Lot-to-lot consistency, immunogenicity, and safety of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults: A randomized, double-blind, phase IV trial

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ABSTRACT
Previous phase I to III clinical trials have shown that the inactivated SARS-CoV-2 vaccine namely CoronaVac has good efficacy, safety, and immunogenicity. This phase IV trial aims to evaluate the lot-to-lot consistency, immunogenicity, and safety on a commercial scale in healthy adults, which could provide data to support stable manufacturing. In this single-center, randomized, double-blind study, 1,080 healthy adults aged 26-45 years were randomly assigned into three groups to receive one of three lots of vaccines. All subjects received two doses of CoronaVac with an interval of 28 days. Serum samples were collected before the first dose and 28 days after the second dose to assess the immunogenicity. Solicited local and systemic adverse events (AEs) within 7 days and unsolicited AEs within 28 days after each dose of vaccination were recorded. A total of 1,039 participants completed the study and were included in the per-protocol set (PPS). The GMTs were 75.2 (68.5, 82.6), 65.0 (59.0, 71.7), and 65.3 (59.4, 71.8), respectively, and the seroconversion rates of neutralizing antibody were all higher than 98%. The GMT ratios of each pair of lots were 1.16 (1.01,1.32), 1.15 (1.01, 1.32), and 0.99 (0.87, 1.14), respectively, meeting the immunological equivalence criteria. The incidence rates of adverse reactions (ARs) were 19.17%, 13.89%, and 18.33%, with no statistical difference. The ARs were all in grade 1 and grade 2, with incidences of 15.46% and 2.50%. Non-vaccine-related serious adverse events (SAEs) were reported. These results showed robust lot-to-lot consistency, immunogenicity, and safety. The stable production indicated that CoronaVac is suitable for large-scale use.

Trial registration number: NCT04894227 (ClinicalTrials.gov).

Introduction
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an emerging pathogen causing coronavirus disease 2019 (COVID-19), which has caused more than 323 million confirmed cases and 6.3 million deaths worldwide as of 20 May 2022.1-3 Epidemiological studies have shown that SARS-CoV-2 is transmitted mainly through respiratory droplets or close contact.4-6 Contacting viral-contaminated objects or exposure to high-concentration aerosols in a closed environment may also cause transmission.7 The common symptoms of COVID-19 include fever, cough, fatigue, shortness of breath, sore throat, headache, nausea, vomiting, and diarrhea.8-10 Elderly patients with underlying diseases, such as diabetes or hypertension, have a higher risk of worsening into septic shock, coagulopathy, or even death after infection with SARS-CoV-2.6,11,12 Because of its high transmissibility and impacts on human health, international efforts are focusing on using vaccines to control the COVID-19 epidemic.

As of 24 May 2022, 358 vaccines are in clinical trials, 47 are in phase III or IV clinical trials, and 11 are approved for the World Health Organization (WHO) emergency use.13 Several phase III clinical trials of COVID-19 vaccines showed that the vaccines had medium to high protective efficacy in preventing infection of SARS-CoV-2 and relatively high efficacy in avoiding severe disease and death related to COVID-19.14-17 With the emergency approval of various COVID-19 vaccines, the number of people vaccinated globally has increased rapidly. As of July 3, 2022, a total of 11,986,040,938 vaccine doses have been administered and 4,762,615,872 persons have been fully vaccinated.18 A steady decline is seen in the case fatality rate (CFR) of COVID-19, which confirmed the importance of widespread vaccination in controlling the COVID-19 epidemic.3

The COVID-19 Vaccine (Vero Cell), Inactivated (hereinafter referred to as “CoronaVac”), was developed by Sinovac Life Sciences Co., Ltd. (hereinafter referred to as “SINOVAC”). CoronaVac received the approval from the National Medical Products Administration (NMPA) in April 2020 to conduct phase I to III clinical trials. The results of phase II clinical trials in Brazil, Turkey, Indonesia, and Chile indicate that
CoronaVac is safe and can trigger a protective immune response against SARS-CoV-2, with efficacy or effectiveness ranging from 50% to 84% against symptomatic COVID-19. With the evidence generated from the trials, NMPA granted conditional market approval to CoronaVac on 5 February 2021. Additionally, CoronaVac was validated by the WHO for emergency use on 1 June 2021. Hence, CoronaVac has been widely administered to respond to the COVID-19 epidemic. As of 31 May 2022, CoronaVac has been approved to be administered in 61 countries or regions with a cumulative vaccination of more than 2.5 billion doses. As required by the Center for Drug Evaluation (CDE), NMPA, a clinical trial was needed to demonstrate the manufacturing consistency by comparing the immunogenicity of three lots of CoronaVac on a commercial scale. Therefore, we carried out this study to evaluate the lot-to-lot consistency, immunogenicity, and safety of the CoronaVac produced by SINOVAC.

Materials and methods

Study design

The phase IV, double-blind, randomized clinical trial was conducted in Huai’an city, Jiangsu Province, China, from May 2021 to November 2021. The trial was approved by the Ethics Committee of Jiangsu Provincial Center for Disease Control and Prevention. The trial was registered at ClinicalTrials.gov (NCT04894227) and was conducted in compliance with the International Conference for Harmonization Good Clinical Practice Guideline.

Participants

Eligible participants were healthy adults aged 26–45 years who were willing to sign informed consent with legal identification. The key exclusion criteria included (1) having contact with COVID-19 patients, previously being infected with COVID-19 or received COVID-19 vaccine; (2) axillary temperature >37.0°C; (3) allergy or serious adverse reactions to any vaccine; (4) severe chronic disease or acute diseases within 7 days before vaccination; (5) any known immunodeficiency; (6) receipt of blood products within the previous 3 months; (7) receipt of any live-attenuated vaccines within the previous 14 days; (8) receipt of any subunit or inactivated vaccines within the previous 7 days; and (9) other conditions that were deemed not suitable for the clinical trial.

After enrollment, all participants were randomly assigned into three groups in a 1:1:1 ratio to receive two doses (Day 0 and 28) of either three lots of CoronaVac by injection into the deltoid muscle.

Vaccine

CoronaVac was prepared by vaccinating African green monkey kidney cell (referred to as “Vero Cell”) with SARS-CoV-2 (CZ02 strain) through the culture, harvesting of virus solution, virus inactivation, concentration, purification, and adsorption of aluminum hydroxide. It is a milky white suspension liquid, which may be stratified due to precipitation and is easy to shake off. Its main component is inactivated SARS-CoV-2, with other auxiliary materials of aluminum hydroxide, disodium hydrogen phosphate dodecahydrate, sodium dihydrogen phosphate monohydrate, and sodium chloride. It contains no preservatives. It is packed in pre-filled syringes, each with 0.5 ml. The vaccination can induce the body to produce immunity to prevent the disease caused by SARS-CoV-2 infection.

The vaccines used in this trial were from three consecutive batches of CoronaVac on a commercial scale developed by SINOVAC. The batch numbers were A202103012, A202103013, and A202103014, respectively. All the vaccines had been verified by the National Institutes for Food and Drug Control (NIFDC). The vaccine was conducted with the specification of 0.5 ml/dose that contained 3.0 µg/0.5 ml SARS-CoV-2 antigen.

Randomization and blinding

A randomization number table was generated by SAS 9.4 software (SAS Institute Inc., Cary, NC, USA) based on a preset block length to mask and label the study vaccines by independent biostatisticians. Every participant was assigned a unique number by the order of enrollment and received the vaccine marked with the same number. All participants and investigators were blinded. After enrollment, subjects were inoculated with the vaccine consistent with their study number.

Randomized statisticians and other blind coding personnel who were not involved in the trial were employed for blind coding of the vaccine. The printed label was pasted on the designated position of each vaccine according to the blind code. Randomized statisticians supervised the vaccine blind coding and guided the blind coding operators to label according to the blind code. After the blind coding was completed, the blind code was sealed by randomized statisticians. The blind coding personnel neither participated in other related work of this clinical trial nor disclosed any information about the blind code to any person participating in this clinical trial.

Immunogenicity assessment

Blood samples were collected from all participants on Day 0 (before the first dose) and Day 56 (28 days after the second dose). The sera-neutralizing antibody was tested in NIFDC using micro-cytopathic effect assay. The COVID-19 spike protein receptor-binding domain antibody (S-protein antibody) was tested using the COVID-19 (SARS-CoV-2) antibody test kit (electrochemiluminescence method) manufactured by Roche Diagnostics (Shanghai) Co., Ltd.

The primary endpoint was geometric mean titer (GMT) of the neutralizing antibody 28 days after the second dose. The secondary endpoints were seropositive rate, seroconversion rate, and geometric mean increase (GMI) of neutralizing antibody 28 days after the second dose, as well as the geometric mean concentration (GMC), seropositive rate, seroconversion rate, and GMI of S-protein antibody 28 days after the second dose. The seropositive rate was defined as antibody titer ≥1:8 for neutralizing antibody and ≥0.8 BAU/mL for S-protein antibody. Seroconversion rate for neutralizing antibody was defined as the percentage of participants with antibody titer of
either (1) <1:8 before vaccination and ≥1:8 after vaccination or (2) ≥1:8 before vaccination and at least a fourfold increase after vaccination. Seroconversion rate for S-protein antibody was defined as the percentage of participants with an antibody concentration of either (1) <0.8 BAU/mL before vaccination and ≥0.8 BAU/mL after vaccination or (2) ≥0.8 BAU/mL before vaccination and at least a fourfold increase after vaccination. The immunogenicity assessment was conducted based on the per-protocol set (PPS), including participants who met eligibility criteria, complied with the protocol, and had immunogenicity results before and after vaccination.

**Safety analysis**

Immediate adverse events (AEs) were observed at the study site for at least 30 minutes after each vaccination. A diary card was used to record solicited local or systemic AEs occurring within 7 days, and unsolicited AEs and serious adverse events (SAEs) occurring within 28 days after each vaccination. At the seventh day after each dose of vaccination, AEs recorded in the diary card will be verified by the investigators via telephone or face-to-face visit. And at the 28th day after each dose of vaccination, the diary card will be recalled and AEs recorded in the diary card will be verified by the investigators via face-to-face visit. Solicited systemic AEs included fever, allergic reaction, skin and mucosal abnormality, irritability, decreased appetite, nausea/vomiting, and diarrhea. Solicited local AEs included pain, induration, redness, swelling, rash, and pruritus. The reported AEs were graded according to the guidelines issued by the NMPA 24. The causal relationship between AEs and vaccination was established by the investigators. Safety assessment was conducted based on the safety set (SS), which included participants who received at least one dose of vaccine.

**Statistical analysis**

The sample size was calculated by GMT using NCSS-PASS 11.0 software (NCSS, Kaysville, UT, USA). The equivalence standard was that the 95%CI of the inter-group GMT ratio was between 2/3 and 3/2, where the GMT difference was between −0.176 and 0.176 after logarithmic transformation with 10 as the base, namely, the equivalence threshold δ was ±0.176. The bilateral a was 0.05, and the overall power was 80%. The power for each comparison was 1−20%/3 = 93.4%, and the standard deviation (σ) after logarithmic transformation was 0.6 by reference to the results of previous studies of CoronaVac. According to these variables, the sample size was 283 cases in each lot. Considering the 20% of loss to follow-up, the sample size of each lot was 360. The total sample size of this study was 1080.

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). The GMT of neutralizing antibody 28 days after full-course immunization in the susceptible population of all lot groups was fitted to the model of analysis of covariance (ANOVA) for equivalence analysis. In the model, the log-transformed GMT of neutralizing antibody 28 days after full-course immunization was treated as the dependent variable, the log-transformed GMT of neutralizing antibody before immunization was the concomitant variable, and the group dummy variables (Lot Groups 1, 2, and 3) were the fixed effect. The corrected GMT in each group and the ratios of GMTs and 95% confidence intervals (CIs) between each pair of groups (Lot 1/Lot 2, Lot 1/Lot 3, and Lot 2/Lot 3) were obtained after inverse logarithmic conversion. If all CIs of the GMT ratios between the three lots fall within (2/3, 3/2), the immunogenicity of the three lots is consistent.

**Results**

**Study population**

Between 11 May 2021 and 14 May 2021, a total of 1,110 participants were screened, of whom 1,080 were enrolled and 1,072 subjects completed two doses of vaccination, with 359 subjects in Lot 1, 1,357 subjects in Lot 2 and 356 subjects in Lot 3. All the subjects completed blood collection before immunization and 1,052 subjects completed blood collection after immunization, where 352 subjects in Lot 1, 349 subjects in Lot 2, and 351 subjects in Lot 3. The reasons for subjects excluded from PPS were due to inclusion criteria violation (three subjects), second dose vaccination with a wrong vaccine (one subject), second dose vaccination beyond the time window (eight subjects), absence of blood sample results after immunization (28 subjects) and concomitant medication related to immune response (one subject). Finally, PPS contained 1039 participants, which had 359 in Lot 1, 357 in Lot 2, and 356 in Lot 3 (Figure 1).

The basic characteristics of the subjects are shown in Table 1 and there was no statistical difference in age, gender, ethnicity, height, and weight.

**Immunogenicity**

All participants in PPS had negative results of neutralizing antibodies before the vaccination and were treated as a susceptible population. The GMTs of Lot 1, Lot 2, and Lot 3 were 75.2 (68.5, 82.6), 65.0 (59.0, 71.7), and 65.3 (59.4, 71.8), respectively, 28 days after the full-course vaccination. Seroconversion rates of 3 lots were 99.71% (98.40, 99.99), 98.56% (96.67, 99.53), and 98.55% (96.65, 99.53), respectively, which were the same as the seroconversion rates. No statistical difference was found in seroconversion/seropositive rates, GMTs, and GMIs among the three groups. See Table 2 for details.

The seropositive rates of anti-RBD antibody in three groups were 0.29%, 0.86%, and 0.87% before vaccination, respectively. After the vaccination, the seropositive rates/seroconversion rates of anti-RBD antibody were 100.00%, 100.00%, and 99.42%, respectively. No statistical difference was found in seroconversion/seropositive rate, GMCs, and GMIs among the three groups. Detailed results are shown in Table S1.

**Lot-to-lot consistency**

The GMT ratios of neutralizing antibody and its 95%CI between Lot 1 and Lot 2, Lot 1 and Lot 3, and Lot 2 and Lot 3 were 1.16 (1.01, 1.32), 1.15 (1.01, 1.32), and 0.99 (0.87, 1.14), respectively. Both sides of 95%CIs were within (2/3, 3/2) and reached the equivalence criterion (Table 2).
Figure 1. Flow chart of subjects through screening, random assignment, and analysis. * A subject was scheduled to receive the second dose of Lot 1, but incorrectly received the vaccine of Lot 3, so the total SS and SS1 sets were included in Lot 1 for analysis and the SS2 set was included in Lot 3 for analysis. Abbreviations: FAS: full analysis set; PPS: per-protocol set; SS: safety set; SS1: safety set of the first dose; SS2: safety set of the second dose; PD: protocol deviations; PV: protocol violations

Table 1. Demographic characteristics and physical examination of subjects.

| Variables          | Lot 1  | Lot 2  | Lot 3  | Total  | P value |
|--------------------|--------|--------|--------|--------|---------|
| N                  | 347    | 347    | 345    | 1039   | -       |
| Age (Year)         | 35.13 (5.20) | 35.16 (5.37) | 35.22 (5.29) | 35.17 (5.28) | 0.9715  |
| Han ethnic, No. (%)| 346 (99.71) | 344 (99.14) | 343 (99.42) | 1033 (99.42) | 0.6053  |
| Male, No. (%)      | 148 (42.65) | 165 (47.55) | 140 (40.58) | 453 (43.60) | 0.1646  |
| Height (m)         | 1.65 (0.08) | 1.66 (0.08) | 1.65 (0.08) | 1.65 (0.08) | 0.6347  |
| Weight (kg)        | 70.63 (14.07) | 70.10 (14.29) | 69.50 (14.53) | 70.08 (14.29) | 0.5793  |

Table 1. Demographic characteristics and physical examination of subjects.

| Variables          | Lot 1  | Lot 2  | Lot 3  | Total  | P value |
|--------------------|--------|--------|--------|--------|---------|
| N                  | 360    | 360    | 360    | 1080   | -       |
| Age (Year)         | 35.09 (5.20) | 35.01 (5.39) | 35.15 (5.29) | 35.08 (5.29) | 0.9325  |
| Han ethnic, No. (%)| 359 (99.72) | 357 (99.17) | 358 (99.44) | 1074 (99.44) | 0.6048  |
| Male, No. (%)      | 155 (43.06) | 177 (49.17) | 145 (40.28) | 477 (44.17) | 0.0489  |
| Height (m)         | 1.65 (0.08) | 1.66 (0.08) | 1.65 (0.08) | 1.65 (0.08) | 0.3784  |
| Weight (kg)        | 70.76 (13.96) | 70.49 (14.43) | 69.26 (14.43) | 70.17 (14.28) | 0.3250  |

Safety

Among the 1,080 participants, the overall incidence of adverse reactions (ARs) was 17.13% (185/1,080), where incidences in Lot 1, Lot 2, and Lot 3 were 19.17% (69/360), 13.89% (50/360), and 18.33% (66/360), respectively, with no statistical difference among the three groups (P = .1261). ARs were mainly solicited ARs, and the incidence rate of overall solicited AR was 15.74% (170/1,080). Within solicited ARs, the incidence rates of systemic ARs and local ARs were 9.17% (99/1,080) and 8.33% (90/1,080), respectively. The incidence rate of unsolicited ARs was 2.69% (29/1080). ARs mainly occurred within 7 days after vaccination, with an overall incidence rate of 16.85% (182/1,080). There was no statistical difference among the three groups in all aspects of safety.

The most common local reaction was injection site pain, with incidences of 8.33% (30/360), 6.94% (25/360), and 7.50% (27/360) in Lot 1, Lot 2, and Lot 3. Fever was the most common systemic reaction, with incidences of 4.72% (17/360) in Lot 1, 4.17% (15/360) in Lot 2, and 5.83% (21/360) in Lot 3. There was no statistical difference among the three groups. During the clinical trial, no SAE related to vaccination occurred. More detailed results on ARs after vaccination are shown in Table 3.

Discussion

This phase IV, randomized, double-blind clinical trial evaluated the lot-to-lot consistency, immunogenicity, and safety of three lots of commercial-scale CoronaVac in the healthy population.
### Table 2. Immunogenicity evaluation in neutralizing antibody (PPS).

| Time                        | Indicator     | Lot 1 (N = 347) | Lot 2 (N = 347) | Lot 3 (N = 345) | Total (N = 1039) | P value (Among 3 groups) |
|-----------------------------|---------------|-----------------|-----------------|-----------------|-------------------|--------------------------|
| Before vaccination          | SPR n(%)      | 0 (0.00)        | 0 (0.00)        | 0 (0.00)        | 0 (0.00)          | 1.0000                   |
| (95%CI)                     |               | (0.00, 1.06)    | (0.00, 1.06)    | (0.00, 1.06)    | (0.00, 0.35)      | 0.2287                   |
| GMT*                        |               | 2.1             | 2.1             | 2.0             | 2.0               | 0.0000                   |
| (95%CI)                     |               | (2.0, 2.1)      | (2.0, 2.1)      | (2.0, 2.1)      | (2.0, 2.1)        | 0.0000                   |
| 28 days after vaccination   | SPR n(%)      | 346 (99.71)     | 342 (98.56)     | 340 (98.55)     | 1028 (98.94)      | 0.2374                   |
| (95%CI)                     |               | (98.40, 99.99)  | (96.67, 99.53)  | (96.65, 99.53)  | (98.11, 99.47)    | 0.2374                   |
| SCR n(%)                    |               | 346 (99.71)     | 342 (98.56)     | 340 (98.55)     | 1028 (98.94)      | 0.2374                   |
| (95%CI)                     |               | (98.40, 99.99)  | (96.67, 99.53)  | (96.65, 99.53)  | (98.11, 99.47)    | 0.2374                   |
| GMT*                        |               | 75.2            | 65.0            | 65.3            | 68.4              | 0.0547                   |
| (95%CI)                     |               | (68.5, 82.6)    | (59.0, 71.7)    | (59.4, 71.8)    | (64.7, 72.2)      | 0.0481                   |
| GMI                         |               | 36.8            | 31.4            | 32.1            | 33.4              | 0.2287                   |
| (95%CI)                     |               | (33.5, 40.4)    | (28.5, 34.7)    | (29.2, 35.3)    | (31.6, 35.3)      | 0.2287                   |
| Adjusted GMT Ratio (95% CI) |               | 1.16            | 1.16            | -               | -                 | -                        |
| Lot 1/Lot 2                 |               | (1.01,1.32)     | (1.01,1.32)     | -               | -                 | -                        |
| Lot 1/Lot 3                 |               | 1.15            | 1.15            | -               | -                 | -                        |
| (1.01,1.32)                 |               | (1.01,1.32)     | (1.01,1.32)     | -               | -                 | -                        |
| Lot 2/Lot 3                 |               | -               | 0.99            | -               | -                 | -                        |
|                            |               |                 | (0.87,1.14)     |                 |                   | 0.87114                 |

Abbreviation: SPR: seropositive rate; SCR: seroconversion rate. GMT: geometric mean titer. GMI: geometric mean increase.

*P value was calculated with Fisher’s exact test.

### Table 3. Overall adverse reactions of subjects in safety analysis population after vaccination.

| Adverse Reactions                          | Lot 1 (N = 360) | Lot 2 (N = 360) | Lot 3 (N = 360) | Total (N = 1080) | P value* |
|--------------------------------------------|-----------------|-----------------|-----------------|------------------|----------|
| **Total**                                  | 69(19.17)       | 50(13.89)       | 66(18.33)       | 185(17.13)       | 0.1261   |
| **General disorders and administration site conditions** |                |                 |                 |                  |          |
| Vaccination site pain                      | 56(15.56)       | 42(11.67)       | 54(15.00)       | 152(14.07)       | 0.2603   |
| Fever                                      | 30(8.33)        | 25(6.94)        | 27(7.50)        | 82(7.59)         | 0.7966   |
| Asthenia                                   | 17(4.72)        | 15(4.17)        | 21(5.83)        | 53(4.91)         | 0.6138   |
| Vaccination site pruritus                  | 5(1.39)         | 20(5.65)        | 5(1.39)         | 12(1.11)         | 0.5139   |
| Injection site induration                  | 0(0.00)         | 1(0.28)         | 4(1.11)         | 5(0.46)          | 0.1347   |
| Injection site swelling                    | 20(5.65)        | 10(2.8)         | 10(2.8)         | 40(3.7)          | 1.0000   |
| Injection site erythema                    | 10(2.8)         | 0(0.00)         | 3(0.83)         | 4(0.37)          | 0.3321   |
| Periarticular swelling                     | 0(0.00)         | 0(0.00)         | 2(0.56)         | 2(0.19)          | 0.3227   |
| Nodule                                     | 10(2.8)         | 0(0.00)         | 0(0.00)         | 1(0.09)          | 1.0000   |
| Chest discomfort                            | 10(2.8)         | 0(0.00)         | 0(0.00)         | 1(0.09)          | 1.0000   |
| **Gastrointestinal disorders**             | 2(0.56)         | 2(0.56)         | 2(0.56)         | 6(0.57)          | 0.0710   |
| **Respiratory, thoracic, and mediastinal disorders** | 7(1.94)         | 4(1.11)         | 6(1.67)         | 17(1.57)         | 0.7499   |
| **Nervous system disorders**               | 20(5.56)        | 10(2.8)         | 10(2.8)         | 40(3.7)          | 0.5543   |
| **Musculoskeletal and connective tissue disorders** | 10(2.8)         | 0(0.00)         | 1(0.28)         | 2(0.19)          | 1.0000   |
| **Metabolism and nutrition disorders**     | 0(0.00)         | 0(0.00)         | 0(0.00)         | 3(0.28)          | 0.1105   |
| **Infections and infestations**            | 0(0.00)         | 10(2.8)         | 10(2.8)         | 3(0.28)          | 0.7772   |
| **Hypersensitivity**                       | 0(0.00)         | 0(0.00)         | 0(0.00)         | 1(0.09)          | 1.0000   |
| **Skin and subcutaneous tissue disorders** | 0(0.00)         | 0(0.00)         | 1(0.28)         | 1(0.09)          | 1.0000   |
| **Myalgia**                                | 3(0.83)         | 3(0.83)         | 10(2.8)         | 7(0.65)          | 0.7103   |
| **Pain in extremity**                      | 10(2.8)         | 0(0.00)         | 0(0.00)         | 1(0.09)          | 1.0000   |
| **Mucocutaneous rash**                     | 0(0.00)         | 0(0.00)         | 1(0.28)         | 1(0.09)          | 1.0000   |

*The P value is calculated using Fisher’s exact probability method.*
aged 26–45 years. For the primary analysis of our clinical trial, the 95% confidence interval of the GMT ratios of neutralizing antibody all reached the lot consistency criteria that indicated a good lot-to-lot consistency of commercial-scale vaccines.

For the analysis of immunogenicity, seroconversion rates of neutralizing antibody in all the three groups were higher than 98% and GMTs of neutralizing antibody were between 65.0 and 75.2 on the 28th day after full vaccination. The seroconversion rates of anti-RBD antibody in all the three groups were higher than 99% and GMTs were between 110.19 and 129.85 U/mL. All the results indicated that CoronaVac could induce a relatively high immune response in the participants aged 26–45 years. The level of GMT of neutralizing antibody was similar to previous results of phase I/II or phase III clinical trials, indicating that SINOVAC could ensure the stability and immunogenicity of different batches of vaccines in participants aged 26–45 years.17,19,23 It should be noted that the level of immunogenicity in our trial does not imply that of CoronaVac in all populations. A cross-sectional study showed that the level of immunogenicity decreased significantly in the elder population, with the seropositivity rate dropping to 72.5% in 61–79 years and 46.6% in 80 years and older.20

In this study, CoronaVac showed an acceptable safety profile among the participants, with no statistical difference among the three groups. CoronaVac’s safety advantage has been confirmed by several studies with low overall incidence of ARs, and most of ARs were mild.25,26 These results demonstrated that CoronaVac manufactured in different batches was stable in terms of safety.

There were some limitations to our study. We only enrolled healthy participants aged 26–45 years to assess the lot-to-lot consistency, immunogenicity, and safety of CoronaVac during commercial scale, which may not fully reflect the immunogenicity and safety in the whole population. Additionally, due to relatively short monitoring period (28 days after the two-dose vaccination), we could not evaluate the long-term immunogenicity of CoronaVac among the participants, as well as the safety. Studies that covered people from different age groups with long observation duration on immunogenicity and safety were suggested to be conducted in the future. Thirdly, in our study, we did not evaluate the immunogenicity consistency of CoronaVac against SARS-CoV-2 variant. In the neutralization test, only the original strain was used. Considering the purpose of this study was to evaluate the consistency of CoronaVac, using the original strain still satisfied our requirements.

The commercial-scale SARS-CoV-2 vaccines produced by SINOVAC have good safety in healthy participants aged 26–45 years. Immunogenicity results of the vaccines from three consecutive batches have reached the equivalence criterion, indicating good lot-to-lot consistency of commercial-scale vaccines.

**Acknowledgements**

We are grateful to all subjects who volunteered to participate in this trial and to all members of the clinical research teams.

**Disclosure statement**

Yuansheng Hu, Tuantuan Yang, Hengming Zhang, and Xing Meng are employees of Sinovac Biotech Co., Ltd. Xiaojuan Lian is an employee of Sinovac Life Sciences Co., Ltd. All the other authors have no conflicts of interest to declare.

**Funding**

This study was funded by Sinovac Life Sciences Co., Ltd.

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