Preplanned Studies

Immunogenicity and Safety of Homologous Booster Doses of CoronaVac COVID-19 Vaccine in Elderly Individuals Aged 60 Years and Older: A Dosing Interval Study — Yunnan Province, China, 2021–2022

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Summary

What is already known about this topic?

Neutralization levels induced by inactivated vaccines rapidly wane after primary immunization, and a homologous booster can recall specific immune memory, resulting in a remarkable increase in antibody concentration. The optimal interval between primary and booster doses has yet to be determined.

What is added by this report?

Booster doses given at three months or more after the two-dose regimen of the CoronaVac COVID-19 vaccine in elderly individuals aged 60 years and older triggered good immune responses. The geometric mean titers of neutralizing antibody on Day 14 after the booster doses increased by 13.3–26.2 fold of baseline levels, reaching 105.45–193.59 in groups with different intervals (e.g., 3, 4, 5, and 6 months).

What are the implications for public health practice?

A 4- to 5-month interval between receiving the primary and booster series of CoronaVac could be an alternative to the 6-month interval in order to promote vaccine-induced immunity in elderly individuals. The findings support the optimization of booster immunization strategies.

Vaccination has been proven to be highly effective in reducing the burden of coronavirus disease 2019 (COVID-19) in the context of emerging severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants based on real-world evidence (*1*–*2*). With the efforts of the whole of Chinese society, vaccine coverage of primary immunization has reached 90% (*3*). As neutralization antibody levels rapidly decline after primary immunization (*4*), especially for vulnerable populations, determining the optimal interval between primary and booster series is an urgent step in promoting vaccine-induced population immunity. To explore the immunogenicity, immune persistence, and safety of homologous booster doses of CoronaVac administered at 3-month, 4-month, 5-month, and 6-month intervals in elderly individuals aged 60 years and older, we conducted a single-center, open-label trial in Yongde County, Yunnan Province. We found that booster doses given at three months or more after the two-dose regimen of CoronaVac in elderly individuals aged 60 years and older could trigger good immune responses, especially at four to six months. This would be conducive to optimizing intervals for the booster vaccination strategy.

In this single-center, open-label clinical trial conducted in Yongde County, Yunnan Province, China, participants aged 60 years and over who had received two doses of CoronaVac three to six months prior were recruited. The detailed inclusion and exclusion criteria are listed in Supplementary Table S1 (available in https://weekly.chinacdc.cn/). Eligible participants were assigned to four groups according to the time elapsed after their two-dose immunization, namely, the 3-month, 4-month, 5-month, and 6-month interval groups. All participants provided written informed consent prior to enrollment. The study protocol and informed consent were approved by the Ethics Committee of Yunnan CDC (#2021-14). This trial was registered with ClinicalTrials.gov, NCT05398926.

Blood samples were collected from participants before booster administration and on Days 14, 28, and 180 after booster doses to assess immunogenicity. Neutralizing antibody levels against live SARS-CoV-2 (virus strain SARS-CoV-2/human/CHN/CN1/2020, GenBank accession number MT407649.1) were quantified using a previously described micro cytopathogenic effect assay (*5*–*6*). Titers lower than the limit of detection (1∶4) were treated as half the limit of

detection. Participants were observed for 30 minutes after vaccine administration in case of any immediate reactions. Solicited local and systemic adverse events within 7 days, unsolicited adverse events within 28 days, and serious adverse events within 6 months were collected after booster doses. All adverse events were graded according to China National Medical Products Administration guidelines and coded by the Medical Dictionary for Regulatory Activities (MedDRA 25.0) System Organ Class. The causal relationships between adverse events and vaccination were assessed by the investigators and an expert committee organized by CDC.

The primary outcomes included geometric mean titers (GMTs) of neutralizing antibodies against live SARS-CoV-2 on Day 14, Day 28, and Day 180, as well as any vaccine-related adverse events within 28 days after booster doses. The incidence of solicited adverse events within 7 days and serious adverse events reported during the 6-month follow-up were evaluated as secondary safety endpoints. Post hoc analysis assessed fold increases in antibody levels before administration to Day 14 and fold decreases from Day 14 to Day 180 after booster doses in each group. The immunogenic outcomes were evaluated in the per-protocol set, comprising participants who completed their assigned vaccination and had available blood samples at prespecified time points. Participants who received booster doses were included in the safety analysis.

We used the Pearson χ^2 test or Fisher's exact test for categorical outcomes and the Clopper-Pearson method for corresponding 95% confidence intervals (*CI*s). GMTs and corresponding 95% *CI*s were calculated on the basis of the standard normal distribution of the log-transformed antibody titers. Fold increases/decreases in antibody levels were calculated as the geometric mean of the ratios of paired sera at two visits. Analysis of variance (ANOVA) with log-transformation was used to test the differences between groups and between follow-up times. Comparisons were performed between groups or by group *t* tests with log-transformation. Bonferroni correction was performed as a post hoc test if variance was significant. Subgroup analyses of immunogenicity were conducted by sex and self-reported comorbidity status. Hypothesis testing was two-sided, and a *P* value <0.05 was considered to indicate statistical significance. We used R (version 4.2.1; R Core Team, Vienna, Austria) for all analyses.

Between December 6 and 24, 2021, a total of 400 participants were enrolled in the study and allocated to four groups according to the interval between their second and booster doses; 101, 99, 100, and 100 participants were allocated to the 3-month, 4-month, 5-month, and 6-month groups, respectively (Supplementary Figure S1, available in https://weekly.chinacdc.cn/). The median age of the participants was 65 [interquartile range (IQR), 63–68] years, and the distribution was balanced among groups. Of the 400 participants, 198 (50%) were male, and 312 (78%) were ethnically Han. Hypertension was the most common comorbidity, present in 102 (26%) participants. The demographic characteristics are detailed in Table 1.

The GMTs of neutralizing antibodies before administration of booster doses were 8.06 (95% *CI*: 6.68–9.72) in the 3-month group, 7.98 (95% *CI*: 6.56–9.70) in the 4-month group, 7.40 (95% *CI*: 6.13–8.94) in the 5-month group, and 5.26 (95% *CI*: 4.43–6.25) in the 6-month group, which were significantly different between the 3-month and 6-month (*P*=0.012), and 4-month and 6-month groups (*P*=0.008), respectively. Remarkable increases in GMTs were observed in all groups on Day 14 after the boosters, reaching 105.45 (95% *CI*: 86.14–129.08), 187.31 (95% *CI*: 152.99–229.33), 193.59 (95% *CI*: 151.84–246.82), and 135.52 (95% *CI*: 111.32–164.99) in the four groups (*P*<0.0001), respectively. Only the antibody levels in the 4-month and 5-month groups significantly exceeded those in the 3-month group (both *P*<0.0001) and there were no significant differences in neutralizing antibody levels between the other three groups and the 6-month group (*P*=0.57, 0.20, 0.11), which was the recommended minimum interval between primary and booster regimens in China before December 2022. No significant differences in fold increases were observed among the four groups. A declining tendency in GMT values was observed in all groups from Day 14 to Day 28 after the booster doses. GMTs by six months after the boosters were highest in the 5-month group (15.45, 95% *CI*: 12.23–19.52), followed by the 4-month group (10.24, 95% *CI*: 8.51–12.32), the 6-month group (9.82, 95% *CI*: 8.03–12.01), and the 3-month group (7.21, 95% *CI*: 6.05–8.58) (Table 2 and Figure 1). The fold decreases from Day 14 to Day 180 after booster doses were similar among the four groups (Table 2). When compared between follow-up times, there was no significant difference between baseline and Day 180, or between Day 14 and Day 28 in all groups, except the 4-month group, in which the GMT on Day 14 was significantly different from Day 28 after the booster

TABLE 1. Baseline demographic characteristics of participants who received booster doses of CoronaVac COVID-19 vaccine.

Characteristics	3-month group (*n*=101)	4-month group (*n*=99)	5-month group (*n*=100)	6-month group (*n*=100)	Total (*N*=400)
Sex					
Male	43 (43%)	49 (49%)	54 (54%)	52 (52%)	198 (50%)
Female	58 (57%)	50 (51%)	46 (46%)	48 (48%)	202 (50%)
Age group (years)					
60–70	74 (73%)	87 (88%)	81 (81%)	85 (85%)	327 (82%)
70–80	26 (26%)	11 (11%)	19 (19%)	15 (15%)	71 (18%)
80+	1 (1%)	1 (1%)	0 (0%)	0 (0%)	2 (1%)
BMI (kg/m^2, IQR)	22.58 (20.86, 24.77)	23.71 (21.00, 25.98)	22.82 (20.83, 24.91)	22.44 (20.67, 24.15)	22.80 (20.83, 24.98)
Ethnicity					
Han	72 (71%)	76 (77%)	68 (68%)	96 (96%)	312 (78%)
Others	29 (29%)	23 (23%)	32 (32%)	4 (4%)	88 (22%)
Comorbidity					
At least one	40 (40%)	42 (42%)	36 (36%)	24 (24%)	142 (36%)
Hypertension	32 (32%)	29 (29%)	28 (28%)	13 (13%)	102 (26%)
Diabetes	6 (6%)	7 (7%)	5 (5%)	2 (2%)	20 (5%)
Cerebral infarction	1 (1%)	9 (9%)	5 (5%)	4 (4%)	19 (5%)
Coronary heart disease	4 (4%)	3 (3%)	3 (3%)	0 (0%)	10 (3%)
Hyperthyroidism	0 (0%)	1 (1%)	1 (1%)	1 (1%)	3 (1%)
Others	6 (6%)	6 (6%)	3 (3%)	12 (12%)	27 (7%)
Interval between 3rd and 2nd doses (days, IQR)	110.00 (98.00, 117.00)	132.00 (131.00, 132.00)	166.00 (163.00, 168.00)	185.00 (185.00, 185.00)	153.50 (117.00, 172.75)

Note: Data are presented as the median (IQR, interquartile range) or number (percentage). Continuous variables were compared using the Kruskal–Wallis H-test. Categorical variables were compared using the chi-square test or Fisher's exact test.
Abbreviation: BMI=body mass index.

TABLE 2. GMTs of neutralizing antibodies in different interval groups at different time points.

Time points	3-month group	4-month group	5-month group	6-month group	*P* value*
Baseline (Pre-booster)					
No. of participants	*n*=101	*n*=99	*n*=100	*n*=100	
GMT (95% *CI*)	8.06 (6.68, 9.72)	7.98 (6.56, 9.70)	7.40 (6.13, 8.94)	5.26 (4.43, 6.25)	0.0036
Day 14 after dose 3					
No. of participants	*n*=101	*n*=98	*n*=98	*n*=99	
GMT (95% *CI*)	105.45 (86.14, 129.08)	187.31 (152.99, 229.33)	193.59 (151.84, 246.82)	135.52 (111.32, 164.99)	<0.0001
Fold increases *vs*. baseline (95% *CI*)	13.26 (10.55, 16.67)	23.09 (18.31, 29.11)	25.82 (19.53, 34.14)	26.22 (20.82, 33.01)	0.17
Day 28 after dose 3					
No. of participants	*n*=97	*n*=97	*n*=96	*n*=92	
GMT (95% *CI*)	90.57 (73.53, 111.54)	138.81 (113.26, 170.11)	169.01 (132.97, 214.82)	123.64 (100.93, 151.46)	0.0006
Day 180 after dose 3					
No. of participants	*n*=87	*n*=85	n=91	*n*=94	
GMT (95% *CI*)	7.21 (6.05, 8.58)	10.24 (8.51, 12.32)	15.45 (12.23, 19.52)	9.82 (8.03, 12.01)	<0.0001
Fold decreases *vs*. Day 14 (95% *CI*)	14.99 (12.62, 17.79)	17.72 (14.51, 21.64)	12.29 (9.97, 15.16)	14.26 (11.85, 17.15)	0.60

Note: GMT was calculated based on log-transformed data.
Abbreviation: GMTs=geometric mean titers; *CI*=confidence interval; ANOVA=analysis of variance.
* ANOVA with log-transformation (GMT) was used to detect differences among the four groups. Differences between groups were assessed by *t* test on log-transformed data.

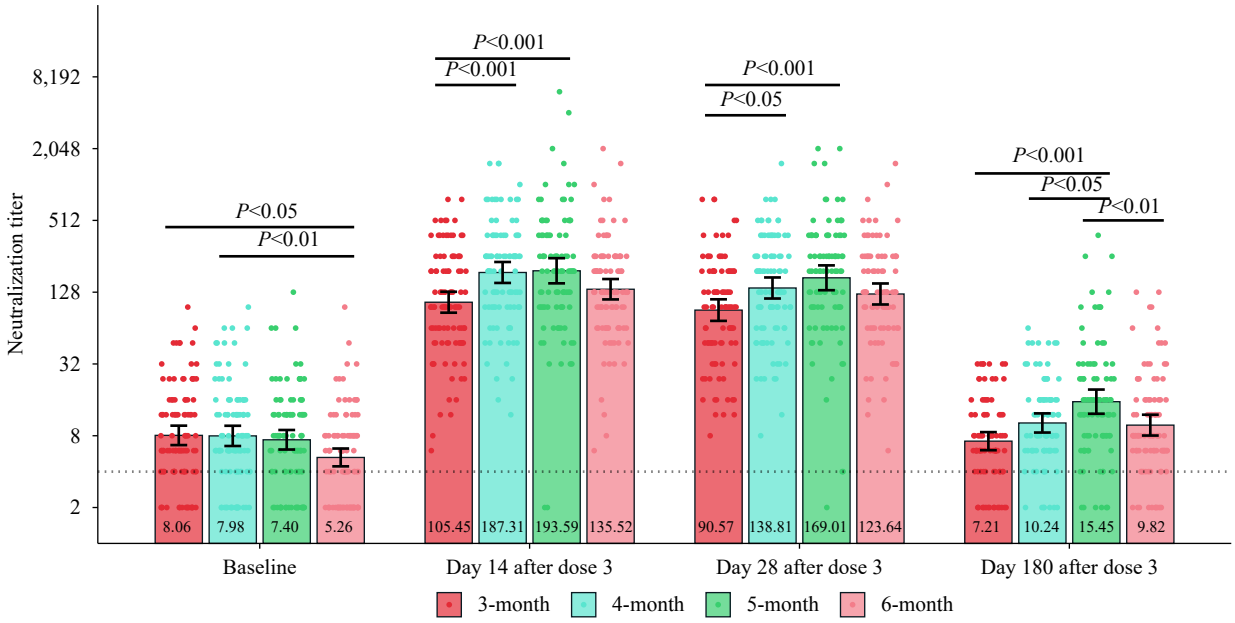

FIGURE 1. Neutralizing antibody levels to live SARS-CoV-2 before and after the booster vaccination in different interval groups.
Note: Numbers at the bottom of the bars are GMTs, and error bars indicate 95% *CI*s. Dots are reciprocal neutralizing antibody titers for individuals in the per-protocol population. Numbers above the short horizontal lines are *P* values for comparisons among the 3-month group, 4-month group, 5-month group, and 6-month group using ANOVA with log-transformation. Bonferroni correction was performed as a post hoc test if the variance was significant. Only *P* values indicating significant differences are marked. The dotted horizontal line represents the limit of detection (1∶4). Titers lower than the limit of detection are presented as half of that.
Abbreviation: SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; GMTs=geometric mean titers; *CI*s=confidence intervals; ANOVA=analysis of variance.

doses. In subgroup analyses, no significant differences in neutralizing antibodies were found between sex groups and comorbidity status (Supplementary Figures S2 and S3, available in https://weekly.chinacdc.cn/).

Solicited adverse events within 7 days were graded as mild (Grade 1) or moderate (Grade 2) in all groups (Supplementary Table S2, available in http://weekly.chinacdc.cn/). The proportions of participants who experienced vaccine-related adverse events within 28 days after the booster dose were 9% in the 3-month group, 8% in the 4-month group, 14% in the 5-month group, and 4% in the 6-month group, with no significant difference among groups (P=0.10; Supplementary Table S3, available in http://weekly.chinacdc.cn/). During the six-month follow-up period after booster doses, no vaccine-related serious adverse events were recorded (Supplementary Table S4, available in http://weekly.chinacdc.cn/).

DISCUSSION

Our study found that neutralization antibody levels continued to decline at three months post vaccination with a two-dose regimen of CoronaVac in elderly individuals aged 60 years and older, were sustained through months three to five, and exhibited an obvious reduction at six months. Waning of antibody levels in infection-naive individuals around a one- to three-month period after the second dose administration has been identified in most COVID-19 vaccines (*7*), which is associated with reduced protection, especially against emerging variants due to immune escape (*8*). The significantly lower antibody level in the 6-month group than other groups could prove that it would be preferable to provide the booster doses no more than six months after primary immunization to avoid the increasing risk of infection among elderly individuals.

None of the participants experienced natural infections before or during the study period, and there were no local outbreaks in Yunnan Province. Booster doses of inactivated vaccines given at three to six months after primary immunization could recall specific immune memory and rebound neutralization antibody levels in elderly individuals. Antibody titers in the 5-month group were numerically higher than those in the other three groups over the six-month follow-up

after booster doses, but there was no significant difference between the 4-month, 5-month, and 6-month groups on Day 14 and 28 after the booster doses. Prolonged intervals between doses could facilitate the affinity maturation of memory B cells (*9*) and several studies indicated that longer intervals before the booster dose elicited better neutralizing antibody levels (*10*–*11*), which was consistent with relatively poor immune responses in the 3-month group in our study. Our results showed that a 4- to 5-month interval between receiving the primary and booster series of CoronaVac would be an alternative choice to the 6-month interval to promote vaccine-induced immunity for elderly individuals.

On Day 180 after the first booster doses, GMTs declined to nearly undetectable levels. Previous follow-up studies (*6*,*12*) also reported a decreasing tendency after the first booster doses, suggesting that a second booster should be administered in a timely manner to provide extra protection against waning of protective antibodies. Real-world studies have reported the relative effectiveness of the second booster, indicating additional protection compared to the first booster (*13*–*14*).

This study has several limitations. First, we did not assess T-cell responses and neutralization tests in vitro against emerging variants of concern, particularly Omicron and its subvariants. Second, the proportion of participants aged 80 years or older and those with severe comorbidities was too small to determine immunogenicity for this older age group and high-risk population. Third, we did not assess the neutralizing antibody level between 28 and 180 days after booster doses to quantify the specific waning pattern.

In summary, homologous inactivated boosters after the two-dose regimen showed good immunogenicity and safety profiles in elderly individuals aged 60 years and older. Since November 29, 2022, the recommended minimum interval between the primary and booster series of COVID-19 vaccines in China has been shortened to three months for elderly individuals aged 60 years and older. Our results also imply that a 4- to 5-month interval between receiving the primary and booster series of CoronaVac could be an alternative choice to the 6-month interval to promote vaccine-induced immunity for elderly individuals. Further studies with more follow-up visits are needed to better understand immunogenicity after the first booster immunization and to help optimize the second booster immunization strategy. Real-world studies on the severity of infection and booster-dose effectiveness should be conducted.

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Conflicts of interest: HJ.Y. has received research funding from Sanofi Pasteur, GlaxoSmithKline, Yichang HEC Changjiang Pharmaceutical Company, Shanghai Roche Pharmaceutical Company and Sinovac Biotech Ltd. X.M., TT.Z. and G.Z. are employees of Sinovac Biotech and Y.H. is an employee of Sinovac Life Sciences. The remaining authors declare no competing interests.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Inclusion and exclusion criteria.

Criteria
Inclusion criteria
(1) People aged 60 years and older;
(2) Able to provide legal proof of identity;
(3) People who have received prime immunization by two doses of CoronaVac 21 to 35 days apart 3 to 6 months earlier;
(4) Able to understand and sign the Informed Consent Form voluntarily, willing to comply with the research plan and complete the study.
Exclusion criteria
(1) History of laboratory-confirmed SARS-CoV-2 infection;
(2) Having received SARS-CoV-2 vaccines other than CoronaVac, or having been boosted after prime immunization of CoronaVac;
(3) History of serious adverse reactions to vaccines or vaccine components, such as urticaria, dyspnea, and angioneuroedema;
(4) Subjects with autoimmune diseases or immune deficiency/immune inhibition;
(5) Subjects with severe chronic diseases, such as severe cardiovascular diseases, hypertension, diabetes, liver and kidney diseases, and malignant tumors that cannot be controlled by drugs;
(6) Subjects with severe nervous system disorders (epilepsy, convulsions or tic) or mental diseases;
(7) Having received the immunosuppressive therapy, cytotoxic therapy or inhaled corticosteroids therapy (excluding corticosteroid spray therapy for allergic rhinitis, and topical corticosteroid therapy for acute non-concurrent dermatitis) in the past 6 months, or are scheduled to receive these treatments during the study period;
(8) Subjects who have received blood products within 3 months before vaccination with the test vaccine, or are scheduled to receive these treatments during the study period;
(9) Subjects who have received other study drugs within 30 days before vaccination with the test vaccine;
(10) Subjects who have received live attenuated vaccines within 14 days before vaccination with the test vaccine, or who have received subunit or inactivated vaccines within 7 days before vaccination with the test vaccine;
(11) Subjects having an attack of various acute or chronic diseases within 7 days;
(12) Subjects with axillary temperature >37.0 ℃ at the time of vaccination;
(13) Subjects who are not suitable for participating in this clinical trial according to the investigator.

Abbreviation: SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

SUPPLEMENTARY TABLE S2. Solicited adverse events within 7 days after administration of booster doses.

Adverse events (MedDRA 25.0)	3-month group (*n*=101)	4-month group (*n*=99)	5-month group (*n*=100)	6-month group (*n*=100)	*P* value*
Total	11	7	16	4	
Any local reaction	2 (2%)	1 (1%)	4 (4%)	0	0.22
Vaccination site pain	0	1 (1%)	2 (2%)	0	0.62
Vaccination site swelling	1 (1%)	0	1 (1%)	0	1.00
Vaccination site pruritus	1 (1%)	0	1 (1%)	0	1.00
Any systemic reaction	9 (9%)	6 (6%)	12 (12%)	4 (4%)	0.10
Fever	2 (2%)	1 (1%)	2 (2%)	1 (1%)	1.00
Acute allergic reaction	1 (1%)	0	0	0	1.00
Diarrhoea	1 (1%)	0	0	0	1.00
Vomiting	1 (1%)	0	0	0	1.00
Nausea	1 (1%)	1 (1%)	2 (2%)	0	0.90
Headache	2 (2%)	2 (2%)	3 (3%)	0	0.53
Cough	1 (1%)	2 (2%)	4 (4%)	3 (3%)	0.71
Fatigue	0	0	1 (1%)	0	1.00

Note: Data are *n* (%).
* *P* value was calculated by Fisher exact probability method and of the comparison of incidence rate among four groups.

SUPPLEMENTARY TABLE S3. Incidence of vaccine-related adverse events by system organ class and preferred term reported within 28 days after administration of booster doses.

Adverse events (MedDRA 25.0)	3-month group (*n*=101)	4-month group (*n*=99)	5-month group (*n*=100)	6-month group (*n*=100)	Total (*N*=400)	*P* value*
No. of participants	9 (9%)	8 (8%)	14 (14%)	4 (4%)	35 (35%)	0.10
No. of events	12	9	16	4	41	
Cardiac disorders						
Arrhythmia	0	1 (1%)	0	0	1 (1%)	1.00
Gastrointestinal disorders						
Abdominal distension	0	0	1 (1%)	0	1 (1%)	1.00
Diarrhea	1 (1%)	0	0	0	1 (1%)	1.00
Nausea	1 (1%)	1 (1%)	2 (2%)	0	4 (4%)	0.90
Vomiting	1 (1%)	0	0	0	1 (1%)	1.00
General disorders and administration site conditions						
Fatigue	0	0	1 (1%)	0	1 (1%)	1.00
Pyrexia	2 (2%)	1 (1%)	2 (2%)	1 (1%)	6 (6%)	1.00
Vaccination site pain	0	1 (1%)	2 (2%)	0	3 (3%)	0.62
Vaccination site pruritus	1 (1%)	0	1 (1%)	0	2 (2%)	1.00
Vaccination site swelling	1 (1%)	0	1 (1%)	0	2 (2%)	1.00
Immune system disorders						
Hypersensitivity	1 (1%)	0	0	0	1 (1%)	1.00
Nervous system disorders						
Dizziness	1 (1%)	0	0	0	1 (1%)	1.00
Headache	2 (2%)	3 (3%)	2 (2%)	0	7 (7%)	0.53
Respiratory, thoracic and mediastinal disorders						
Cough	1 (1%)	2 (2%)	2 (2%)	2 (2%)	7 (7%)	1.00
Nasal obstruction	0	0	1 (1%)	0	1 (1%)	1.00
Rhinorrhea	0	0	1 (1%)	1 (1%)	2 (2%)	1.00

Note: Data are *n* (%).
* *P* value was calculated by Fisher exact probability method and of the comparison of incidence rate among four groups.

SUPPLEMENTARY TABLE S4. Serious adverse events by system organ class and preferred term reported during 6-month follow-up after administration of booster doses.

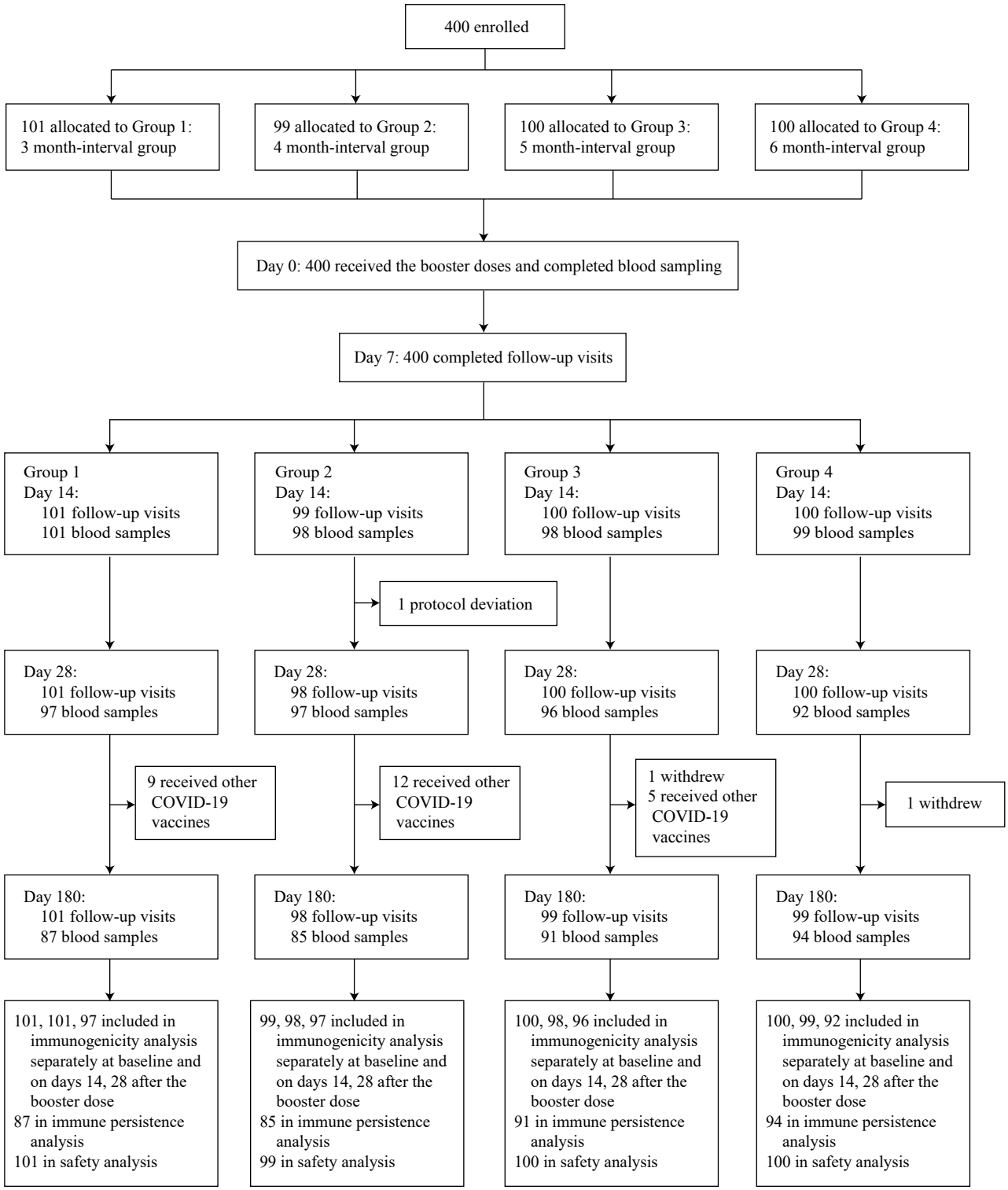
Adverse events (MedDRA 25.0)	3-month group (*n*=101)	4-month group (*n*=99)	5-month group (*n*=100)	6-month group (*n*=100)	Total (*N*=400)	*P* value*
No. of participants	5 (5%)	4 (4%)	7 (7%)	6 (6%)	22 (22%)	0.88
No. of events	6	7	22	13	48	
Cardiac disorders						
Cardiac failure	0	0	1 (1%)	0	1 (1%)	1.00
Sinus tachycardia	0	0	1 (1%)	0	1 (1%)	1.00
Ear and labyrinth disorders						
Vertigo	0	1 (1%)	0	0	1 (1%)	1.00
Eye disorders						
Cataract	1 (1%)	0	1 (1%)	1 (1%)	3 (3%)	1.00
Gastrointestinal disorders						
Duodenal bulb deformity	0	0	0	1 (1%)	1 (1%)	1.00
Duodenitis	0	0	0	1 (1%)	1 (1%)	1.00
Gastritis	0	0	0	2 (2%)	2 (2%)	0.25
Oesophagitis	0	0	0	1 (1%)	1 (1%)	1.00

TABLE S4. (Continued)

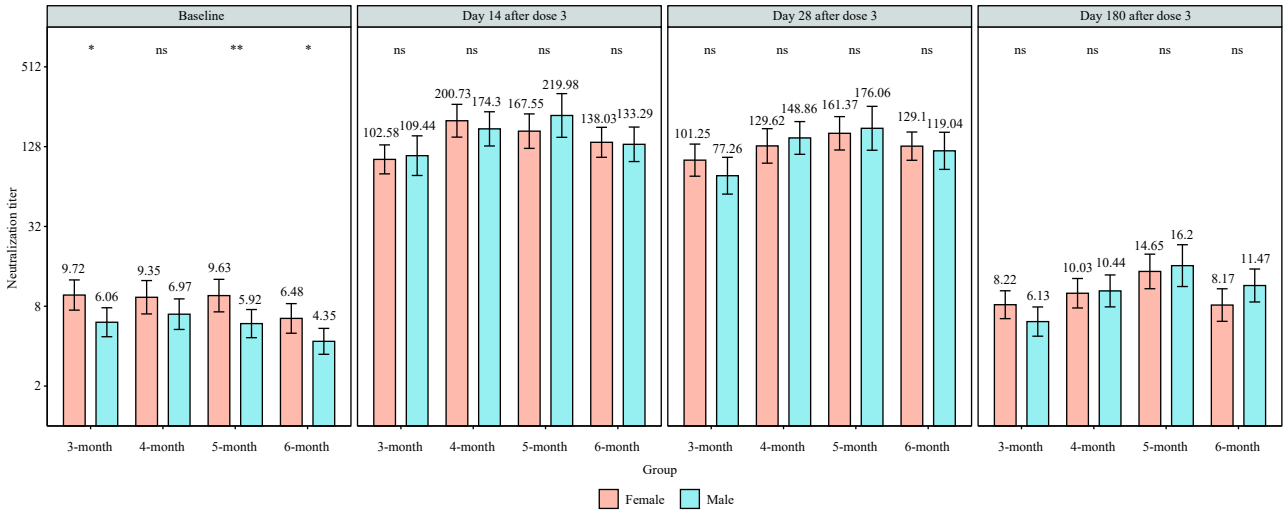
Adverse events (MedDRA 25.0)	3-month group (*n*=101)	4-month group (*n*=99)	5-month group (*n*=100)	6-month group (*n*=100)	Total (*N*=400)	*P* value*
Hepatobiliary disorders						
Cholecystitis	0	0	0	1 (1%)	1 (1%)	1.00
Cholecystitis chronic	0	0	1 (1%)	0	1 (1%)	1.00
Infections and infestations						
Bronchitis	0	0	1 (1%)	0	1 (1%)	1.00
Cervicitis	0	0	1 (1%)	0	1 (1%)	1.00
Herpes zoster	0	1 (1%)	0	0	1 (1%)	1.00
Infective exacerbation of bronchiectasis	1 (1%)	0	0	0	1 (1%)	1.00
Pneumonia	0	0	1 (1%)	1 (1%)	2 (2%)	1.00
Injury, poisoning and procedural complications						
Brain contusion	0	0	1 (1%)	0	1 (1%)	1.00
Fracture	1 (1%)	0	0	0	1 (1%)	1.00
Radius fracture	0	0	1 (1%)	0	1 (1%)	1.00
Skull fractured base	0	0	1 (1%)	0	1 (1%)	1.00
Musculoskeletal and connective tissue disorders						
Arthritis	0	1 (1%)	0	0	1 (1%)	1.00
Arthropathy	1 (1%)	1 (1%)	0	0	2 (1%)	1.00
Intervertebral disc protrusion	0	0	1 (1%)	1 (1%)	2 (2%)	1.00
Spinal osteoarthritis	0	1 (1%)	0	0	1 (1%)	1.00
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Cervix carcinoma	1 (1%)	0	0	0	1 (1%)	1.00
Gastric cancer	0	0	0	1 (1%)	1 (1%)	1.00
Lung neoplasm malignant	0	0	1 (1%)	0	1 (1%)	1.00
Metastases to lung	0	0	0	1 (1%)	1 (1%)	1.00
Pericardial effusion malignant	0	0	1 (1%)	0	1 (1%)	1.00
Nervous system disorders						
Cerebral infarction	1 (1%)	0	1 (1%)	1 (1%)	3 (3%)	1.00
Epilepsy	0	1 (1%)	0	0	1 (1%)	1.00
Lacunar infarction	0	0	1 (1%)	0	1 (1%)	1.00
Partial seizures with secondary generalization	0	1 (1%)	0	0	1 (1%)	1.00
Subarachnoid hemorrhage	0	0	1 (1%)	0	1 (1%)	1.00
Subdural effusion	0	0	1 (1%)	0	1 (1%)	1.00
Renal and urinary disorders						
Renal cyst	0	0	1 (1%)	0	1 (1%)	1.00
Respiratory, thoracic and mediastinal disorders						
Atelectasis	0	0	1 (1%)	0	1 (1%)	1.00
Bronchitis chronic	0	0	1 (1%)	0	1 (1%)	1.00
Pleural effusion	0	0	1 (1%)	0	1 (1%)	1.00
Pleurisy	0	0	1 (1%)	0	1 (1%)	1.00
Vascular disorders						
Venous thrombosis	0	0	0	1 (1%)	1 (1%)	1.00

Note: Data are *n* (%).

* *P* value was calculated by Fisher exact probability method and of the comparison of incidence rate among four groups.



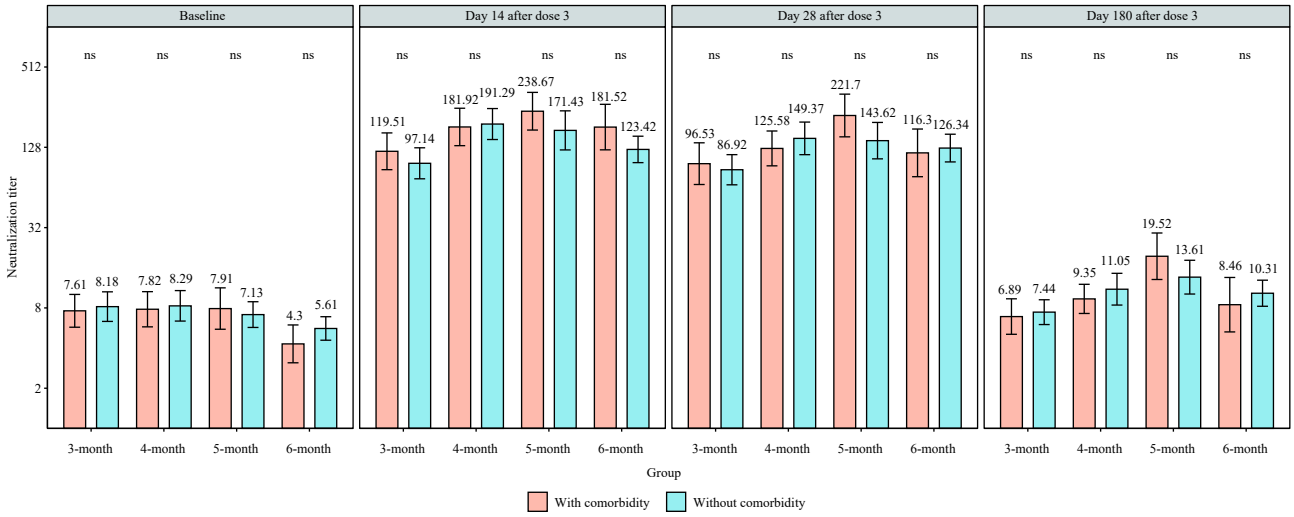
SUPPLEMENTARY FIGURE S1. Inclusion and follow-up in analyses of immunogenicity and safety of CoronaVac in elderly individuals aged 60 years and older.



SUPPLEMENTARY FIGURE S2. Geometric mean titers of neutralizing antibodies against live SARS-CoV-2 before and after booster vaccination stratified by sex groups.

Note: Numbers above the error bars are GMTs, and error bars indicate 95% *CI*s. Symbols at the top are *P* values for comparisons between subgroups using ANOVA with log-transformation. **, *, ns denote $P<0.01$, $P<0.05$, $P\geq0.05$, respectively.

Abbreviation: SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; GMTs=geometric mean titers; *CI*s=confidence intervals; ANOVA=analysis of variance.



SUPPLEMENTARY FIGURE S3. Geometric mean titers of neutralizing antibodies against live SARS-CoV-2 before and after booster vaccination stratified by comorbidity status.

Note: Numbers above the error bars are GMTs, and error bars indicate 95% *CI*s. Symbols at the top are *P* values for comparisons between subgroups using ANOVA with log-transformation. ns denotes $P\geq0.05$.

Abbreviation: SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; GMTs=geometric mean titers; *CI*s=confidence intervals; ANOVA=analysis of variance.