%)	13 (56.5)	26 (52.0)	9 (18.0)	14 (28.0)	<0.0001
Post-boosting IGRA positive among baseline negative participants, n (%)	0/10 (0)	0/24 (0)	31/41 (75.6)	24/26 (66.7)	<0.0001

*The post primary series GMC was derived from the study in the same setting as the current study [7]. The post primary series GMC (95% CI) at 2 weeks after the second dose of the 2-dose homologous CoronaVac, 4 weeks apart, was 164.4 (133.55, 202.43); and after 2-dose homologous ChAdOx1, 10 weeks apart, was 278.5 (195.66, 396.33).

CI: confidence interval; IQR: interquartile range

Figure 1.





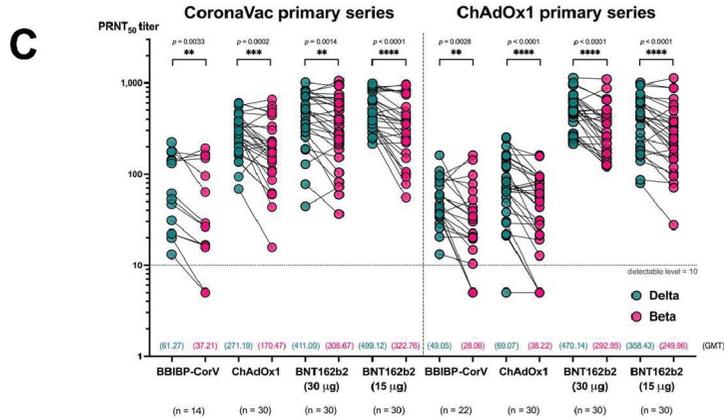
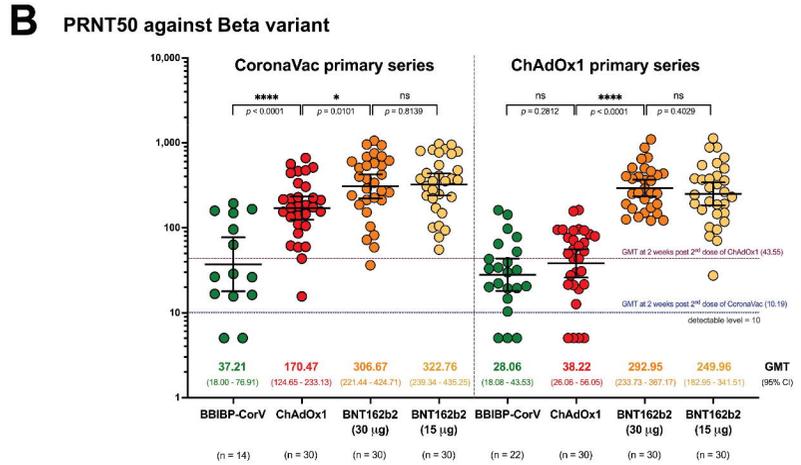
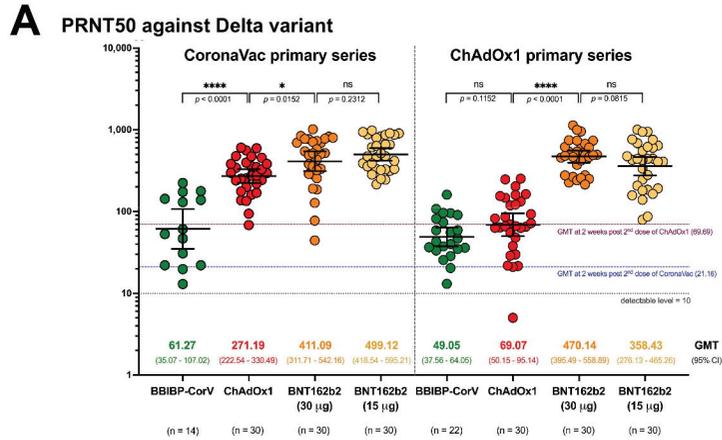
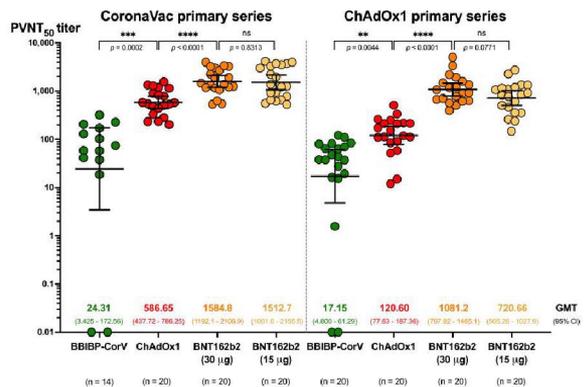


Figure 3.

A

PVNT50 against Delta variant

**B**

PVNT50 against Omicron variant

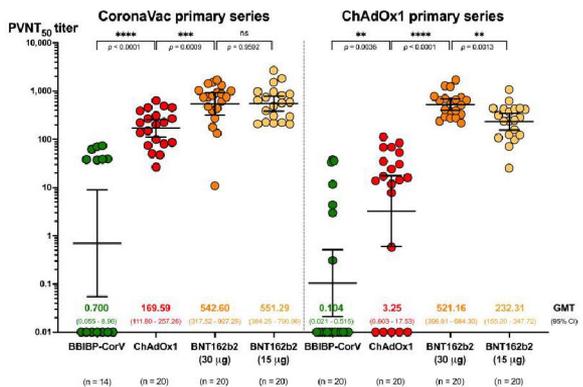
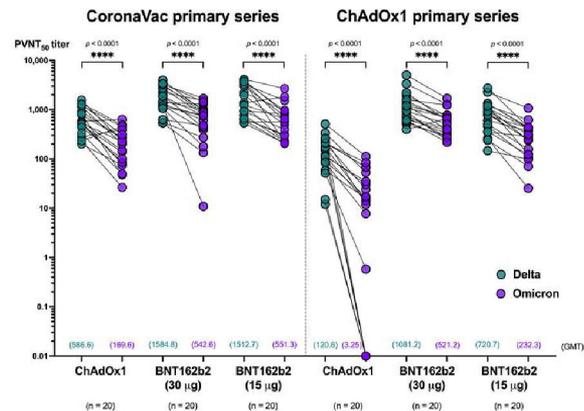
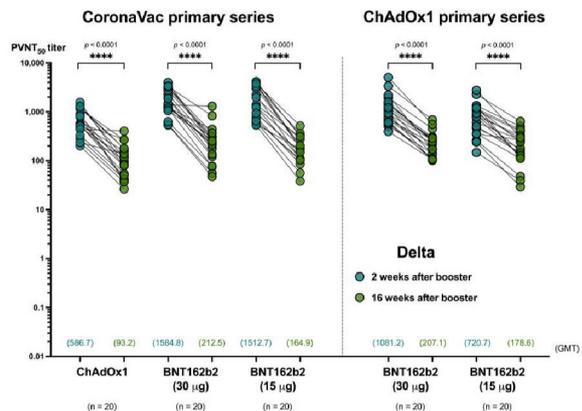
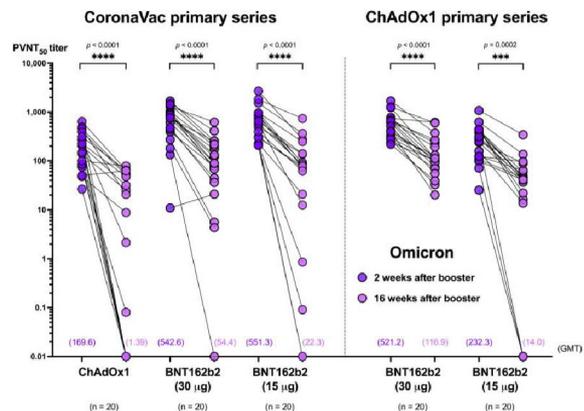
**C****D****E**

Figure 4.

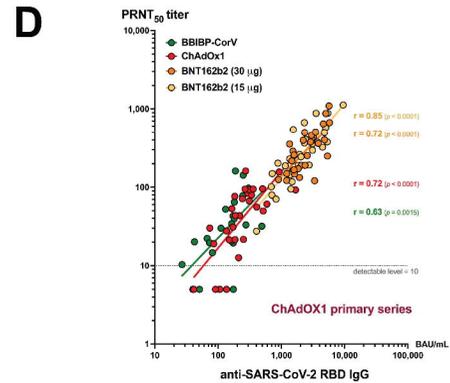
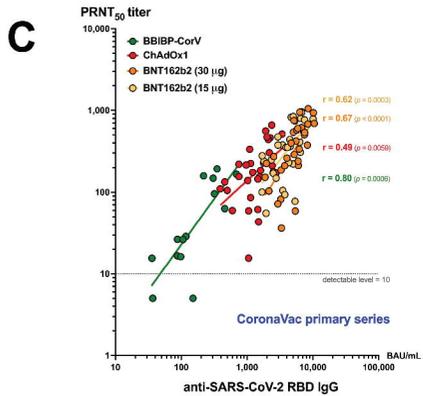
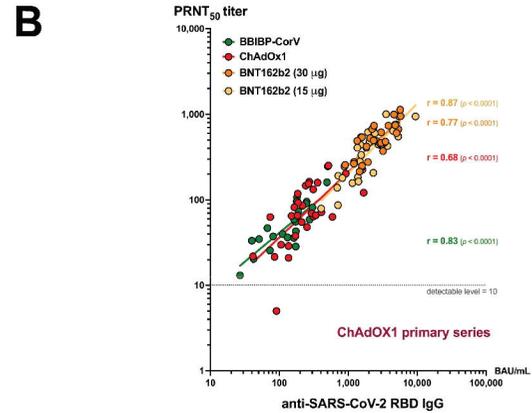
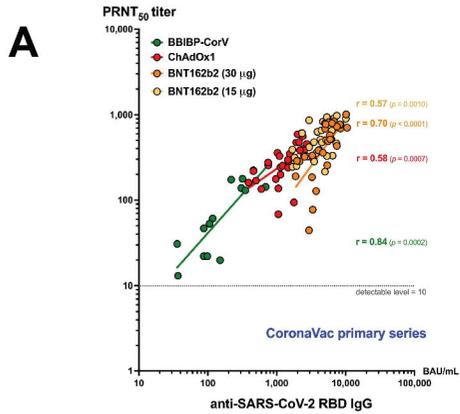
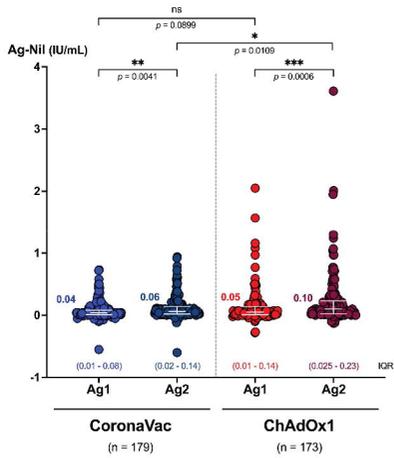
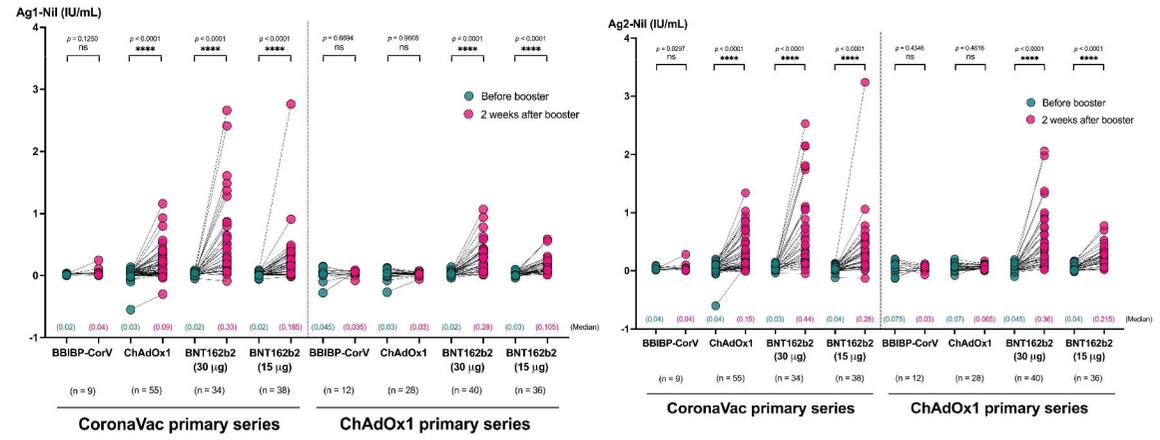


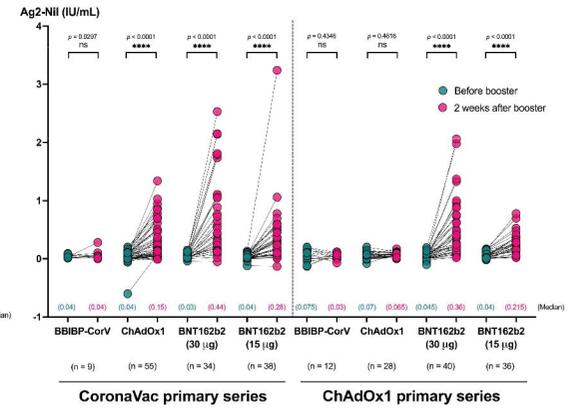
Figure S1.



A



B



C

Figure S2