Safety and superior immunogenicity of heterologous boosting with an RBD-based SARS-CoV-2 mRNA vaccine in Chinese adults

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23 **Abstract**

24 Homologous and heterologous booster with COVID-19 mRNA vaccines represent the

25 most effective strategy to prevent the ongoing Omicron pandemic. The additional

26 protection from these prototype SARS-CoV-2 S-targeting vaccine was attributed to the

27 increased RBD-specific memory B cells with expanded potency and breadth. Herein,

28 we show the safety and immunogenicity of heterologous boosting with the RBD-

29 targeting mRNA vaccine AWcorna (also term ARCoV) in Chinese adults who have

30 received two doses inactivated vaccine. The superiority over inactivated vaccine in

31 neutralization antibodies, as well as the safety profile, support the use of AWcorna as

32 heterologous booster in China.

33 **Introduction**

34 To May 2022, the COVID-19 pandemic has claimed more than 6.28 million lives, with

35 more than 524 million confirmed cases worldwide. The recent emergence of highly

36 transmissible Omicron variant of severe acute respiratory syndrome coronavirus 2

37 (SARS-CoV-2) has triggered another major surge in both confirmed cases and deaths[1].

38 Ten COVID-19 vaccines have been approved by the World Health Organization (WHO)

39 for emergency use, including the two mRNA vaccines, BNT162b2 and mRNA-1273,

40 and two Chinese inactivated vaccines, CoronaVac and BBIBP-CorV. However, the

41 rapid waning of vaccine-induced virus-neutralizing antibody titers and the continuous

42 emergence of variants of concern (VOCs), including Alpha, Beta, Delta and Omicron,

43 have created unprecedented challenges in the eradication of COVID-19 pandemic[2-4].

44 Especially, the heavily mutated Omicron variant has been well characterized to escape

45 from most therapeutic monoclonal antibodies, as well as sera from convalescent

46 patients or fully vaccinated individuals[5,6]. Recent data has indicated that neutralizing

47 antibody against Omicron was absent or undetectable in most Chinese populations who

48 received two-dose inactivated vaccines[7]. Interestingly, preliminary data have suggested

49 that a booster dose with mRNA vaccine BNT162b2 showed significant superiority over

50 homologous booster in titers and protection against Omicron[7-9]. However, the two

51 commercial mRNA vaccines, encoding the full S protein of SARS-CoV-2, are not

52 available in mainland China. The "made-in-China" mRNA vaccine candidate AWcorna

53 (originally termed ARCoV), which encodes the Receptor Binding domain (RBD) of

54 SARS-CoV-2 S protein, is being tested in the final stage of multiple-center phase III

55 trials (https://clinicaltrials.gov/ct2/show/NCT04847102). It is of highly priority and

56 urgency to provide evidence to support a better boosting strategy in mainland China for

57 decision maker.

Results

59 Herein, we reported the safety and immunogenicity of a third dose of heterologous

60 boosting with AWcorna in Chinese adults who have received two-dose inactivated

61 vaccines. The randomized clinical trial (ChiCTR2100053701) enrolled 300 adults

62 (ages≥18 years). All eligible subjects received 2-dose priming vaccination with the

63 inactivated vaccine, CoronaVac or BBIBP-CorV. At about 6-month post-priming, all

64 subjects were randomly assigned to either the AWcorna (n=200; heterologous) or

65 CoronaVac (n=100; homologous) booster group (Supplementary information, **Fig.**

66 **S1a**). In the AWcorna group, the median age was 43.0 years (Interquartile rate, IQR:

67 36.5-49.0), and the CoronaVac group was 40.0 years (IQR: 34.0-48.5) (P=0.5165)

68 (Supplementary information, **Table S1**). There were 116 (58%) and 55 (55%) male

69 participants in the AWcorna and CoronaVac groups, respectively (P=0.6208).

70 Meanwhile, no significant differences were observed in the Body Mass Index (BMI),

71 vital signs, and comorbid condition between the two groups at the baseline (All P>0.05).

72 All subjects completed the enrollment vaccination and three blood examinations

73 consecutively at pre-booster or 0 days, 14±2 days, and 28±2 days post-booster

74 vaccination. Subsequently, the neutralization and IgG antibody titers against wild-type

75 (WT) SARS-CoV-2 and VOCs were assessed at pre-booster, 14- and 28-day post-

76 booster by the standard cytopathic effect (CPE) based assay and ELISA, respectively

77 (Supplementary information, Methods). The WHO standard IgG antibody (NIBSC

78 code 20/136) was used as a reference sample for all serological assays.

79 As expected, the live virus neutralization titers against WT SARS-CoV-2 were below

80 the detection limit before boosting in all participants from both groups (**Fig. 1a**).

81 Remarkably, AWcorna booster induced a 66.59-fold increase against WT SARS-CoV-

82 2, and the geometric mean titers (GMTs) reached 293.9 and 242.4 at 14 and 28 days

83 post booster, respectively (WHO Reference cut-off 1:139), while the GMTs in

84 CoronaVac booster groups was only 89.1 and 64.3, respectively (**Fig. 1a** and

85 supplementary information, **Table S2**). Similarly, the neutralization antibody titers

86 against the Delta variant also increased significantly after the third dose booster either

87 with AWcorna and CoronaVac, while the GMTs in Awcorna groups were 5.1- and 6.5-

88 fold higher than that in CoronaVac group at 14 and 28 days post booster (**Fig. 1b** and

89 supplementary information, **Table S2**). In addition, the increasing trends are similar in

90 both 18-59 and ≥60 years old participants (Supplementary information, **Fig. S2a,b**).

91 Despite the neutralization antibody titers against the Omicron variant showed

92 significant reduction in comparison with that against the WT virus in both groups, the

93 GMTs against Omicron maintained 28.1 at 28-day after AWcorna booster, while the

94 GMT in the CoronaVac booster group was only 6.4 (**Fig. 2a** and supplementary

95 information, **Table S2**). Most importantly, 83.75% of participants in the AWcorna

96 booster group achieved the 1:8 threshold of neutralization antibody titers against the

97 Omicron relative to that of only 35% of participants in the CoronaVac booster group

98 (**Fig. 2b**; 95% Confidence Interval, CI: 30.82-63.84; *P*<0.0001).

99 Moreover, the RBD-specific IgG antibodies titers also showed a sharp increasement in

100 both booster groups, and the GMT in AWcorna booster group was 6.8- and 7.1- fold

101 higher than that in the CoronaVac booster group at both 14-day and 28-day time points,

102 respectively (all *P*<0.0001) (**Fig. 3a** and supplementary information, **Table S3**). Taken

103 together, these results demonstrate that heterologous boosting with AWcorna induces

104   higher neutralization and IgG antibodies against WT, Delta and Omicron variants than

105   homologous booster.

106   Additionally, we observed the safety profile of the booster dose of AWcorna. Solicited

107   local and systemic adverse events (AEs) were recorded within 30 mins and in a window

108   of 0-14 days, and unsolicited AEs were documented within 0-28 days post-booster

109   vaccination (Supplementary information, **Table S4**). For both vaccines, pain at the

110   injection site is the most reported local AE (incidence rate, IR:17% in AWcorna vs. 2%

111   in CoronaVac; *P*<0.0001), mostly at the Grade 1 level (**Fig. 4a**). Fever was the most

112   common systemic AE (IR: 33.5%), followed by headache (IR: 26.0%) and muscle

113   aches (IR: 7.5%) in AWcorna group (**Fig. 4b**). A total of 8 subjects reported grade 3

114   fever (IR:4%) among the 200 participants in AWcorna group. For the CoronaVac group,

115   headache represented as the most frequent systemic AE (IR: 7.0%), followed by fever

116   (IR: 4.0%). No serious adverse events (SAE) were reported in both groups.

Discussion

118   Collectively, our present study clearly demonstrated that a 3rd dose of heterologous

119   boosting with AWcorna was safe and potential protective against the circulating Delta

120   and Omicron variants. Compared with phase 1 trial, the total IRs of local and systemic

121   AEs for AWcorna booster showed significant improvement[10], especially the IR of grade

122   3 fever reduced to 4% (Supplementary information, **Table S4**), which was comparable

123   to the other two approved mRNA vaccines[11]. The phase 1 trial of AWcorna only

124   included 20 adults aged 18-59 (15 μg group), while our present cohort enrolled 200

125   participants, including 10 subjects aged over 60. The expansion of sample size and

126   improvement in vaccine manufacturing technologies contributed to the improved safety

127   profile observed in our present study. The ongoing international phase 3 trials with

128   28,000 participants will provide more meaningful data about the safety profile of

129   AWcorna.

130 Previously, we have demonstrated that homologous boosting with AWcorna readily

131 induced high neutralization antibodies against WT and Omicron variant in mice[12], our

132 present data in human further supported heterologous booster with this China-made

133 mRNA vaccine AWcorna in Chinese populations. Many cities in China are under the

134 attack of Delta and Omicron variants, while few or no neuralization antibodies against

135 Omicron was detected in most Chinese populations[7,13], a third dose of booster has been

136 recommended by the WHO and National Health Commission of China. Of all COVID-

137 19 vaccines generated from different technology platform, mRNA vaccine represents

138 as the most reasonable choice as either homologous or heterologous booster. The

139 neutralization titers against Delta and Omicron variants in AWcorna booster group were

140 6.5-fold and 4.4-fold higher than that in CoronaVac booster group, respectively (**Fig.**

141 **1b, c**), and the AWcorna booster induced the seroconversion of Omicron neutralization

142 in over 83% individuals (**Fig. 1d**). A third dose of S-targeting mRNA vaccine was

143 evidenced to increase the number of RBD-specific memory B cells with expanded

144 potency and breadth, thus contributing to the additional protection against VOCs

145 including Omicron[14,15], highlighting the rationale of RBD-targeting mRNA vaccine as

146 booster. Given that more and more Chinese population have received three-dose

147 inactivated vaccines, additional clinical trials are being conducted to assay the benefits

148 of heterologous boosting with AWcorna.

149 Finally, despite the vaccine effectiveness of AWcorna booster in preventing infection

150 by SARS-CoV-2 and other VOCs remains to be determined, the induction of potent

151 neutralization antibodies against WT and VOCs, as well as the affordable safety profile,

152 support the emergency use of AWcorna as heterologous booster in China. A more

153 potent mRNA vaccine and improved booster strategy should be warranted to meet the

154 urgent and huge need to stop the ongoing Omicron outbreaks in China and COVID-19

155 pandemic worldwide.

156 **METHODS AND MATERIALS**

157 **Study design**

158   We conducted a randomized clinical trial involving 300 adults (≥18 years of age) who

159   were tested negative by RT-PCR screening for COVID-19 at the time of participation

160   to elucidate the immunogenicity and safety of an mRNA-based vaccine (AWcorna) as

161   a booster compared to that of homologous booster using an inactivated viral vaccine

162   (CoronaVac).

163   **Ethics statement**

164   The trial was reviewed and approved by the Research Ethics Committee of the Center

165   for Disease Control and Prevention of Yunnan province. The study protocol and related

166   materials were approved by the independent Ethics Committees as well, and this trial

167   was conducted in accordance with the Declaration of Helsinki and Good Clinical

168   Practice with the register number of ChiCTR2100053701 (NO. 2021-15). Written

169   informed consents were obtained from each participant before the screening.

170   **Participants**

171   Eligible participants met all inclusion criteria and did not trigger any exclusion criteria.

172   Those aged 18 years and above, received full 2-dose inactivated viral priming around

173   6 months ago. Of the 300 participants, 175 received 2-dose CoronaVac, 14 received 2-

174   dose BBIBP CorV, and 111 received one-dose CoronaVac and 1-dose BBIBP CorV.

175   Participants with a previous clinical or virologic COVID-19 diagnosis or SARS-CoV-

176   2 infection or women with positive urine pregnancy test results were excluded from this

177   study. Participants with a medical history of convulsion, serious acute hypersensitive

178   reaction to vaccines, acute febrile diseases or infectious diseases, congenital or acquired

179   angioedema, asplenia or functional asplenia, thrombocytopenia or other coagulation

180   disorders, anti-allergy therapy, or blood products within 3 months were also excluded.

181   **Randomization**

182   Each participant was assigned a unique subject ID by authorized assigners successively

183   according to a Prespecified allocation kit, which was generated by an independent

184   randomization statistician from Beijing Key Tech Statistical Consulting Co., Ltd. via

185   SAS software (SAS® Institute, Cary, North Carolina, USA) with the ratio of 2:1 to the

186   AWcorna and CoronaVac groups. Since the different appearances of the two kinds of

187   vaccines, inoculators could not keep in blind when vaccines had been used. And hence,

188   staff who were assigned to inoculate would not be involved in any other research jobs,

189   especially for subjects' safety follow-up procedures. Participants would be masked

190   when receiving the jab by a special curtain in the injection room to avoid the

191   identification of he or she, and disclosure of the allocated group. Other investigators,

192   laboratory staff, and outcome assessors were kept blinded also.

193   **Interventions**

194   The AWcorna vaccine (15 μg/dose) (batch number RR202109006) is manufactured by

195   Yuxi Walvax Biotechnology Co. Ltd. (an affiliate of Walvax Biotechnology Co., Ltd.),

196   and supplied in pre-filled 0.5 ml syringes. The CoronaVac (Sinovac) vaccine, is an

197   inactivated whole-virion vaccine with aluminum hydroxide as the adjuvant. Each dose

198   of CoronaVac contains 3 μg SARS CoV-2 virion in a 0.5 ml aqueous suspension for

199   injection with 0.45 mg/ml aluminum.

200   **Assessments**

201   After injection, subjects received an in-site 30-minutes safety observation conducted

202   by research staff to confirm if any immediate reactions occurred. Any adverse events

203   (AEs) discovered or any relevant concomitant medications declared within 28 days

204   after vaccination were recorded by subjects with the help of the daily cards and

205   connections cards which were prepared and managed by the study team. For each

206   subject, serious adverse events (SAEs), adverse events of interest (AESI), and

207   pregnancy were collected from the enrollment till 12 months after his/her booster dose.

208   Up to 6 ml of blood sample was collected from each participant at baseline pre-booster

209   vaccination and on day 14 and day 28 after receiving the booster dose.

Endpoints

The primary endpoints for safety were: 1) The incidence rates of adverse reactions/adverse events within 30 minutes, during Day 0-14 and Day 0-28 after vaccination; and 2) The incidence rates of adverse reactions/adverse events with a severity of grade 3 and above within 30 minutes and during Day 0-14 and Day 0-28 after vaccination. The primary immunogenicity endpoint was the titers of neutralizing antibody against wild type SARS-CoV-2 as measured by live virus neutralization assay 14 days post booster.

Laboratory assays

The neutralizing antibodies in sera against the wild-type strain (GenBank: MT123291), Delta variant (IQTC-IM2175251), and Omicron variant (IQTC-Y216017) (Guangzhou Customs Technology Center, Guangzhou, China) were determined by using a cytopathic effect (CPE)-based microneutralization assay. Two-fold serial dilutions (starting from 1:4) of heat-inactivated sera were tested in duplicate wells for the presence of neutralizing antibodies in the monolayer of Vero E6 cells. 100 $TCID_{50}$ of virus in 50 μl/well was incubated with 50 μl of serum in 96-well plates for 2 h. Vero E6 cells were trypsinized and resuspended in Dulbecco's Modified Eagle Medium (DMEM) containing 4% of fetal bovine serum and 1% of pen/strep at a concentration of 1.2×10^5 cells/ml and 100 μl of cells suspension were then added into the 96-well plates, followed by incubation at 37 °C, 5% CO_2 for 4 days. The neutralization was determined by the appearance of CPE in images captured with Celigo Image Cytometer on day 4 post-infection. The neutralizing antibody titer was defined as the reciprocal of the highest sample dilution that protected at least 50% of cells from CPE.

RBD-specific ELISA antibody responses were measured using an indirect ELISA assay with a cutoff titer of 1:10. The commercial Anti-SARS-CoV-2 RBD IgG ELISA kit was used for detection. Measurement was performed using a Multiskan GO reader

236 (Thermo Fisher) to detect optical density at 450 and 630 nm using SkanIt Software for

237 Microplate Readers (version 4.1.0.43).

238 The WHO international standard for anti-SARS-CoV-2 IgG (NIBSC code 20/136) was

239 used as a reference with the serum samples measured in this study for calibration of the

240 serological assays. The WHO reference (NIBSC code: 20/136) is equivalent to a live

241 viral neutralizing antibody titer of 1:139 against wild-type SARS-CoV-2 and a titer of

242 1:213 against the Delta variant B.1.617.2, while the WHO reference (1,000 BAU/ml in

243 serum) is equivalent to an RBD-specific IgG ELISA antibody titer of 1:5,490. Live

244 viral neutralizing antibodies against wild-type strain and the Delta variant and levels of

245 RBD-binding IgG isotypes in serum were measured on days 0, 14, and 28 after the

246 booster. Live viral neutralizing antibodies against the Omicron variant BA.1.1 were

247 detected only on day 28 after the booster in a subgroup randomly selected from both

248 groups.

Sample size

250 The sample size was determined based on the hypothesis that the booster vaccination

251 of mRNA vaccine following the two-dose inactivated vaccine regimen be non-inferior

252 to that of the booster of inactivated vaccine in neutralizing antibody. It was assumed

253 that the pooled standard deviation of $\log_{10}$-transformed neutralizing data was 0.5 and

254 equal GMT in both the mRNA vaccine group and CoronaVac group. 200 participants

255 in the mRNA group and 100 participants in the CoronaVac group could have at least

256 80% power to observe that the lower limit of the 95% confidence interval of GMT ratio

257 between the two groups was greater than the non-inferiority margin (2/3), with the one-

258 sided significance level of 2.5%.

Statistical analysis

260 The geometric mean titer (GMT) and 95% confidence interval (CI) were used to

261 describe neutralizing results in the mRNA vaccine group and CoronaVac group after

262 booster vaccination, and the GMT ratio between the two groups and 95% CI were

263 estimated. The non-inferiority result would be concluded if the lower bound of 95%CI

264 was larger than 2/3. When the non-inferiority conclusion was concluded, the superiority

265 would be considered sequentially if the lower bound was larger than 1. The

266 seroconversion rate and Clopper-Pearson 95%CI after booster vaccination were

267 estimated as well, and the difference between the two groups was calculated using the

268 Miettinen-Nurminen method.

269 We assessed the number and proportion of participants with adverse reactions 0-28 days

270 after the booster dose. For fever, besides the NMPA standard, we also derived the oral

271 temperature by adding $0.2°C$ to the collected auxiliary temperature, and then re-graded

272 the adverse reaction based on the FDA standard to provide more comparable results

273 with marketed vaccines. We used the $\chi2$ test or Fisher's exact test to analyze categorical

274 data, the t-test to analyze the log-transformed antibody titers, and the Wilcoxon rank-

275 sum test for data not following a normal distribution. The correlation between

276 concentrations of log-transformed neutralizing antibody and binding antibody levels

277 was analyzed using Pearson's correlation. The primary analysis was performed based

278 on the per-protocol population. Statistical analyses were performed using SAS (version

279 9.4).

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293   Science.

294   **AUTHOR CONTRIBUTIONS**

295   J.Z., Z.H. and C.-F.Q. conceived and supervised the project. X.L., J.Z., Z.W. and L.Y.
296   designed and coordinated the experiments. J.Z. and Z.W. performed the laboratory
297   assays. Y.L., W.H., and S.C. completed the quality assurance of this product and
298   provided essential guidance on laboratory assays. J.S. and B.Y. provided technical
299   expertise on mRNA vaccine production. Y.Z. and J.C. analyzed the data. L.Y., J.C., Y.-
300   J.H., Z.X. and C.-F.Q. drafted the manuscript. All authors revised and approved the
301   final version.

302   **COMPETING INTERESTS**

303   This trial was sponsored by the Walvax Biotechnology. AWcorna was co-developed by
304   AMMS, Abogen, and Walvax. C.-F. Q. and B.Y. are co-inventor of AWcorna. Z.H.,
305   L.Y., J.C., Z.X. and J.S. are employees of Walvax. B. Y. is the founder of Abogen. The
306   other authors declare no conflicts of interest.

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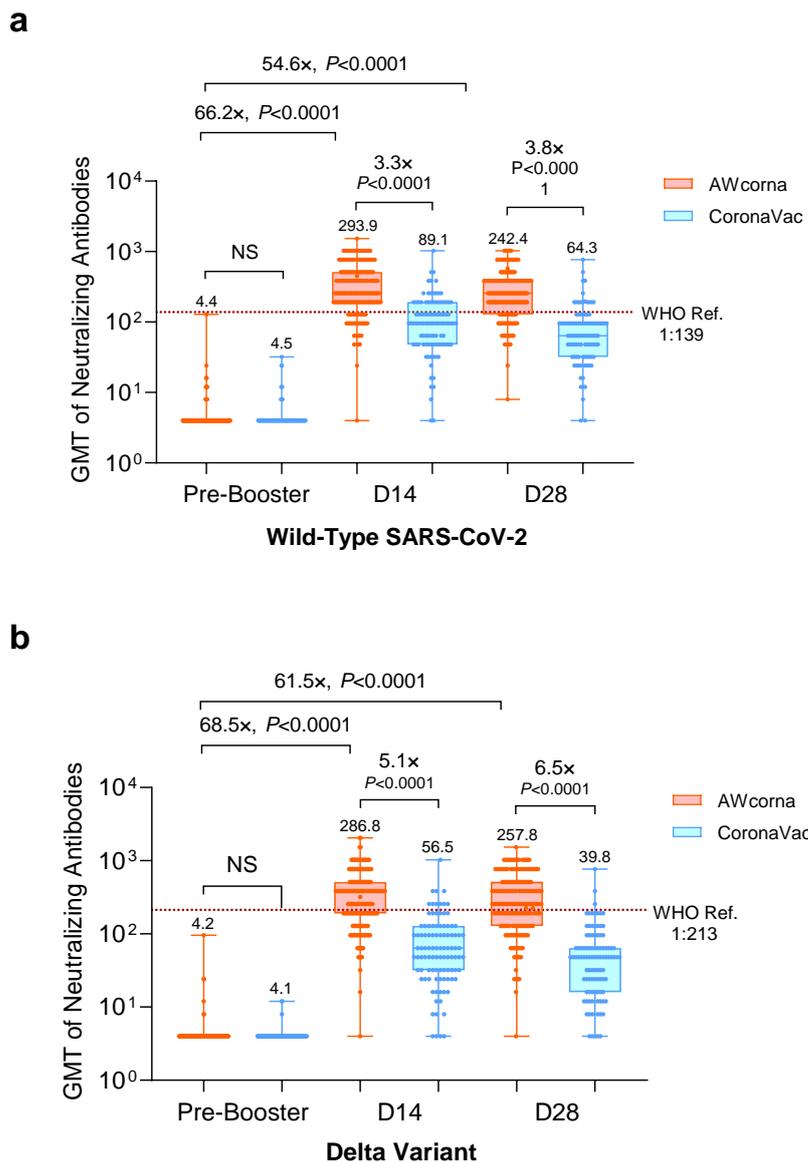
Fig.1 GMT of neutralizing antibodies to live wild-type SARS-CoV-2 or Delta variant.

a Geometric mean titer (GMT) of neutralizing antibodies to live wild-type (WT) SARS-CoV-2. The WHO reference serum (1,000 IU/ml) was equivalent to a live viral neutralizing antibody titer of 1:139 against WT. **b** GMT of neutralizing antibodies to the Delta variant. The WHO reference was 1:213 against the Delta variant (the dash line in red). Eligible participants primed with 2-does of inactivated vaccine were randomly allocated to AWcorna group (n=200) and CoronaVac group (n=100) to receive a booster dose respectively. GMT data are presented in box-and-whisker plots. The figures above error bars indicate the percentage. *P* values were obtained from comparisons between the two treatment groups using *t*-tests for log-transformed antibody or two-sided χ2 tests for categorical data.

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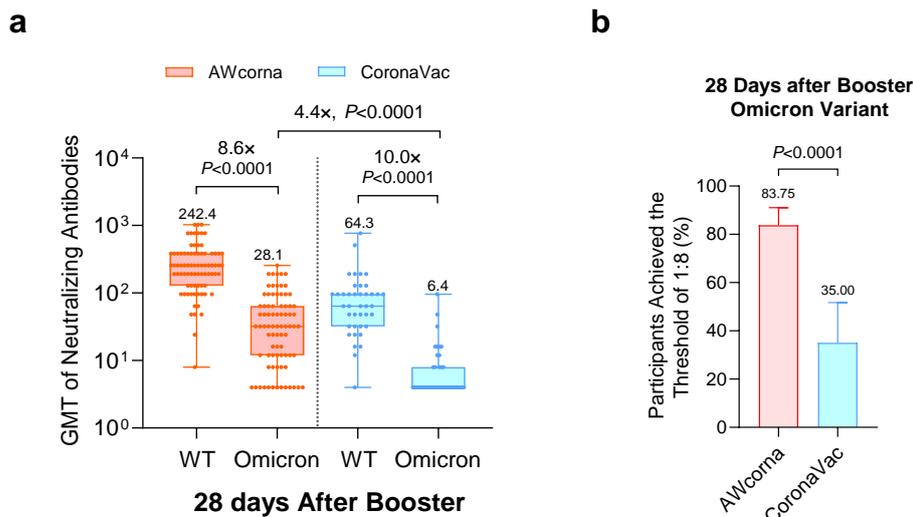
Fig.2 GMT of neutralizing antibodies to Omicron variant.

a GMT of neutralizing antibodies to the Omicron variant was measured in the subgroup (120 participants with the first 120 subject numbers, 80 from AWcorna and 40 from CoronaVac group). Sera were measured 28 days after booster only, thus no baseline analysis was performed. **b** Seropositive rates (%) of neutralizing antibody to the Omicron variant. GMT data are presented in box-and-whisker plots. The figures above error bars indicate the percentage. *P* values were obtained from comparisons between the two treatment groups using *t*-tests for log-transformed antibody or two-sided $\chi2$ tests for categorical data.

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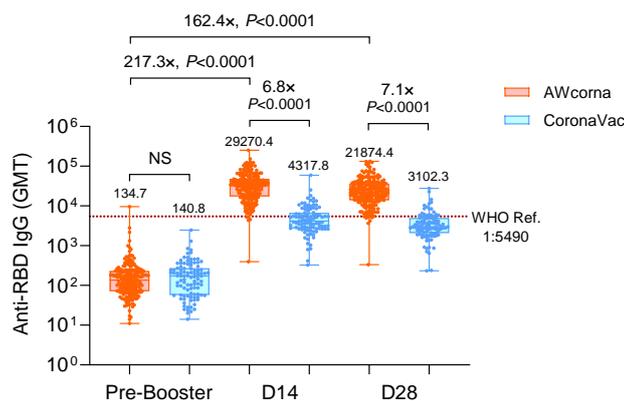
Fig.3 GMT of anti-RBD IgG antibodies to WT SARS-CoV-2.

a GMTs of anti-RBD IgG antibodies to WT SARS-CoV-2. The WHO reference (1,000 binding antibody unit (BAU)/ml in serum) is equivalent to an RBD-specific IgG ELISA antibody titer of 1:5490. The cutoff value for the response was 1:8 for live virus neutralizing antibody and 1:10 for anti-RBD IgG. GMT data are presented in box-and-whisker plots. The figures above error bars indicate the percentage. *P* values were obtained from comparisons between the two treatment groups using *t*-tests for log-transformed antibody or two-sided $\chi 2$ tests for categorical data.

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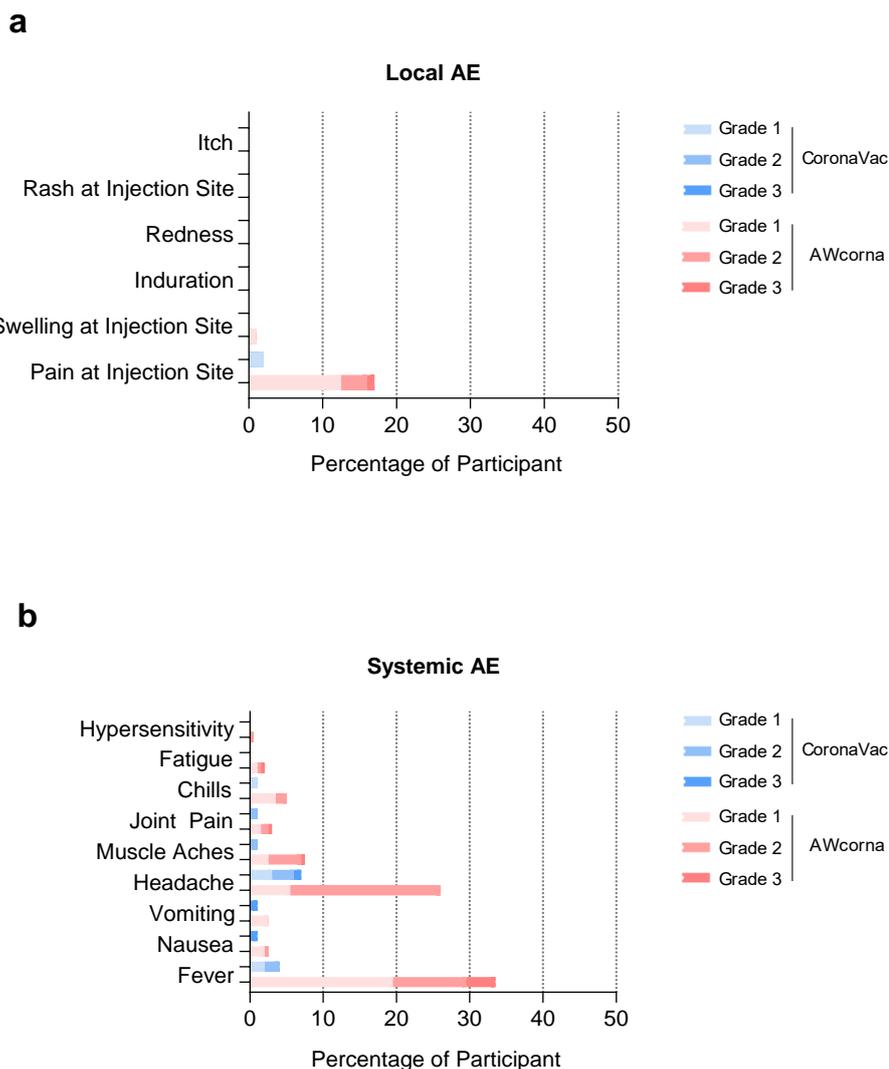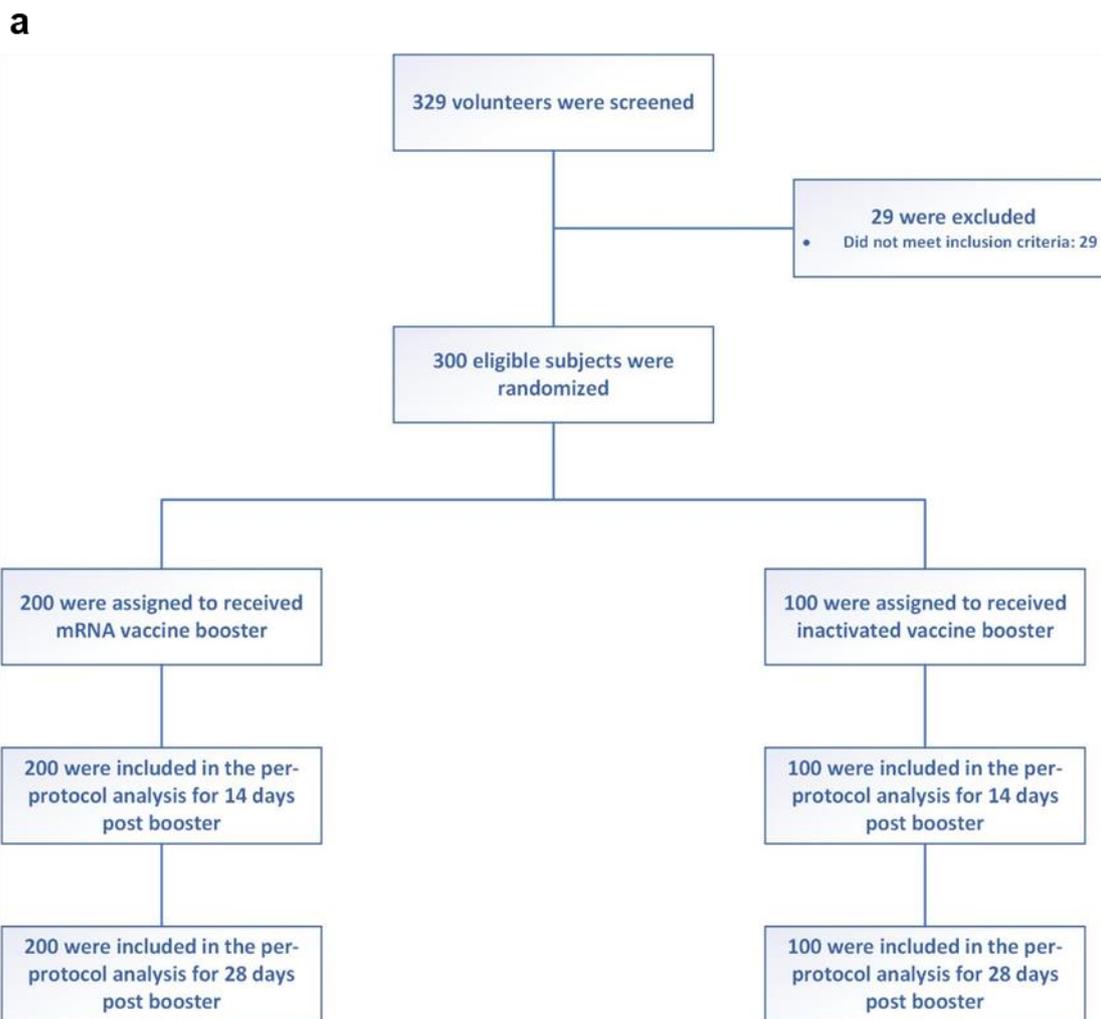

Fig.4 Safety of Heterologous boosting with AWcorna in Chinese adults.

a The percentage of participants with local adverse events (AEs). **b** The percentage of participants with systemic AEs. These AEs were monitored in the 14 days window after the administration of the booster.

17

a


Fig. S1 Consolidated standards of reporting trials (CONSORT) flow diagram

a Between the trial screening and randomization, 29 volunteers were excluded. All of them triggered the exclusion criteria. A total of 300 eligible subjects, who had received 2 doses of inactivated vaccine about 6 months ago, were randomly assigned to either the AWcorna (n=200; heterologous) or CoronaVac (n=100; homologous) booster group. All the randomized participants received vaccines at their free will and received all the scheduled follow-ups.
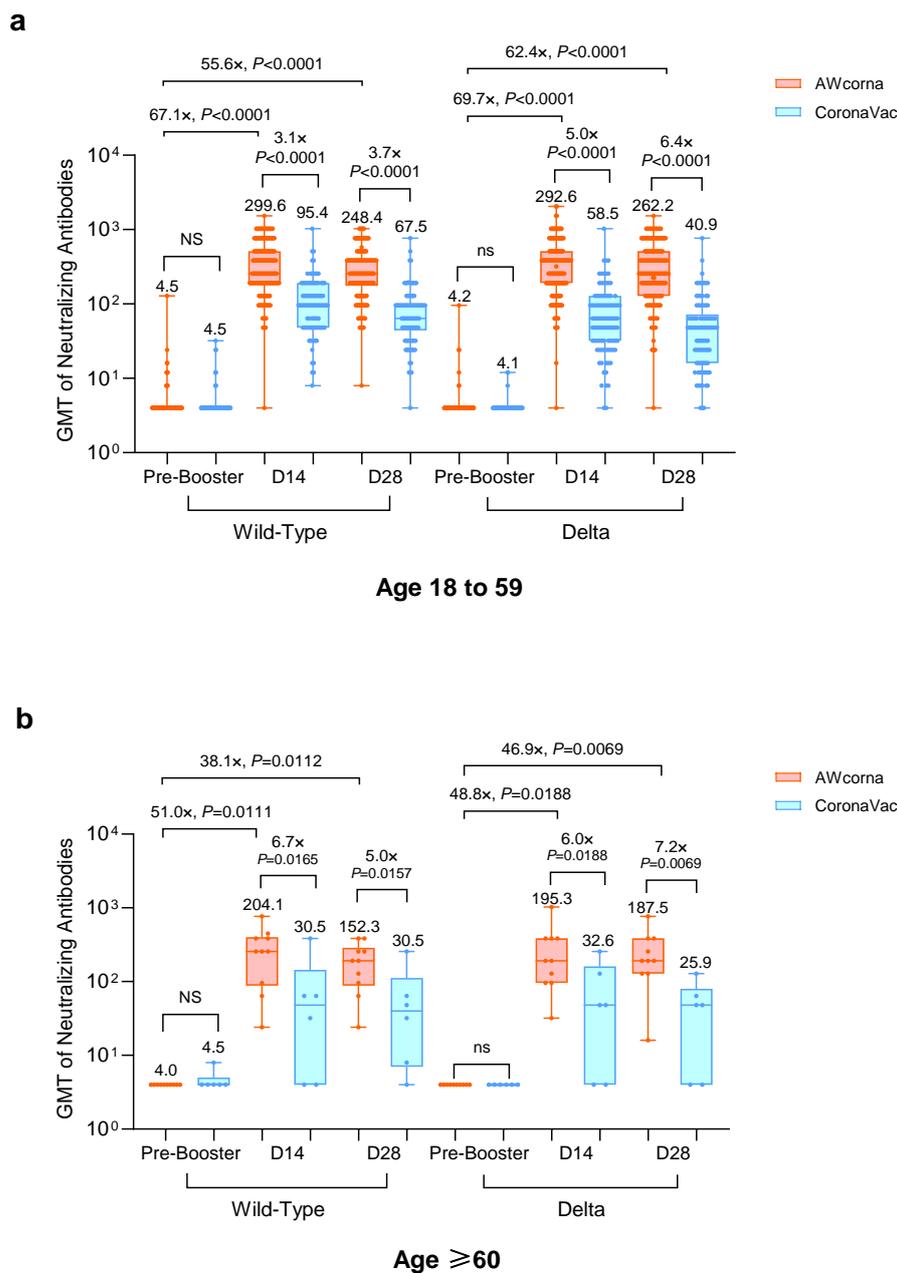
18

Fig.S2 Cross neutralization against WT and Delta viruses in different age groups.

a,b GMT of neutralizing antibodies to wild-type SARS-CoV-2 and Delta variant for younger adult population aged 18-59 (AWcorna=190, CoronaVac=90) (**a**) and elder population aged 60 and above (AWcorna=10, CoronaVac=6) (**b**). GMT data are presented in box-and-whisker plots. The whiskers indicate the range, the top and bottom of the boxes indicate the interquartile range, and the horizontal line within each box indicates the median. Figures with the x suffix indicate the GMT ratio between groups or GMT increase fold raised from pre- to post-booster level. *P* values were obtained from comparisons between the two treatment groups using *t*-tests for log-transformed antibody.

418   **Table S1. Baseline characteristics of the trial participants, who had received two doses of**

419   **priming inactivated vaccine.** [*]

	AWcorna (N=200)	CoronaVac (N=100)	*P*-Value
Age(Median, IQR)	43.0 (36.5,49.0)	40.0 (34.0,48.5)	0.5165
Sex, male(%)	116 (58.00)	55 (55.00)	0.6208
BMI(min-max) [†]	23.56 (15.58-34.53)	23.22 (18.31-33.31)	0.3998
Ethnicity[‡]			
Lahu, n(%)	179 (89.50)	88 (88.00)	0.5418
Wa, n(%)	1 (0.50)	0 (0.00)	
Hani, n(%)	10 (5.00)	3 (3.00)	
Yi, n(%)	2 (1.00)	1 (1.00)	
Dai, n(%)	0 (0.00)	0 (0.00)	
Other, n(%)	8 (4.00)	8 (8.00)	
RT-PCR, negative(%)	200(100)	100(100)	1.0000
Vital Signs			
Systolic Pressure	118(81-141)	118(85-140)	0.9615
Diastolic Pressure	73(48- 89)	74(56-90)	0.3679
Pulse	79(56-114)	81(53-110)	0.2182
Comorbidities			
Any (%)	9	9	1.0000
Gastrointestinal disorders (%)	3.5	2	0.7227
Vascular disorders (%)	1	2	0.6030
Respiratory, thoracic and mediastinal disorders (%)	1.5	0	0.5533
Infections and infestations (%)	1	1	1.0000
Musculoskeletal and connective tissue disorders (%)	0.5	1	1.0000
Nervous system disorders (%)	0.5	1	1.0000
Blood and lymphatic system disorders (%)	1	0	0.5541
Endocrine disorders (%)	0	1	0.3333
Investigations (%)	0.5	0	1.0000
Reproductive system and breast disorders (%)	0	1	0.3333
SARS-CoV-2 specific antibody titers on day 0[§]			
Geometric Mean Titer of anti-RBD IgG (Mean, 95%CI)			
	134.7	140.8	0.7061

20

	(118.3, 153.4)	(115.3, 172.0)	
Geometric Mean Titer of nAb against Wild-Type SARS-CoV-2 (Mean, 95%CI)			
	4.4(4.2, 4.7)	4.5(4.2, 4.9)	0.7831
Geometric Mean Titer of nAb against Delta Variant (Mean, 95%CI)			
	4.2(4.0, 4.4)	4.1(4.0, 4.3)	0.5951

420   * The first trial visit occurred before the booster, and the second and third trial visit occurred 14- and 28-days after

421   administration of the booster. IQR denotes interquartile range.

422   † The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

423   ‡ Categories were reported by the participants. The categories shown are those used by the investigators to denote

424   ethnicity.

425   § In the two groups, blood was drawn on day 0, which was the day of the first trial visit. Day 0 was also the day of

426   the booster in the two groups.

427

428   **Table S2. Neutralizing antibodies to the wild-type SARS-CoV-2 as well as Delta and Omicron variants before and after booster.**

	AWcorna N=200	CoronaVac N=100	GMT/GMI Ratio (AWcorna /CoronaVac) or Diff. in % (AWcorna -CoronaVac)	Statistics	*P* value
Wild-Type					
Pre-Booster					
GMT	4.4(4.2, 4.7)	4.5(4.2, 4.9)	NA	*t*=-0.275	0.7831
Seropositive[*] (%)	9.00(5.42, 13.85)	10.00(4.90, 17.62)	NA	χ^2=0.079	0.7790
D14					
GMT	293.9(260.4, 331.7)	89.1(73.7, 107.8)	3.3(2.7, 4.1)	NA	<0.0001
GMI	66.2(58.3, 75.1)	19.8(16.3, 24.0)	3.3(2.7, 4.2)	NA	<0.0001
Seroconversion[*] (%)	99.00(96.43, 99.88)	98.00(92.96, 99.76)	1.00(-1.92, 6.08)	NA	0.6030
4-Fold Increase (%)	99.00(96.43, 99.88)	95.00(88.72, 98.36)	4.00(0.37, 10.27)	NA	0.0433
D28					
GMT	242.4(216.4, 271.4)	64.3(53.6, 77.2)	3.8(3.1, 4.6)	NA	<0.0001
GMI	54.6(48.4, 61.6)	14.3(11.9, 17.1)	3.8(3.1, 4.7)	NA	<0.0001
Seroconversion[**] (%)	99.50(97.25, 99.99)	98.00(92.96, 99.76)	1.50(-1.08, 6.55)	NA	0.2585
4-Fold Increase (%)	99.00(96.43, 99.88)	94.00(87.40, 97.77)	5.00(1.11, 11.57)	NA	0.0183
Delta					
Pre-Booster					
GMT	4.2(4.0, 4.4)	4.1(4.0, 4.3)	NA	*t*=0.532	0.5951

Seropositive[*] (%)	3.00(1.11, 6.42)	3.00(0.62, 8.52)	NA	NA	1.0000
D14					
GMT	286.8(252.9, 325.3)	56.5(45.6, 70.0)	5.1(4.0, 6.4)	NA	<0.0001
GMI	68.5(60.1, 78.0)	13.7(11.1, 17.0)	5.0(3.9, 6.3)	NA	<0.0001
Seroconversion	99.00(96.43, 99.88)	96.00(90.07, 98.90)	3.00(-0.38, 8.93)	NA	0.0979
4-Fold Increase (%)	99.00(96.43, 99.88)	91.00(83.60, 95.80)	8.00(3.35, 15.32)	NA	0.0011
D28					
GMT	257.8(225.7, 294.5)	39.8(32.1, 49.3)	6.5(5.1, 8.2)	NA	<0.0001
GMI	61.5(53.7, 70.5)	9.7(7.8, 11.9)	6.4(5.0, 8.1)	NA	<0.0001
Seroconversion[*] (%)	99.00(96.43, 99.88)	95.00(88.72, 98.36)	4.00(0.37, 10.27)	NA	0.0433
4-Fold Increase (%)	99.00(96.43, 99.88)	81.00(71.93, 88.16)	18.00(11.27, 26.87)	NA	<0.0001
Omicron (For Subgroup)	**N=80**	**N=40**			
D28					
GMT	28.1(21.4, 36.8)	6.4(5.0, 8.3)	4.4(2.9, 6.7)	NA	<0.0001
Seropositive[*] (%)	83.75(73.82, 91.05)	35.00(20.63, 51.68)	48.75(30.82, 63.84)	NA	<0.0001

The geometric mean of titer (GMT) and geometric mean of increase against the pre-booster level (GMI) are presented with corresponding 2-sided 95% confidence interval (CI) respectively in AWcorna and CoronaVac groups, and the ratios of GMT or GMI between the two groups and corresponding 95% CI are accordingly showed.

The non-inferiority result would be concluded if the lower bound of 95% CI of the ratio between groups (AWcorna/CoronaVac) is larger than 2/3 When the non-inferiority conclusion is concluded, the superiority would be considered sequentially if the lower bound was larger than 1.

434   The seroconversion rate and the 4-fold Increase rate with their corresponding Clopper-Pearson 95% CI are shown, and the difference between the two groups

435   were calculated using Miettinen-Nurminen method.

436   N=the number of participants included the per-protocol population. The p values are the results of comparison between the AWcorna and CoronaVac groups.

437

438   *Seropositive defined as the status that the nAb level of a subject achieved the threshold of 1:8 (Limit of Detection, LOD).

439   **Seroconversion due to booster dose at a subject level is defined as a change from below the LOD to equal or above LOD, or for those who above the LOD

440   pre-booster experienced at least a 4-fold rise in terms of nAbs.

441

442 **Table S3. RBD-Specific antibodies before and after booster.**

	AWcorna	CoronaVac	GMT/GMI Ratio (AWcorna /CoronaVac)	Statistics	*P* value
	N=200	N=100	or Diff. in % (AWcorna -CoronaVac)		
Pre-Booster					
GMT	134.7(118.3, 153.4)	140.8(115.3, 172.0)	NA	*t*=-0.378	0.7061
Seropositive[*](%)	100.00(98.17, 100.00)	100.00(96.38, 100.00)	NA	NA	1.0000
D14					
GMT	29270.4(26074.5, 32858.1)	4317.8(3680.1, 5065.9)	6.8 (5.6, 8.3)	NA	<0.0001
GMI	217.3(184.9, 255.3)	30.7(25.5, 36.9)	7.1 (5.5, 9.2)	NA	<0.0001
Seroconversion[*](%)	99.50(97.25, 99.99)	98.00(92.96, 99.76)	1.50(-1.08, 6.55)	NA	0.2585
4-Fold Increase(%)	99.50(97.25, 99.99)	98.00(92.96, 99.76)	1.50(-1.08, 6.55)	NA	0.2585
D28					
GMT	21874.4(19568.4, 24452.3)	3102.3(2661.8, 3615.8)	7.1 (5.8, 8.5)	NA	<0.0001
GMI	162.4(138.0, 191.1)	22.0(18.4, 26.4)	7.4 (5.7, 9.6)	NA	<0.0001
Seroconversion[*](%)	99.00(96.43, 99.88)	95.00(88.72, 98.36)	4.00(0.37, 10.27)	NA	0.0433
4-Fold Increase(%)	99.00(96.43, 99.88)	95.00(88.72, 98.36)	4.00(0.37, 10.27)	NA	0.0433

443 The geometric mean of titer (GMT) and geometric mean of increase against the pre-booster level (GMI) are presented with corresponding 2-sided 95%

444 confidence interval (CI) respectively in AWcorna and CoronaVac groups, and the ratios of GMT or GMI between the two groups and corresponding 95% CI

445 are accordingly showed.

446   The seroconversion rate and the 4-fold Increase rate with their corresponding Clopper-Pearson 95% CI are shown, and the difference between the two groups
447   were calculated using Miettinen-Nurminen method.

448   N=the number of subjects included the per-protocol population. The p values are the results of comparison between the AWcorna and CoronaVac groups.

449   *Seropositive defined as the status that the nAb level of a subject achieved the threshold of 1:10 (Limit of Detection, LOD).

450   ** Seroconversion due to booster dose at a subject level is defined as a change from below the LOD to equal or above LOD, or for those who above the LOD
451   pre-booster experienced at least a 4-fold rise in terms of nAbs.

Table S4. Soliclited and unsolicited adverse reactions that occurred within 28 days after booster
vaccination.

Event Name	AWcorna (N=200)	CoronaVac (N=100)	P-Value
Severity	n(%)	n(%)	
AE (Any)	139(69.5)	20(20)	**<0.0001**
Grade1	85(42.5)	12(12)	**<0.0001**
Grade2	71(35.5)	6(6)	**<0.0001**
Grade3	22(11)	3(3)	**0.0246**
Grade4	0(0)	0(0)	1
Grade5	0(0)	0(0)	1
≥Grade2	84(42)	9(9)	**<0.0001**
≥Grade3	22(11)	3(3)	**0.0246**
Solicited AE (Any)	138(69)	20(20)	**<0.0001**
Grade1	85(42.5)	12(12)	**<0.0001**
Grade2	69(34.5)	6(6)	**<0.0001**
Grade3	22(11)	3(3)	**0.0246**
Grade4	0(0)	0(0)	1
≥Grade2	83(41.5)	9(9)	**<0.0001**
≥Grade3	22(11)	3(3)	**0.0246**
Systemic (Any)	131(65.5)	20(20)	**<0.0001**
Grade1	73(36.5)	12(12)	**<0.0001**
Grade2	67(33.5)	6(6)	**<0.0001**
Grade3	20(10)	3(3)	**0.0372**
Grade4	0(0)	0(0)	1
≥Grade2	82(41)	9(9)	**<0.0001**
≥Grade3	20(10)	3(3)	**0.0372**
Fever (FDA Standard, Any)	67(33.5)	4(4)	**<0.0001**
Grade1	39(19.5)	2(2)	**<0.0001**
Grade2	20(10)	2(2)	**0.0100**
Grade3	8(4)	0(0)	0.0555
Grade4	0(0)	0(0)	1
≥Grade2	28(14)	2(2)	**0.0008**
≥Grade3	8(4)	0(0)	0.0555

Diarrhea (Any)	0(0)	0(0)	1
Grade1	0(0)	0(0)	1
Grade2	0(0)	0(0)	1
Grade3	0(0)	0(0)	1
Grade4	0(0)	0(0)	1
≥Grade2	0(0)	0(0)	1
≥Grade3	0(0)	0(0)	1
Nausea (Any)	5(2.5)	1(1)	0.6674
Grade1	4(2)	0(0)	0.3052
Grade2	1(0.5)	0(0)	1
Grade3	0(0)	1(1)	0.3333
Grade4	0(0)	0(0)	1
≥Grade2	1(0.5)	1(1)	1
≥Grade3	0(0)	1(1)	0.3333
Vomiting (Any)	5(2.5)	1(1)	0.6674
Grade1	5(2.5)	0(0)	0.1734
Grade2	0(0)	0(0)	1
Grade3	0(0)	1(1)	0.3333
Grade4	0(0)	0(0)	1
≥Grade2	0(0)	1(1)	0.3333
≥Grade3	0(0)	1(1)	0.3333
Headache (Any)	52(26)	7(7)	**<0.0001**
Grade1	11(5.5)	3(3)	0.3993
Grade2	41(20.5)	3(3)	**<0.0001**
Grade3	0(0)	1(1)	0.3333
Grade4	0(0)	0(0)	1
≥Grade2	41(20.5)	4(4)	<0.0001
≥Grade3	0(0)	1(1)	0.3333
Muscle Aches (Any)	15(7.5)	1(1)	**0.0255**
Grade1	5(2.5)	0(0)	0.1734
Grade2	9(4.5)	1(1)	0.1732
Grade3	1(0.5)	0(0)	1
Grade4	0(0)	0(0)	1

≥Grade2	10(5)	1(1)	0.1073
≥Grade3	1(0.5)	0(0)	1
Joint Pain (Any)	6(3)	1(1)	0.4310
Grade1	3(1.5)	0(0)	0.5533
Grade2	2(1)	1(1)	1
Grade3	1(0.5)	0(0)	1
Grade4	0(0)	0(0)	1
≥Grade2	3(1.5)	1(1)	1
≥Grade3	1(0.5)	0(0)	1
Chills (Any)	10(5)	1(1)	0.1073
Grade1	7(3.5)	1(1)	0.2765
Grade2	3(1.5)	0(0)	0.5533
Grade3	0(0)	0(0)	1
Grade4	0(0)	0(0)	1
≥Grade2	3(1.5)	0(0)	0.5533
≥Grade3	0(0)	0(0)	1
Fatigue (Any)	4(2)	0(0)	0.3052
Grade1	2(1)	0(0)	0.5541
Grade2	1(0.5)	0(0)	1
Grade3	1(0.5)	0(0)	1
Grade4	0(0)	0(0)	1
≥Grade2	2(1)	0(0)	0.5541
≥Grade3	1(0.5)	0(0)	1
Rash (Not at Injection Site, Any)	0(0)	1(1)	0.3333
Grade1	0(0)	0(0)	1
Grade2	0(0)	0(0)	1
Grade3	0(0)	1(1)	0.3333
Grade4	0(0)	0(0)	1
≥Grade2	0(0)	1(1)	0.3333
≥Grade3	0(0)	1(1)	0.3333
Hypersensitivity (Any)	1(0.5)	0(0)	1
Grade1	0(0)	0(0)	1
Grade2	1(0.5)	0(0)	1

Grade3	0(0)	0(0)	1
Grade4	0(0)	0(0)	1
≥Grade2	1(0.5)	0(0)	1
≥Grade3	0(0)	0(0)	1
Local AE (Any)	34(17)	2(2)	**<0.0001**
Grade1	26(13)	2(2)	**0.0013**
Grade2	7(3.5)	0(0)	0.0998
Grade3	2(1)	0(0)	0.5541
Grade4	0(0)	0(0)	1
≥Grade2	9(4.5)	0(0)	**0.0319**
≥Grade3	2(1)	0(0)	0.5541
Pain at Injection Site (Any)	34(17)	2(2)	**<0.0001**
Grade1	25(12.5)	2(2)	**0.0021**
Grade2	7(3.5)	0(0)	0.0998
Grade3	2(1)	0(0)	0.5541
Grade4	0(0)	0(0)	1
≥Grade2	9(4.5)	0(0)	**0.0319**
≥Grade3	2(1)	0(0)	0.5541
Induration (Any)	0(0)	0(0)	1
Grade1	0(0)	0(0)	1
Grade2	0(0)	0(0)	1
Grade3	0(0)	0(0)	1
Grade4	0(0)	0(0)	1
≥Grade2	0(0)	0(0)	1
≥Grade3	0(0)	0(0)	1
Redness (Any)	0(0)	0(0)	1
Grade1	0(0)	0(0)	1
Grade2	0(0)	0(0)	1
Grade3	0(0)	0(0)	1
Grade4	0(0)	0(0)	1
≥Grade2	0(0)	0(0)	1
≥Grade3	0(0)	0(0)	1
Rash (at Injection Site, Any)	0(0)	0(0)	1

Grade1	0(0)	0(0)	1
Grade2	0(0)	0(0)	1
Grade3	0(0)	0(0)	1
Grade4	0(0)	0(0)	1
≥Grade2	0(0)	0(0)	1
≥Grade3	0(0)	0(0)	1
Swelling (Any)	2(1)	0(0)	0.5541
Grade1	2(1)	0(0)	0.5541
Grade2	0(0)	0(0)	1
Grade3	0(0)	0(0)	1
Grade4	0(0)	0(0)	1
≥Grade2	0(0)	0(0)	1
≥Grade3	0(0)	0(0)	1
Itch (Any)	0(0)	0(0)	1
Grade1	0(0)	0(0)	1
Grade2	0(0)	0(0)	1
Grade3	0(0)	0(0)	1
Grade4	0(0)	0(0)	1
≥Grade2	0(0)	0(0)	1
≥Grade3	0(0)	0(0)	1
Unsolicited AE (Any)	2(1)	1(1)	1
Grade1	0(0)	0(0)	1
Grade2	2(1)	0(0)	0.5541
Grade3	0(0)	1(1)	0.3333
Grade4	0(0)	0(0)	1
Grade5	0(0)	0(0)	1
≥Grade2	2(1)	1(1)	1
≥Grade3	0(0)	1(1)	0.3333

454 Data are n (%). n, number of participants; %, percentage of participants; any, all participants with any grade
455 of adverse reactions. The analysis was based on the per-protocol population. *P* values shown in bold are
456 <0.05.