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# Immunogenicity and safety of a SARS-CoV-2 inactivated vaccine (CoronaVac) co-administered with an inactivated quadrivalent influenza vaccine: A randomized, open-label, controlled study in healthy adults aged 18 to 59 years in China

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ABSTRACT

Background: Studies are needed for evidence of inactivated COVID-19 vaccine co-administered with influenza vaccine.
Methods: A randomized, open-label, controlled study was conducted in Zhejiang Province, China. Eligible healthy adults aged 18–59 years underwent randomization at a ratio of 1:1:2 to receive inactivated quadrivalent influenza vaccine (IIV4) either concomitantly with the first (C1 subgroup) or the second (C2 subgroup) dose of CoronaVac, or 14 days after the first dose of CoronaVac (S group). The primary purpose of the study was to prove the non-inferiority in seroconversion rate of antibody against SARS-CoV-2.
Results: Overall, 480 participants were enrolled, with 120, 120, and 240 randomly assigned to the C1, C2, and S groups, respectively. As lower bound of the two-sided 95% confidence interval (CI) of the difference for the seroconversion rate of antibodies against SARS-CoV-2 was over −10%, the immune response for CoronaVac in the C group (93.1% [89.0, 96.0]) was non-inferior to that in the S group (95.2% [91.5, 97.6]) in the per-protocol set. A lower GMT of antibody against SARS-CoV-2 was observed in the C group as compared to the S group (27.5 vs. 38.1, P = 0.0001). Decrease of immune response to CoronaVac was mainly observed in participants received IIV4 concomitantly with their second dose of CoronaVac (C2 subgroup), with a seroconversion rate of 89.7% (95CI: 82.6%-94.5%) and a GMT of 23.3. The occurrences of vaccine related adverse reactions were no more than 20% and comparable among different groups. Most of the adverse reactions were mild and moderate.
Conclusion: Co-administration of inactivated COVID-19 vaccine and seasonal influenza vaccine, especially the administration regimen that the seasonal influenza vaccine co-administered with the first dose of the inactivated COVID-19 vaccine, would be feasible.

## 1. Introduction

The novel coronavirus disease 2019 (COVID-19) pandemic, caused by a new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that emerged in late 2019, is still ongoing worldwide and has resulted in more than 4.1 billion confirmed cases, including more than 5.8 million deaths, as of 16 February 2022 [1–2]. Influenza, also caused by an RNA virus with clinical manifestations consisting mainly in acute respiratory disorders, is a seasonal epidemic disease worldwide [3]. COVID-19 and influenza share many similarities, such as the transmission route, disease mechanism, clinical presentation, seasonal coincidence, and susceptibility [4–7]. Coinfection with SARS-CoV-2 and influenza virus

during the COVID-19 epidemic could result in poor clinical outcomes among patients and an increased disease burden on the society [8–10].

Annual vaccination is the most effective strategy to prevent seasonal influenza [11–12]. To date, it is believed that the COVID-19 vaccine is a powerful approach to prevent COVID-19 diseases, especially severe illness and death [13–15]. High immunization coverage of two vaccines could facilitate effective control of the spread of corresponding viruses [16]. However, the *Technical guideline for the use of COVID-19 vaccines (1st Edition)* issued by the National Health Commission of the People's Republic of China requires a minimum interval of 14 days between the COVID-19 vaccine and any other vaccines. Additional clinical visits are inconvenient for many people and thus could have a negative impact on vaccine uptake. Concomitant administration may help to ease the inconvenience, minimize distress caused by multiple injections, and reduce vaccine stocking and administration costs associated with separate vaccinations [17]. However, evidence about the safety and immunogenicity of concomitant administration of inactivated COVID-19 vaccine and influenza vaccine are limited up to date.

Therefore, we conducted a phase 4 clinical trial to prove that the immunogenicity of CoronaVac was non-inferior between healthy adults aged 18–59 years who received the CoronaVac and IIV4 concomitantly and those who received two vaccines separately with 14 days apart.

## 2. Methods

### 2.1. Study design and participants

We conducted a randomized, open-label, noninferiority, phase 4 clinical trial in Kaihua County, Zhejiang, China, from March to May 2021 (clinicaltrials.gov number, NCT04801888). The study protocol and informed consent form were approved by the ethics committee of the Zhejiang Provincial Center for Disease Control and Prevention (ZJCDC). This study was performed by investigators from the ZJCDC following the Declaration of Helsinki of the World Medical Association Good Clinical Practice and the Chinese regulatory requirements. Before enrolment, written informed consent was obtained from each participant.

Healthy adults aged 18–59 years who provided written informed consent were eligible for enrolment in this study. The exclusion criteria included: history of any direct or indirect contact with suspected or confirmed COVID-19 cases within the previous 14 days, history of infection with SARS-CoV-2, any history of a severe allergy to any vaccination, any specified comorbidities that may influence the immune response of vaccination or lead to severe adverse events, and any prior administration of the influenza vaccines, investigational products, blood products, or immunosuppressive therapy, within a defined period (Supplementary appendix 1). The eligibility of participants was assessed through medical history inquiry and physical examination by the investigators.

### 2.2. Vaccines

CoronaVac is an inactivated vaccine against COVID-19 developed by Sinovac Life Sciences Co., Ltd. The production process of CoronaVac was consistent with vaccines used in the previous series of clinical trials [18–20]. Briefly, CoronaVac was prepared by vaccinating African green monkey kidney cells (World Health Organization, WHO Vero 10–87 Cells) with the novel coronavirus (CZ02 strain) through culture, harvesting of virus solution, virus inactivation (with β-propiolactone), concentration, purification and adsorption onto aluminum hydroxide. CoronaVac was packed in

vials with 0.5 ml each containing 600 SU/0.5 ml of SARS-CoV-2 antigen.

IIV4 is developed by Sinovac Biotech Co., Ltd. Briefly, IIV4 was prepared by inoculation of the influenza virus A strains and B strains in chicken embryos, and then through cultivation, harvesting virus solution, virus inactivation, purification, and lysis. IIV4 was formulated to contain 15 μg haemagglutinin/strain/0.5 ml per prefilled syringe, containing A/Guangdong-Maonan/SW L1536/2019(H1N1)pdm09, A/Hongkong/2671/2019(H3N2), B/Washington/02/2019(B/Victoria lineage), B/Phuket/3073/2013(B/Yamagata lineage), which were recommended by WHO for Northern Hemisphere in 2020–2021 season.

Both vaccines were prepared in Good Manufacturing Practice-accredited facilities. Both vaccines were stored at 2–8 °C and administered intramuscularly to each participant, with different vaccines injected into different arms. Two doses of CoronaVac (lot number: 20200412) were given 28 days apart and IIV4 (lot number: 202007007) was given in single dose.

### 2.3. Randomization

Each eligible participants was assigned a random number according to the sequence of enrolment and then randomized into two groups (C group: concomitant administration group, S group: separate administration group) at a ratio of 1:1. Meanwhile, participants in the C group were concomitantly randomly assigned into two subgroups (C1 and C2) at a ratio of 1:1. The randomization was carried out according to a randomization list (block size = 8) prepared by an independent statistician using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). The random allocation was sealed using a numbered "scratch card". The opaque material covered on the grouping information were not allowed to be scratched off unless the randomization has completed.

### 2.4. Procedures

After obtaining the first blood samples from all the participants at baseline (Day 0), two doses of CoronaVac and one dose of IIV4 were administered: for participants in the C group, IIV4 was administered concomitantly with the 1st dose (C1 subgroup, Day 0) or 2nd dose (C2 subgroup, Day 28) of the CoronaVac; for participants in the S group, IIV4 was administered between the two doses of CoronaVac, 14 days apart from each dose. Subsequent blood samples were collected as scheduled: on Day 28 (before the 2nd vaccination) and Day 56 after the first dose from participants in the C groups; on Day 14 (before IIV4 administration), Day 42 and Day 56 after the first dose from participants in the S group. Blood samples collected on Day 14 and Day 42 in the S group were for the detection of antibodies against influenza viruses only.

The participants were observed for immediate adverse events (AEs) for 30 min after each dose. Fever or any other AEs occurring within 28 days after each dose were recorded on diary cards (solicited AEs were collected during Days 0–7), which were checked by investigators to assure completeness and accuracy. The AEs were graded according to a scale issued by the National Medical Product Administration [21].

### 2.5. Immunogenicity assessment

The Immunogenicity of CoronaVac and IIV4 were evaluated by comparing the seropositivity rate and seroconversion rate of neutralizing antibodies, and the geometric mean titer (GMT) and geometric mean increase (GMI) of neutralizing antibody to live SARS-CoV-2 (virus strain SARS-CoV-2/human/CHN/CN1/2020, GenBank number MT407649.1) or to four seasonal influenza strains (A/Guangdong-Maonan/SWL1536/2019, A/Hongkong/2671/2019, B/

Washington/02/2019, B/Phuket/3073/2013) at baseline and 28 days after the last dose of each vaccine. The primary endpoint for immunogenicity was the seropositive rate of neutralizing antibodies against SARS-CoV-2 28 days after the second dose of CoronaVac. The neutralizing antibody titers against SARS-CoV-2 and influenza virus were measured by the quantified micro cytopathogenic effect assay (CPE) [22] and the hemagglutinin inhibition (HI) assays [23], respectively.

For antibody responses to SARS-CoV-2, seropositivity was defined as the neutralizing antibody titer to be ≥ 1:8, seroconversion was defined as that the neutralizing antibody titer is < 1:8 before immunization and ≥ 1:8 after immunization, or the neutralizing antibody titer is ≥ 1:8 before immunization and increases by 4 times and above after immunization. For antibody responses to influenza strains, seropositivity was defined as the HI antibody titer against certain antigen to be ≥ 1:40, seroconversion was defined as that the HI antibody titer is < 1:10 before vaccination and ≥ 1:40 after vaccination, or the HI antibody titer is ≥ 1:10 before vaccination and increased by four times after vaccination.

### 2.6. Statistical analysis

The assessment of immunogenicity was performed in corresponding per-protocol population, i.e., in those who were eligible, had received full doses of corresponding vaccines, and donated all blood samples required with corresponding detective neutralizing antibody values. Participants who received at least one dose of any vaccine were included in the safety analysis set (SS). The incidence rates of adverse reactions within 7 days, adverse reactions within 56 days, and SAE within 56 days were calculated as endpoints for the safety assessment.

The sample size was calculated using NCSS-PASS software (version 11.0) according to the seroconversion rate of SARS-CoV-2 neutralizing antibody at 28 days after the 2nd dose under a non-inferiority design between the C and S groups. Non-inferiority would be considered as achieved if lower bound of the two-sided 95% CI of the difference for the seroconversion rate of antibodies against corresponding virus was > -10%. Assuming the seroconversion rate of SARS-CoV-2 neutralizing antibody in the S group was 90%, we estimated that a sample size of 205 in each group would achieve 90% power to detect a 10% difference between groups with an α of 0.05. Considering the potential loss to follow-up of 15%, the final sample size was 480 participants, with 240 in each group. The chi-square test or Fisher's exact test was used to analyze categorical data. The Wilcoxon rank sum test or log-transformed Group *t* test was used to compare the log-transformed antibody titer. Statistical analyses were performed by independent statisticians using SAS 9.4, and the hypothesis tests were two-sided with an α value of 0.05.

## 3. Results

### 3.1. Participants

In total, 484 volunteers were recruited from March 23 to March 30, 2021, of whom 480 (99.7%) were enrolled and underwent randomization, with 120, 120, or 240 assigned into the C1 subgroup, C2 subgroup or S group, respectively. Overall, 459 participants were included in the PPS including 116 in the C1, 116 in the C2 subgroup, and 227 in the S group for the CoronaVac immunogenicity analysis. A total of 462 participants were included in the PPS including 118 in the C1, 116 in the C2, and 228 in the S group for the IIV4 immunogenicity analysis. Information on recruitment, enrolment, randomization, withdrawal and study completion were illustrated in Fig. 1. Participants in three groups were comparable in terms of mean age, sex, ethnicity, height and weight (Table 1).

### 3.2. Immunogenicity

At baseline, all participants were seronegative for SARS-CoV-2 (Table 2, Fig. 2). The baseline seropositivity rates and GMT of antibodies against four types of influenza strain (A/H1N1, A/H3N2, B/Yamagata, B/Victoria) showed no difference among the three groups. Pre-existing antibodies against A/H3N2 and B/Yamagata strain were observed with the pre-vaccination seropositivity rates to be over 60% and approximately 30%, respectively (Table 2, Table 3).

Twenty-eight days after the 2nd dose of CoronaVac, 216 out of 232 (93.1%) participants in the C group and 216 out of 227 (95.2%) in the S group developed neutralizing antibodies against SARS-CoV-2 with no significantly different seroconversion rate (P = 0.351). Participants in the S group had higher GMT (38.1 vs. 27.5, P < 0.001) and GMI (19.0 vs. 13.8, P < 0.001) of antibodies against SARS-CoV-2 as compared to the C group.

In the analysis performed between subgroups within the C group, only 29 out of 116 (25.0%) participants and 30 out of 116 (25.9%) in the C1 and C2 subgroup, respectively, developed neutralizing antibodies against SARS-CoV-2 28 days after the 1st does of CoronaVac, with no significantly different seroconversion rate (P = 0.880). Twenty-eight days after the 2nd dose of CoronaVac, participants in the C1 subgroup showed significantly higher seroconversion rate (96.6% vs. 89.7%, P = 0.038), GMT (32.6 vs. 23.3, P = 0.015) and GMI (16.3 vs. 11.6, P = 0.015) of antibodies against SARS-CoV-2 as compared to the C2 subgroup. Additional analyses were performed to explore whether pre-vaccination antibodies against influenza virus would affect the immune response against SARS-CoV-2. Participants without pre-existing antibodies against influenza viruses A/H3N2 or B/Yamagata showed similar immune responses against SARS-CoV-2 among different groups (Supplementary appendixes 2–3).

There was no difference, in terms of seropositivity rate, seroconversion rate, GMT and GMI of antibodies against four types of influenza strains that contained in the IIV4 vaccine between participants in C1/C2 subgroup and S group, except that: 1) as compared to S group, participants in the C group had a higher seropositivity rate of antibody against A/H1N1 (93.6% vs. 87.3%, P = 0.021) with more participants getting higher antibody titer; 2) participants in the C1 group showed a higher seroconversion rate (95.8% vs. 88.8%, P = 0.046) of antibodies against A/H3N2 than that in the C2 subgroup.

Comparison of antibody responses of C1 subgroup with S group showed similar result with the comparison result between C group and S group that participants in the S group had higher GMT (38.1 vs. 32.6, P = 0.01) and GMI (19.0 vs. 16.3, P = 0.01) of antibodies against SARS-CoV-2 as compared to the C1 subgroup, while the participants in the C1 subgroup had a higher seropositivity rate of antibody against A/H1N1 (94.9% vs. 87.3%, P = 0.025) as compared to the S group (Supplementary appendix 4).

According to predefined non-inferiority margin, non-inferiority of the C group versus the S group in antibody responses against 4 types of viruses was achieved, not including antibody against the B/Yamagata. However, non-inferiority of the C group versus the S group in antibody responses against B/Yamagata was achieved if analysis was performed based on participants without pre-vaccination antibodies against corresponding virus strain based on an exploratory analysis.

### 3.3. Safety

Overall, 91 participants reported 130 vaccine-related adverse reactions during the 0–56 Day period after the first dose, with a rate of 20.0% in the S group, 16.7% in the C1 subgroup, and 19.2% in the C2 subgroup, respectively. The occurrence rates of both

**Fig. 1. Trial profile.** CoronaVac: tested SARS-CoV-2 inactivated vaccine; IIV4: inactivated quadrivalent influenza vaccine; C group: concomitant administration group; C1: concomitant administration subgroup 1, IIV4 was administered concomitantly with the 1st dose of the inactivated COVID-19 vaccine on Day 0; C2: concomitant administration subgroup 2, IIV4 was administered concomitantly with the 2nd dose of the inactivated COVID-19 vaccine on Day 28; S group: separate administration group, IIV4 was administered separately on Day 14; AE: adverse event; FAS: full analysis set; PPS: per-protocol set.

solicited and vaccination-related unsolicited AEs were similar among three groups (Table 4). Relative higher occurrence rate of pain at the injection site within 0–7 days after co-administration of IIV4 and CoronaVac in the C2 subgroup and after administration of IIV4 in the S group were observed (Supplementary appendixes 5–8). The most frequently reported adverse reaction was a pain at the injection site, with an occurrence rate over 10% in all three groups. Most of the AEs were mild and moderate. Only one grade 3 (severe) fever with a maximum axillary temperature of 39.3 °C

in the C1 subgroup was observed and verified not due to SARS-CoV-2. This case was resolved within one week. No vaccine-related serious adverse events were observed in this study.

## 4. Discussion

This is the first report on the immunogenicity and safety of inactivated COVID-19 vaccine concomitantly administered with IIV4 among adults aged 18–59 years. Our study indicated that both

**Table 1**
Baseline characteristics of the study participants in safety set.

| Characteristics | C group | | S group(N = 240) | P value |
|---|---|---|---|---|
| | C1 subgroup(N = 120) | C2 subgroup(N = 120) | | |
| Male [n (%)] | 40 (33.3) | 47 (39.2) | 87 (36.3) | 0.643 |
| Ethnic Han [n (%)] | 119 (99.2) | 120 (100.0) | 239 (99.6) | 1.000 |
| Age (years), mean ± SD* | 43.7 ± 9.6 | 46.1 ± 8.6 | 44.8 ± 9.2 | 0.130 |
| Temperature (℃), mean ± SD* | 36.2 ± 0.4 | 36.1 ± 0.4 | 36.2 ± 0.4 | 0.788 |
| Height (m), mean ± SD* | 1.6 ± 0.1 | 1.6 ± 0.1 | 1.6 ± 0.1 | 0.724 |
| Weight (kg), mean ± SD* | 62.6 ± 12.4 | 62.6 ± 10.71 | 61.8 ± 10.9 | 0.712 |

N, n: number of participants; C group: concomitant administration group; C1: concomitant administration subgroup 1, IIV4 was administered concomitantly with the 1st dose of the inactivated COVID-19 vaccine on Day 0; C2: concomitant administration subgroup 2, IIV4 was administered concomitantly with the 2nd dose of the inactivated COVID-19 vaccine on Day 28; S group: separate administration group, IIV4 was administered separately on Day 14.

**Table 2**
Antibody responses to SARS-Cov-2, four types of influenza strain before and 56 days after first vaccination (per protocol sets).

| | C group | | S group | | P value | Estimate of the difference | 95% CI | Non-inferiority |
|---|---|---|---|---|---|---|---|---|
| | values | 95% CI | values | 95% CI | | | | |
| **SARS-CoV-2 (N)** | 232 | | 227 | | | | | |
| Seropositivity-BI [n (%)] | 0 (0.0) | 0.0–1.6 | 0 (0.0) | 0.0–1.6 | NA | | | |
| GMT-BI | 2.0 | NA | 2.00 | NA | 1.000 | | | |
| Seropositivity [n (%)] | 216 (93.1) | 89.0–96.0 | 216 (95.2) | 91.5–97.6 | 0.351 | −2.05 | −6.6–2.4 | Yes* |
| Seroconversion [n (%)] | 216 (93.1) | 89.0–96.0 | 216 (95.2) | 91.5–97.6 | 0.351 | −2.05 | −6.6–2.4 | Yes* |
| GMT | 27.5 | 24.4–31.1 | 38.1 | 33.6–43.2 | <0.001 | | | |
| GMI | 13.8 | 12.2–15.6 | 19.0 | 16.8–21.6 | <0.001 | | | |
| **Influenza A/H1N1 (N)** | 234 | | 228 | | | | | |
| Seropositivity-BI [n (%)] | 18 (7.69) | 4.62–11.88 | 16 (7.0) | 4.1–11.2 | 0.781 | | | |
| GMT-BI | 4.57 | 4.03–5.20 | 4.5 | 4.0–5.1 | 0.714 | | | |
| Seropositivity [n (%)] | 219 (93.6) | 89.65–96.37 | 199 (87.3) | 82.3–91.3 | 0.021 | 6.31 | 1.0–11.9 | Yes* |
| Seroconversion [n (%)] | 216 (92.3) | 88.12–95.38 | 199 (87.3) | 82.3–91.3 | 0.074 | 5.03 | −0.5–10.8 | Yes* |
| GMT | 462.03 | 376.40–567.14 | 342.1 | 270.9–432.2 | 0.062 | | | |
| GMI | 101.0 | 81.22–125.59 | 75.9 | 60.3–95.5 | 0.084 | | | |
| **Influenza A/H3N2 (N)** | 234 | | 228 | | | | | |
| Seropositivity-BI [n (%)] | 156 (66.7) | 60.2–72.7 | 152 (66.7) | 60.1–72.8 | 1.000 | | | |
| GMT-BI | 39.53 | 35.5–44.0 | 42.25 | 37.7–47.4 | 0.501 | | | |
| Seropositivity [n (%)] | 233 (99.6) | 97.6–100.0 | 228 (100.0) | 98.4–100.0 | 1.000 | −0.43 | −2.4–1.2 | Yes* |
| Seroconversion [n (%)] | 216 (92.3) | 88.1–95.4 | 214 (93.9) | 89.9–96.6 | 0.511 | −1.55 | −6.4–3.2 | Yes* |
| GMT | 724.8 | 630.1–833.6 | 703.3 | 611.8–808.4 | 0.937 | | | |
| GMI | 18.3 | 15.48–21.7 | 16.7 | 14.2–19.6 | 0.377 | | | |
| **Influenza B/Victoria (N)** | 234 | | 228 | | | | | |
| Seropositivity-BI [n (%)] | 22 (9.40) | 6.0–13.9 | 18 (7.9) | 4.8–12.2 | 0.565 | | | |
| GMT-BI | 10.77 | 9.8–11.8 | 9.85 | 9.0–10.8 | 0.114 | | | |
| Seropositivity [n (%)] | 197 (84.2) | 78.9–88.6 | 195 (85.5) | 80.3–89.8 | 0.688 | −1.34 | −8.0–5.3 | Yes* |
| Seroconversion [n (%)] | 183 (78.2) | 72.4–83.3 | 184 (80.7) | 75.0–85.6 | 0.507 | −2.49 | −9.9–4.9 | Yes* |
| GMT | 95.6 | 82.1–111.2 | 100.8 | 86.3–117.7 | 0.686 | | | |
| GMI | 8.9 | 7.6–10.3 | 10.23 | 8.8–11.9 | 0.276 | | | |
| **Influenza B/Yamagata (N)** | 234 | | 228 | | | | | |
| Seropositivity-BI [n (%)] | 71 (30.3) | 24.5–36.7 | 59 (25.9) | 20.3–32.1 | 0.286 | | | |
| GMT-BI | 17.45 | 15.6–19.5 | 17.23 | 15.4–19.3 | 0.638 | | | |
| Seropositivity [n (%)] | 220 (94.0) | 90.2–96.7 | 221 (96.9) | 93.8–98.8 | 0.133 | −2.91 | −7.1–1.0 | Yes* |
| Seroconversion [n (%)] | 193 (82.5) | 77.0–87.1 | 199 (87.3) | 82.3–91.3 | 0.150 | −4.80 | −11.4–1.8 | No |
| GMT | 154.0 | 134.6–176.1 | 161.7 | 142.9–183.6 | 0.605 | | | |
| GMI | 8.8 | 7.7–10.1 | 9.4 | 8.2–10.8 | 0.386 | | | |

*Non-inferiority was achieved, as the lower bound of the two-sided 95% CI was > − 10% for seropositive rate and seroconversion rate.
N, n: number of participants; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; C group: concomitant administration group, IIV4 was administered concomitantly with the 1st or 2nd dose of the SARS-CoV-2 inactivated vaccine on Day 0 or Day 28, respectively; S group: separate administration group, IIV4 was administered separately on Day 14; BI: before injection; GMT: geometric mean titre; GMI: geometric mean increase of titre.
For antibody responses to SARS-CoV-2, seropositivity criteria: The neutralizing antibody titer is ≥ 1:8; seroconversion criteria: the neutralizing antibody titer is < 1:8 before immunization and ≥ 1:8 after immunization; or the neutralizing antibody titer is ≥ 1:8 before immunization and increases by 4 times and above after immunization.
For antibody responses to influenza strains, seropositivity criteria: The protective level of HI antibody titer against certain antigen is ≥ 1:40; seroconversion criteria: with 1:10 as the minimum dilution of HI antibody against certain antigen, the HI antibody titer is < 1:10 before vaccination and ≥ 1:40 after vaccination; the HI antibody titer is ≥ 1:10 before vaccination and increased by four times after vaccination.

concomitant or separate administration of CoronaVac and IIV4 could induce sufficient immunogenicity and had satisfactory safety profiles that concomitant administration strategy would be feasible. The outcome provided the scientific evidence for improving the immunization strategy of both inactivated COVID-19 vaccine and IIV4.

In the previous phase 2 clinical trial of CoronaVac conducted in the same age group, the seroconversion rate of antibody against SARS-CoV-2 was 97.4% (114 out of 117) with a GMT of 44.1 (95 %CI: 37.2–52.2) in participants receiving 3 μg CoronaVac following a 0–28 Day schedule [18]. The same vaccine formulation and vaccination schedule were used in this study. In our study, the immune response against SARS-CoV-2 in participants receiving COVID-19 and influenza vaccines separately showed similar results with previous phase 2 trial, while a moderate decrease of the immune response to CoronaVac was observed in the participants

**Fig. 2.** Reverse cumulative curves for antibody titers against SARS-CoV-2 of participants included in the per-protocol set for CoronaVac pre- (day 0) and 28 days post full vaccination by treatment groups (2A) and subgroups (2B). The limit of detection was a ti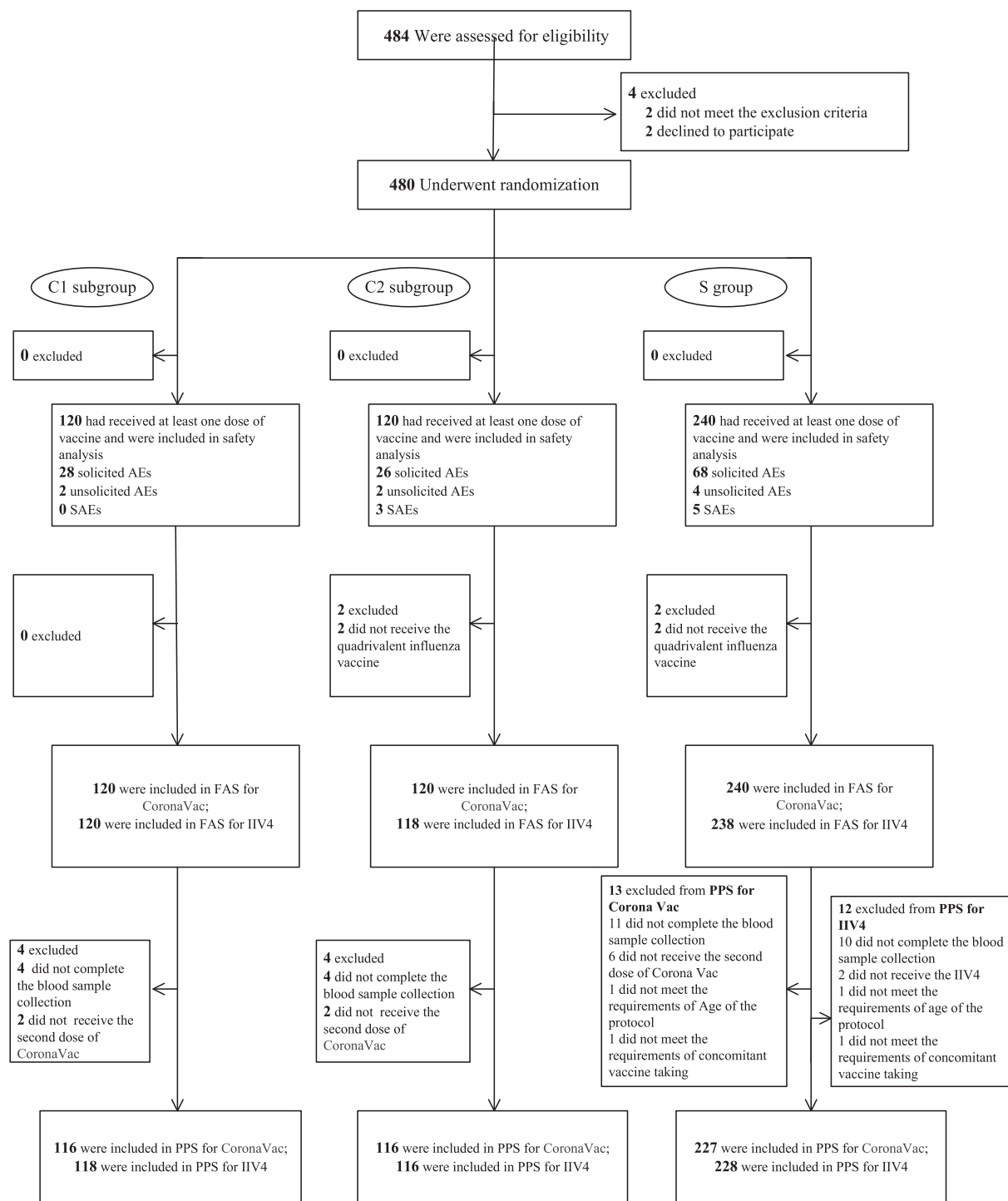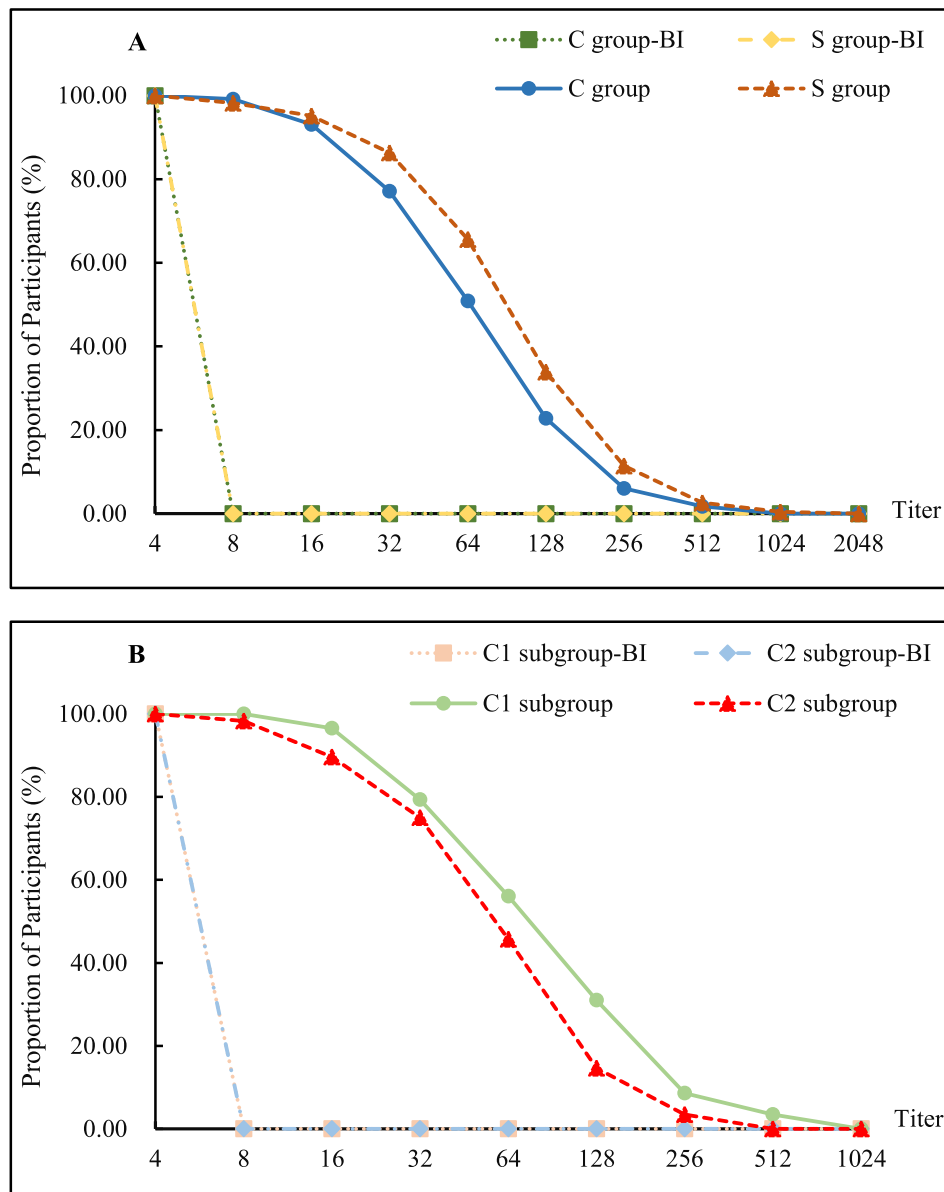ter of 1:8 for SARS-CoV-2. Titres are expressed as the reciprocal of the dilution. CoronaVac: tested SARS-CoV-2 inactivated vaccine; IIV4: inactivated quadrivalent influenza vaccine; C group: concomitant administration group; C1: concomitant administration subgroup 1, IIV4 was administered concomitantly with the 1st dose of CoronaVac on Day 0; C2: concomitant administration subgroup 2, IIV4 was administered concomitantly with the 2nd dose of CoronaVac on Day 28; S group: separate administration group, IIV4 was administered separately on Day 14; BI: before injection of the first dose of CoronaVac, which means baseline antibody titer.

receiving vaccines under a concomitant administration regimen (IIV4 with the first or second CoronaVac). However, a similar immune response against SARS-CoV-2 was detected 28 days after the first vaccination in participants receiving either their first CoronaVac dose and IIV4 concomitantly or their first CoronaVac dose alone. The unexpected decrease in the immune response against SARS-CoV-2 seemed to be mainly observed in participants receiving IIV4 concomitantly with their second dose of CoronaVac, suggesting that this regimen may induce a slight interference with the immune response to CoronaVac.

Up to date, three reports of co-administration of seasonal influenza vaccine or high-dose seasonal influenza vaccine with a protein subunit COVID-19 vaccine with Matrix-M adjuvant (NVX-CoV2373) [24–25], or an adenoviral vector (ChAdOx1) or mRNA COVID-19 vaccine (BNT162b2) [26] have been published. In the

study of NVX-CoV2373 [24], decrease of the immune response against NVX-CoV2373 was observed following a concomitant regimen of seasonal influenza vaccine with the first dose of NVX-CoV2373 which may suggest an immune interference. However, there was no comparison group included to study the concomitant administration of the seasonal influenza vaccine with the second dose of NVX-CoV2373, as well as no detection of the immune response to the COVID-19 vaccine before the second dose [24]. Therefore, it is not clarified whether the immune interference observed in the study of NVX-CoV2373 would be consistent with our findings if the comparison group was included and the detection was performed. However, for the study of NVX-CoV2373 concomitantly administered with a high-dose quadrivalent influenza vaccine in adults aged ≥ 65 years [25], no decrease or increase of immune response against each influenza strain (A/H1N1, A/

**Table 3**
Antibody responses to SARS-CoV-2, 4 types of influenza strain before first vaccination and 28 days after last vaccination (per protocol sets) by subgroups.

| | C1 subgroup | | C2 subgroup | | P value |
|---|---|---|---|---|---|
| | values | 95% CI | values | 95% CI | |
| **SARS-CoV-2 (N)** | 116 | | 116 | | |
| **Pre-vaccination** | | | | | |
| Seropositivity [n (%)] | 0 (0.0) | 0.0–3.1 | 0 (0.0) | 0.0–3.13 | NA |
| GMT | 2.0 | NA | 2.0 | NA | 1.000 |
| **28 days after the 1st dose** | | | | | |
| Seropositivity [n (%)] | 29 (25.0) | 17.4–33.9 | 30 (25.9) | 18.2–34.8 | 0.880 |
| Seroconversion [n (%)] | 29 (25.0) | 17.4–33.9 | 30 (25.9) | 18.2–34.8 | 0.880 |
| GMT | 3.6 | 3.1–4.2 | 3.9 | 3.4–4.5 | 0.322 |
| GMI | 1.8 | 1.6–2.1 | 2.0 | 1.7–2.3 | 0.322 |
| **28 days after the 2nd dose** | | | | | |
| Seropositivity [n (%)] | 112 (96.6) | 91.4–99.05 | 104 (89.7) | 82.6–94.5 | 0.038 |
| Seroconversion [n (%)] | 112 (96.6) | 91.4–99.05 | 104 (89.7) | 82.6–94.5 | 0.038 |
| GMT | 32.6 | 27.3–38.9 | 23.3 | 19.7–27.4 | 0.015 |
| GMI | 16.3 | 13.7–19.5 | 11.6 | 9.9–13.7 | 0.015 |
| **Influenza A/H1N1 (N)** | 118 | | 116 | | |
| Seropositivity-BI [n (%)] | 11 (9.3) | 4.8–16.1 | 7 (6.0) | 2.5–12.0 | 0.345 |
| GMT-BI | 4.9 | 4.1–5.9 | 4.26 | 3.6–5.1 | 0.285 |
| Seropositivity [n (%)] | 112 (94.9) | 89.3–98.1 | 107 (92.2) | 85.8–96.4 | 0.404 |
| Seroconversion [n (%)] | 111 (94.1) | 88.2–97.6 | 105 (90.5) | 83.7–95.2 | 0.308 |
| GMT | 527.2 | 398.7–697.1 | 404.0 | 298.5–546.7 | 0.310 |
| GMI | 107.3 | 79.5–145.0 | 94.9 | 68.9–130.7 | 0.764 |
| **Influenza A/H3N2 (N)** | 118 | | 116 | | |
| Seropositivity-BI [n (%)] | 76 (64.4) | 55.8–73.0 | 80 (69.0) | 59.7–77.2 | 0.460 |
| GMT-BI | 40.0 | 34.2–46.8 | 39.1 | 33.7–45.3 | 0.875 |
| Seropositivity [n (%)] | 118 (100.0) | 96.9–100.0 | 115 (99.1) | 95.3–100.0 | 0.496 |
| Seroconversion [n (%)] | 113 (95.8) | 90.4–98.6 | 103 (88.8) | 81.6–93.9 | 0.046 |
| GMT | 776.9 | 642.2–939.9 | 675.4 | 548.9–831.0 | 0.442 |
| GMI | 19.4 | 15.2–24.7 | 17.3 | 13.6–22.0 | 0.726 |
| **Influenza B/Victoria (N)** | 118 | | 116 | | |
| Seropositivity-BI [n (%)] | 10(8.5) | 4.1–15.0 | 12 (10.3) | 5.5–17.4 | 0.624 |
| GMT-BI | 10.1 | 8.9–11.5 | 11.5 | 10.0–13.1 | 0.141 |
| Seropositivity [n (%)] | 95 (80.5) | 72.2–87.2 | 102 (87.9) | 80.6–93.2 | 0.120 |
| Seroconversion [n (%)] | 91 (77.1) | 68.5–84.4 | 92 (79.3) | 70.8–86.3 | 0.685 |
| GMT | 95.4 | 75.8–120.1 | 95.7 | 78.4–116.9 | 0.875 |
| GMI | 9.4 | 7.5–11.8 | 8.34 | 6.8–10.2 | 0.384 |
| **Influenza B/Yamagata (N)** | 118 | | 116 | | |
| Seropositivity-BI [n (%)] | 37 (31.4) | 23.1–40.5 | 34 (29.3) | 21.2–38.5 | 0.734 |
| GMT-BI | 17.3 | 14.8–20.2 | 17.6 | 15.1–20.7 | 0.865 |
| Seropositivity [n (%)] | 111 (94.1) | 88.2–97.6 | 109 (94.0) | 88.0–97.5 | 0.974 |
| Seroconversion [n (%)] | 98 (83.1) | 75.0–89.3 | 95 (81.9) | 73.7–88.4 | 0.816 |
| GMT | 169.7 | 138.5–208.0 | 139.5 | 117.0–166.2 | 0.237 |
| GMI | 9.8 | 8.0–12.1 | 7.9 | 6.6–9.5 | 0.190 |

N, n: number of participants; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; C1: concomitant administration subgroup 1, IIV4 was administered concomitantly with the 1st dose of the SARS-CoV-2 inactivated vaccine on Day 0; C2: concomitant administration subgroup 2, IIV4 was administered concomitantly with the 2nd dose of SARS-CoV-2 inactivated vaccine on Day 28; BI: before injection; GMT: geometric mean titre; GMI: geometric mean increase of titre.
For antibody responses to SARS-CoV-2, seropositivity criteria: The neutralizing antibody titer is $\geq$ 1:8; seroconversion criteria: the neutralizing antibody titer is < 1:8 before immunization and $\geq$ 1:8 after immunization; or the neutralizing antibody titer is $\geq$ 1:8 before immunization and increases by 4 times and above after immunization.
For antibody responses to influenza strains, seropositivity criteria: The protective level of HI antibody titer against certain antigen is $\geq$ 1:40; seroconversion criteria: with 1:10 as the minimum dilution of HI antibody against certain antigen, the HI antibody titer is ＜1:10 before vaccination and $\geq$ 1:40 after vaccination; the HI antibody titer is $\geq$ 1:10 before vaccination and increased by four times after vaccination.

H3N2, B/Yamagata and B/Victoria) or SARS-CoV-2 were observed, which is different from the previous NVX-CoV2373 study and our findings, but similar with the study of ChAdOx1 and BNT162b2 [26], in which no interference of the immune response to COVID-19 vaccines were observed in participants receiving seasonal influenza vaccine with the second dose of ChAdOx1 or BNT162b2. Further studies are needed to explain this finding and assess whether such limited differences in immunogenicity are clinically relevant.

Moreover, the low seropositivity of antibody against SARS-CoV-2 twenty-eight days after the first vaccination with CoronaVac provided additional evidence in line with results acquired in the previous phase 2 clinical trial of CoronaVac that at least 2 doses are needed for the primary immunization of inactivated COVID-19 vaccines.

Considering the immune response of antibodies against influenza strains, antibody GMT against influenza A/H3N2 was observed to be relatively high in both study groups (703.3 to 724.8) while the value was 193.7 in a previous phase 3 clinical trial [27]. As the baseline value of seropositivity rate of antibody against influenza A/H3N2 and the GMT were respectively 66.7% and 40.0, this could indicate that participants in our study already had relatively high pre-existing antibodies as compared to those in a previous phase 3 clinical trial. Furthermore, our reanalysis of non-inferiority of antibody responses against influenza B/Yamagata based on data from participants with or without pre-existing antibodies were different, suggesting that corresponding pre-existing antibodies may affect post-vaccination immune responses and further study are needed to address this aspect.

Concomitant administration of CoronaVac with IIV4 and separate administration of the corresponding two vaccines 14 days apart in this study showed satisfactory and good safety profiles. The occurrence of vaccine-related adverse reactions through all treatment groups was no more than 20%, within which 98.9% were mild or moderate. These findings were similar to previous clinical trials of both inactivated COVID-19 vaccine and seasonal influenza vaccine [18,27], and also to other inactivated COVID-19 vaccines

**Table 4**
Adverse reactions reported within 56 days corresponding to different treatment groups.

| | C1 subgroup N = 120 n (%) | C2 subgroup N = 120 n (%) | S group N = 240 n (%) | P value |
|---|---|---|---|---|
| **Solicited adverse reactions within 0–7 days** | | | | |
| Any | 19 (15.8) | 22 (18.3) | 45 (18.8) | 0.837 |
| Grade 1 | 17 (14.2) | 19 (15.8) | 41 (17.1) | |
| Grade 2 | 1 (0.8) | 3 (2.5) | 4 (1.8) | |
| Grade 3 | 1 (0.8) | 0 (0.0) | 0 (0.0) | |
| **Injection site adverse reactions** | | | | |
| Any | 16 (13.3) | 18 (15.0) | 36 (15.0) | 0.942 |
| Grade 1 | 15 (12.5) | 17 (14.2) | 35 (14.6) | |
| Grade 2 | 1 (0.8) | 1 (0.8) | 1 (0.4) | |
| Pain | 11 (9.2) | 16 (13.3) | 28 (11.7) | 0.621 |
| Grade 1 | 11 (9.2) | 15 (12.5) | 28 (11.7) | |
| Grade 2 | 0 (0.0) | 1 (0.8) | 0 (0.0) | |
| Swelling | 3 (2.5) | 0 (0.0) | 9 (3.8) | 0.080 |
| Grade 1 | 3 (2.5) | 0 (0.0) | 9 (3.8) | |
| Induration | 5 (4.2) | 1 (0.8) | 4 (1.7) | 0.211 |
| Grade 1 | 5 (4.2) | 1 (0.8) | 4 (1.7) | |
| Erythema | 2 (1.7) | 0 (0.0) | 5 (2.1) | 0.366 |
| Grade 1 | 2 (1.7) | 0 (0.0) | 5 (2.1) | |
| Pruritus | 2 (1.7) | 2 (1.7) | 7 (2.9) | 0.784 |
| Grade 1 | 1 (0.8) | 2 (1.7) | 6 (2.5) | |
| Grade 2 | 1 (0.8) | 0 (0.0) | 1 (0.4) | |
| **Systematic adverse reactions** | | | | |
| Any | 3 (2.5) | 5 (4.2) | 12 (5.0) | 0.609 |
| Grade 1 | 2 (1.7) | 3 (2.5) | 9 (3.8) | |
| Grade 2 | 0 (0.0) | 2 (1.7) | 3 (1.3) | |
| Grade 3 | 1 (0.8) | 0 (0.0) | 0 (0.0) | |
| Fever | 1 (0.8) | 1 (0.8) | 3 (1.3) | 1.000 |
| Grade 1 | 0 (0.0) | 1 (0.8) | 3 (1.3) | |
| Grade 2 | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Grade 3 | 1 (0.8) | 0 (0.0) | 0 (0.0) | |
| Cough | 0 (0.0) | 1 (0.8) | 3 (1.3) | 0.811 |
| Grade 1 | 0 (0.0) | 0 (0.0) | 1 (0.4) | |
| Grade 2 | 0 (0.0) | 1 (0.8) | 2 (0.8) | |
| Headache | 0 (0.0) | 1 (0.8) | 2 (0.8) | 0.811 |
| Grade 1 | 0 (0.0) | 0 (0.0) | 1 (0.4) | |
| Grade 2 | 0 (0.0) | 1 (0.8) | 1 (0.4) | |
| Vomiting | 0 (0.0) | 0 (0.0) | 1 (0.4) | 1.000 |
| Grade 1 | 0 (0.0) | 0 (0.0) | 1 (0.4) | |
| Diarrhea | 0 (0.0) | 0 (0.0) | 2 (0.8) | 0.499 |
| Grade 1 | 0 (0.0) | 0 (0.0) | 2 (0.8) | |
| Nausea | 0 (0.0) | 1 (0.8) | 0 (0.0) | 0.500 |
| Grade 1 | 0 (0.0) | 1 (0.8) | 0 (0.0) | |
| Mucocutaneous eruption | 1 (0.8) | 0 (0.0) | 1 (0.4) | 1.000 |
| Grade 1 | 1 (0.8) | 0 (0.0) | 1 (0.4) | |
| Muscle pain | 1 (0.8) | 1 (0.8) | 1 (0.4) | 1.000 |
| Grade 1 | 1 (0.8) | 1 (0.8) | 1 (0.4) | |
| Fatigue | 1 (0.8) | 0 (0.0) | 1 (0.4) | 1.000 |
| Grade 1 | 1 (0.8) | 0 (0.0) | 1 (0.4) | |
| **Unsolicited adverse reactions within 0–56 days** | | | | |
| Any | 2 (1.7) | 2 (1.7) | 4 (1.7) | 1.000 |
| Grade 1 | 2 (1.7) | 2 (1.7) | 3 (1.3) | |
| Grade 2 | 0 (0.0) | 0 (0.0) | 1 (0.4) | |
| **Overall adverse reactions within 0–56 days** | | | | |
| Any | 20 (16.7) | 23 (19.2) | 48 (20.0) | 0.757 |
| Grade 1 | 18 (15.0) | 20 (16.7) | 43 (17.9) | |
| Grade 2 | 1 (0.8) | 3 (2.5) | 5 (2.1) | |
| Grade 3 | 1 (0.8) | 0 (0.0) | 0 (0.0) | |

N, n: number of participants; C1: concomitant administration subgroup 1, IIV4 was administered concomitantly with the 1st dose of the inactivated COVID-19 vaccine on Day 0; C2: concomitant administration subgroup 2, IIV4 was administered concomitantly with the 2nd dose of the inactivated COVID-19 vaccine on Day 28; S group: separate administration group, IIV4 was administered separately on Day 14.

studies [28,29], indicating that co-administration of these two vaccines did not increase reactivity in any concerning manner.

There are some limitations of this study. First, no parallel control groups with participants receiving CoronaVac or IIV4 only were included during the time of this study, which may have affected the explanation of the absolute immune response of the concomitant administration of the corresponding two vaccines. However, the phase 2 clinical trial of CoronaVac and phase 3 clinical trial of IIV4 were performed within 1–3 years before this study

in a similar population (18–59 aged adults). The results of this study showed similar immunogenicity and safety profiles with two previous clinical trials, which may indirectly indicate the reliability of this study. Second, as the primary endpoint of this study focused on the immune response against SARS-CoV-2, the sample size of each group may not have been sufficient to power the conclusion about influenza viruses, and further studies are needed. Third, this study was conducted on 18–59 aged people that the result of this study couldn't be used to support the immunization

strategy of concomitant injection of CoronaVac and IIV4 in older people aged 60 years and older, and further studies are needed. Finally, further immunological studies are warranted to precisely explain the differences of the immune response to CoronaVac when IIV4 is co-administered with the first or with the second dose of CoronaVac, which has not been previously reported in the literature to our knowledge.

## 5. Conclusions

Co-administration of inactivated COVID-19 vaccine and seasonal influenza vaccine, especially the administration regimen that the seasonal influenza vaccine co-administered with the first dose of the inactivated COVID-19 vaccine, would be feasible.

*CRediT authorship contribution statement*

**Wang Shenyu:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Duan Xiaoqian:** Data curation, Writing – review & editing. **Chen Bo:** Data curation, Investigation, Writing – review & editing. **Deng Xuan:** Data curation, Investigation, Writing – review & editing. **Wang Zeng:** Formal analysis. **Zhang Hangjie:** Data curation, Investigation, Writing – review & editing. **Zheng Qianhui:** Investigation, Writing – review & editing. **Liang Zhenzhen:** Data curation, Investigation. **Yan Chuanfu:** Investigation. **Yang Juan:** Data curation. **Zeng Gang:** Conceptualization, Data curation, Methodology, Supervision, Writing – review & editing. **Lv Huakun:** Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.07.021.

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