Supporting Information

Materials and methods

Study design and participants

We conducted a prospective, single-center, double-blind randomized, phase IV clinical trial (ClinicalTrials.gov, registered number: NCT05165966) measuring immunogenicity with two different dosages administered. The trial was conducted by investigators from Beijing Youan hospital. Data were analyzed independently by investigators from Beijing Center for Disease Prevention and Control. The detailed study protocol was provided in Supplementary material.

Sample size calculation

In terms of GMT ratio between the high-dosage group and the medium-dosage group, superiority was demonstrated if the lower bound of the 95% CI of the ratio estimate was higher than δ (0.176). Parameters values were set as: two-sided α=0.05, the power of test=80%, and the log-transformed standard deviation σ=0.5 with reference to the previous research results of the experimental vaccine. Sample size was calculated by the NCSS-PASS software (version 11, NCSS, LLC) and the number of samples in each batch was 139 cases. Considering a dropout rate of ≥ 15%, the sample size of each group was 170, for a total of 340 cases.

Subject recruitment

Healthy adults who were 5-9 months after being vaccinated with CoronaVac according to the two-dose schedule and aged over 18 were recruited to Beijing Youan hospital. Initially 369 participants were enrolled for screening. Key exclusion criteria included any history of SARS-CoV-2 infection; received 3 or more doses of COVID-19 vaccine, or any immunosuppressive condition (details in Supporting Information, **Study Protocol**). After screening, 340 participants

who met the eligibility criteria were finally included in the trial. Of all, 50 healthy subjects who were received two doses of CoronaVac between January and February 2021 (cohort A) (PMID: 34021265) were continued in the current study. The rest of 290 subjects were newly recruited from October to November in 2021 (cohort B) (Figure 1).

Written informed consent was obtained from each eligible participant both before enrollment and administration of the booster dose CoronaVac. General information including age, gender, body weight, height and disease history were also recorded.

Randomization and blinding

The eligible participants were randomly assigned to single intramuscular injection of either 3 μg (medium dosage or the current vaccine regimen) or 6 μg (high dosage) of CoronaVac by block randomization method. Randomization code generated by a computer was given to each syringe. Syringes containing different dosage of CoronaVac were identical in appearance. After CoronaVac booster administration, participants were followed up at day 7, 14, 28 for blood collections. Both the participants and the investigators who performed booster vaccination were blinded in the study.

NAb measurements

After centrifugation at 2000g for 10 minutes at room temperature, serum was collected from blood and stored at -80 ℃. NAb were determined with a modified cytopathogenic neutralization assay based on live SARS-CoV-2. Antibody titers were assigned values on 2 to the ‘x’ times, respectively. NAb measurements were conducted at baseline, day 7, 14 and 28 after receiving booster dose. We also compared NAb responses to the wildtype strain (SARS-CoV-2/human/CHN/CN1/2020, GenBank number MT407659.1), Delta (SARS-CoV-2 Delta variants,

GISAID number Delta EPI_ISL_1911197), and Omicron (variant, respectively. We defined seropositivity as a titer of 8 or greater for NAbs to infectious SARS-CoV-2.

Outcomes

The aim of the trial was to measure the immunogenicity induced by different dosages. Therefore, the primary and the secondary endpoint were to determine the geometric mean titers (GMTs), geometric mean increases (GMI) and seropositivity of NAb at different time points, respectively.

Statistical analysis

GMIs were calculated using antibody titers at baseline and at 7, 14, 28 days after the booster dose. Comparisons were done between groups by group t-tests or rank-sum test with a significant level of 0.05 (2-sided). Data analysis and visualization were conducted using Stata/IC Version 16.0 (StataCorp, College Station, Texas) and R Studio Version 3.6.3.

Table 1. Baseline demographic characteristics of subjects (N=340) who received either medium- or high- dosage of the booster dose of CoronaVac.

Variables	Medium Dosage	High Dosage	*P* value
Number	**170**	**170**	
Gender-n (%)			
Male	63 (37.1)	57 (33.5)	0.50
Female	107 (62.9)	113 (66.5)	
Diabetes only-n (%)	1 (0.6)	2 (1.2)	0.56
Hypertension only-n (%)	8 (4.7)	12 (7.1)	0.36
Diabetes and Hypertension -n (%)	1 (0.6)	4 (2.4)	0.18
Median (IQR)			
Age-Median (yrs)	38 (36, 40)	38 (37, 40)	0.43
Days between 2nd and 3rd dose	271 (208, 273)	268 (182, 274)	0.37
Body Mass Index (kg/m^2)	23.9 (21.5, 26.6)	23.4 (21.1, 25.8)	0.43

Notes:

A total of 170 participants were recruited for both medium- and high-dosage groups, respectively. Medium-dosage is the current vaccine regimen for CoronaVac.

Table 2. GMT of subjects after receiving high and medium booster dose of CoronaVac against wildtype, Delta (B.1.617.2) and Omicron (B.1.529) strains.

	Wildtype			B.1.617.2			B.1.529		
Days after booster dose	High GMT	Medium GMT	*P*	High GMT	Medium GMT	*P*	High GMT	Medium GMT	*P*
0	10.6	9.7	0.843	2.2	2.1	0.369	2.0	2.0	0.408
7	216.1	113.8	0.003	13.1	7.7	0.054	4.8	3.3	0.014
14	428.9	222.2	<0.001	87.5	47.9	<0.001	15.3	10.4	0.002
28	329.1	169.7	<0.001	64.4	35.8	0.004	11.8	8.3	0.001

Notes:
Medium-dosage is the current vaccine regimen for CoronaVac.
Seropositivity is defined as a titer of 8 or greater for NAbs to infectious SARS-CoV-2.

Table 3: GMI after receiving high and medium booster dose of CoronaVac against wildtype, Delta (B.1.617.2) and Omicron (B.1.529) strains.

	Wildtype			**B.1.617.2**			**B.1.529**		
Days after booster dose	High	Medium	*P*	High	Medium	*P*	High	Medium	*P*
7	20.4	11.7	0.004	6	3.6	0.012	2.4	1.7	0.013
14	40.6	22.9	0.002	39.9	22.3	<0.001	7.7	5.2	0.002
28	31.1	17.5	<0.001	29.4	16.7	<0.001	5.9	4.2	0.002

Notes:
Medium-dosage is the current vaccine regimen for CoronaVac

Table 4. Seropositivity rates and subjects after receiving high and medium booster dose of CoronaVac against wildtype, Delta (B.1.617.2) and Omicron (B.1.529) strains.

	Wildtype			B.1.617.2			B.1.529		
Days after booster dose	High Seropositive (%)	Medium Seropositive (%)	*P*	High Seropositive (%)	Medium Seropositive (%)	*P*	High Seropositive (%)	Medium Seropositive (%)	*P*
0	86 (50.6)	78 (45.9)	0.385	3 (1.8)	2 (1.2)	0.652	0 (0)	0 (0)	-
7	166 (99.4)	162 (98.2)	0.004	145 (86.8)	68 (41.2)	0.012	50 (32.9)	24 (17.3)	0.013
14	157 (100)	151 (100)	0.002	154 (98.1)	144 (95.4)	<0.001	110 (70.1)	78 (51.7)	0.002
28	164 (100)	167 (99.4)	<0.001	156 (95.1)	152 (90.5)	<0.001	99 (60.4)	68 (40.5)	0.002

Notes:
Medium-dosage is the current vaccine regimen for CoronaVac.
Data are presented as number and percentage.

Table 5. GMT of subjects after receiving high and medium booster dose of CoronaVac against wildtype, Delta (B.1.617.2) and Omicron (B.1.529) strains among participants with diabetes only at baseline.

		Wildtype		Delta		Omicron	
GMT	**Days after booster dose**	**High**	**Medium**	**High**	**Medium**	**High**	**Medium**
	0	4.0	8.0	2.0	2.0	2.0	2.0
	7	110.9	128.0	6.9	2.0	3.5	2.0
	14	768.0	64.0	128.0	6.0	19.6	8.0
	28	627.1	64.0	78.4	2.0	13.9	2.0
GMI	**7**	27.7	16.0	3.5	1.0	1.8	1.0
	14	192.0	8.0	64.0	3.0	9.8	4.0
	28	156.8	8.0	39.2	1.0	7.0	1.0
Seropositivity %	**0**	0.0	0.0	0.0	0.0	0.0	0.0
	7	100.0	100.0	0.0	0.0	0.0	0.0
	14	100.0	100.0	100.0	0.0	100.0	0.0
	28	100.0	100.0	100.0	0.0	100.0	0.0

Notes:
Medium-dosage is the current vaccine regimen for CoronaVac.
Seropositivity is defined as a titer of 8 or greater for NAbs to infectious SARS-CoV-2.

Table 6. GMT of subjects after receiving high and medium booster dose of CoronaVac against wildtype, Delta (B.1.617.2) and Omicron (B.1.529) strains among participants with hypertension only at baseline.

		Wildtype		Delta		Omicron	
GMT	**Days after booster dose**	**High**	**Medium**	**High**	**Medium**	**High**	**Medium**
	0	8.9	6.3	2.3	2.0	2.0	2.0
	7	263.7	93.2	17.7	4.8	6.6	2.9
	14	396.0	221.7	109.4	49.4	17.1	12.6
	28	120.9	312.6	70.4	27.7	11.9	7.2
GMI	**7**	75.1	21.1	17.5	3.3	8.6	1.7
	14	73.2	49.3	83.2	30.7	22.1	8.8
	28	93.0	26.8	68.2	19.5	21.5	5.3
Seropositivity %	**0**	16.7	12.5	8.3	0.0	0.0	0.0
	7	100.0	100.0	66.7	25.0	33.3	0.0
	14	91.7	75.0	91.7	75.0	58.3	50.0
	28	91.7	100.0	91.7	87.5	50.0	37.5

Notes:
Medium-dosage is the current vaccine regimen for CoronaVac.
Seropositivity is defined as a titer of 8 or greater for NAbs to infectious SARS-CoV-2.

Table 7. GMT of subjects after receiving high and medium booster dose of CoronaVac against wildtype, Delta (B.1.617.2) and Omicron (B.1.529) strains among participants with both diabetes and hypertension at baseline.

		Wildtype		Delta		Omicron	
GMT	**Days after booster dose**	**High**	**Medium**	**High**	**Medium**	**High**	**Medium**
	0	8.0	8.2	2.0	2.0	2.0	2.0
	7	110.9	512.0	6.9	48.0	5.8	32.0
	14	347.0	384	72.9	256.0	7.4	64.0
	28	184.6	96.0	66.6	128.0	5.0	32.0
GMI	**7**	13.7	64.0	5.3	24.0	4.0	16.0
	14	59.0	48.0	63.5	128.0	9.7	32.0
	28	29.3	12.0	81.3	64.0	8.5	16.0
Seropositivity %	**0**	75.0	0.0	0.0	0.0	0.0	0.0
	7	100.0	100.0	50.0	100.0	25.0	100.0
	14	100.0	100.0	100.0	100.0	50.0	100.0
	28	75.0	100.0	50.0	100.0	25.0	100.0

Notes:
Medium-dosage is the current vaccine regimen for CoronaVac.
Seropositivity is defined as a titer of 8 or greater for NAbs to infectious SARS-CoV-2.

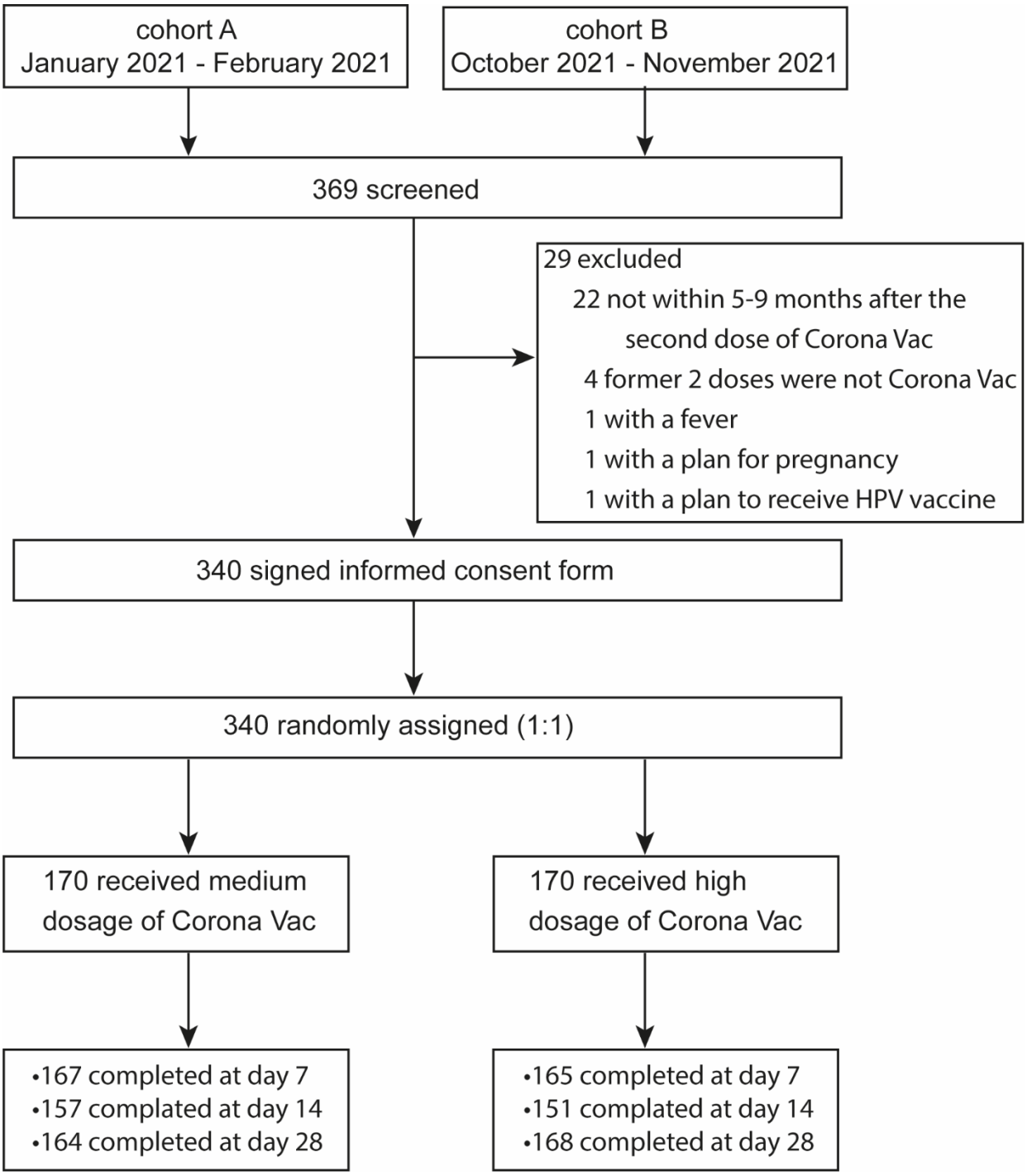

Figure 1: Flow chart of the randomized, double-blinded clinical trial on CoronaVac booster dose.

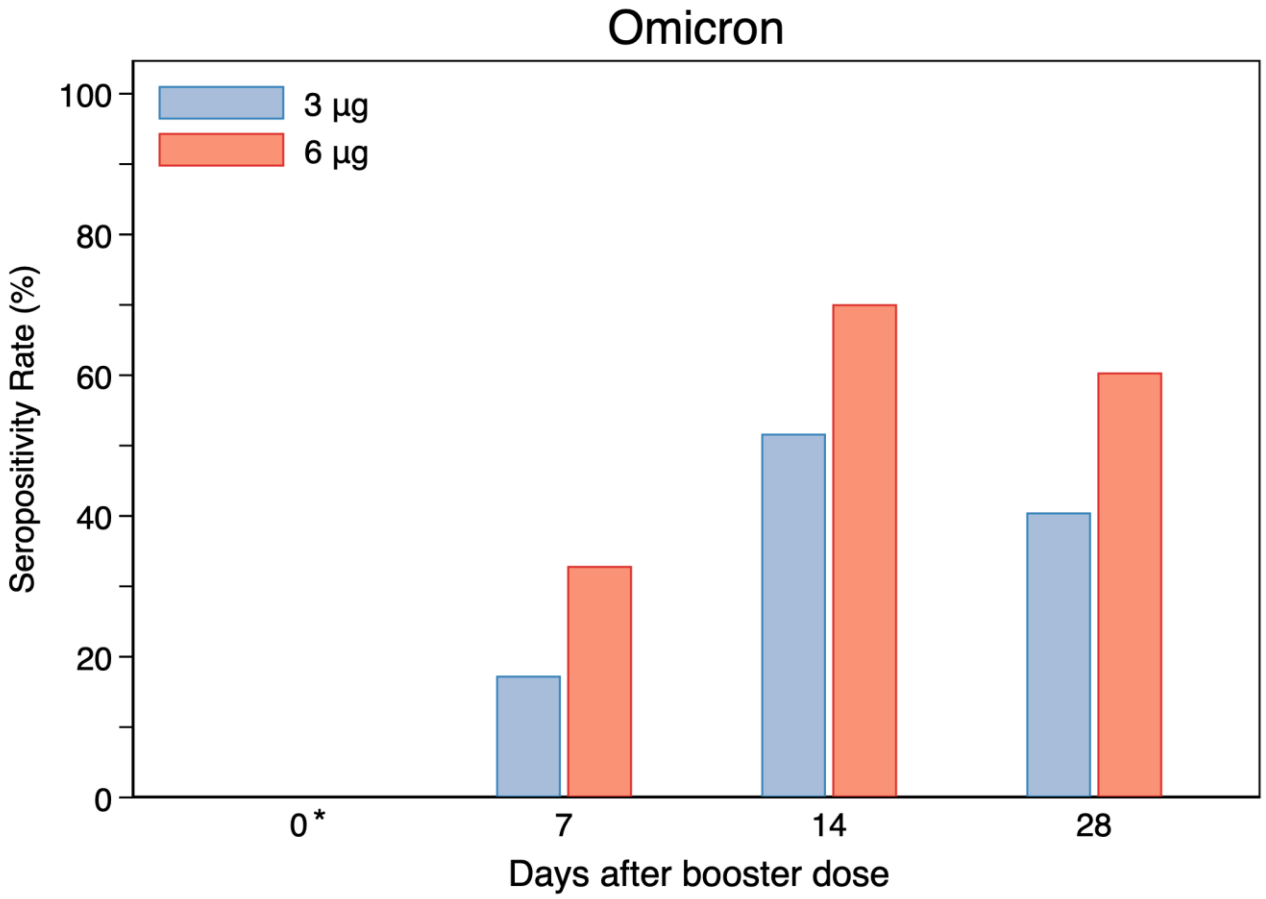

Figure 2: Seropositivity rate of the booster vaccination of medium- and high-dosage of CoronaVac against B.1.529 (Omicron) strain.
Notes: * represents no seropositive subjects at baseline with the criteria of seropositivity >1:8 in neutralizing antibody titers. 3 µ g (medium dosage) is the current vaccine regimen for CoronaVac.