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Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial

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Summary

Background A vaccine against COVID-19 is urgently needed for older adults, in whom morbidity and mortality due to the disease are increased. We aimed to assess the safety, tolerability, and immunogenicity of a candidate COVID-19 vaccine, CoronaVac, containing inactivated SARS-CoV-2, in adults aged 60 years and older.

Methods We did a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial of CoronaVac in healthy adults aged 60 years and older in Renqiu (Hebei, China). Vaccine or placebo was given by intramuscular injection in two doses (days 0 and 28). Phase 1 comprised a dose-escalation study, in which participants were allocated to two blocks: block 1 (3 µg inactivated virus in 0·5 mL of aluminium hydroxide solution per injection) and block 2 (6 µg per injection). Within each block, participants were randomly assigned (2:1) using block randomisation to receive CoronaVac or placebo (aluminium hydroxide solution only). In phase 2, participants were randomly assigned (2:2:2:1) using block randomisation to receive either CoronaVac at 1·5 µg, 3 µg, or 6 µg per dose, or placebo. All participants, investigators, and laboratory staff were masked to treatment allocation. The primary safety endpoint was adverse reactions within 28 days after each injection in all participants who received at least one dose. The primary immunogenicity endpoint was seroconversion rate at 28 days after the second injection (which was assessed in all participants who had received the two doses of vaccine according to their random assignment, had antibody results available, and did not violate the trial protocol). Seroconversion was defined as a change from seronegative at baseline to seropositive for neutralising antibodies to live SARS-CoV-2 (positive cutoff titre 1/8), or a four-fold titre increase if the participant was seropositive at baseline. This study is ongoing and is registered with ClinicalTrials.gov (NCT04383574).

Findings Between May 22 and June 1, 2020, 72 participants (24 in each intervention group and 24 in the placebo group; mean age 65·8 years [SD 4·8]) were enrolled in phase 1, and between June 12 and June 15, 2020, 350 participants were enrolled in phase 2 (100 in each intervention group and 50 in the placebo group; mean age 66·6 years [SD 4·7] in 349 participants). In the safety populations from both phases, any adverse reaction within 28 days after injection occurred in 20 (20%) of 100 participants in the 1·5 µg group, 25 (20%) of 125 in the 3 µg group, 27 (22%) of 123 in the 6 µg group, and 15 (21%) of 73 in the placebo group. All adverse reactions were mild or moderate in severity and injection site pain (39 [9%] of 421 participants) was the most frequently reported event. As of Aug 28, 2020, eight serious adverse events, considered unrelated to vaccination, have been reported by seven (2%) participants. In phase 1, seroconversion after the second dose was observed in 24 of 24 participants (100·0% [95% CI 85·8–100·0]) in the 3 µg group and 22 of 23 (95·7% [78·1–99·9]) in the 6 µg group. In phase 2, seroconversion was seen in 88 of 97 participants in the 1·5 µg group (90·7% [83·1–95·7]), 96 of 98 in the 3 µg group (98·0% [92·8–99·8]), and 97 of 98 (99·0% [94·5–100·0]) in the 6 µg group. There were no detectable antibody responses in the placebo groups.

Interpretation CoronaVac is safe and well tolerated in older adults. Neutralising antibody titres induced by the 3 µg dose were similar to those of the 6 µg dose, and higher than those of the 1·5 µg dose, supporting the use of the 3 µg dose CoronaVac in phase 3 trials to assess protection against COVID-19.

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Introduction

The ongoing COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread across the world and led to more than 94 million infections and more than 2 million deaths worldwide as of Jan 19, 2021.[1] Studies have shown

Research in context

Evidence before this study

We searched PubMed and the American Medical Association website on Dec 1, 2020, for published research articles, with no language or date restrictions, using the search terms "SARS-CoV-2", "COVID-19", "vaccine", and "clinical trial". We identified a phase 1/2 study of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV, developed by Sinopharm (Beijing, China), which showed that the vaccine was safe, tolerable, and immunogenic in healthy people in China. Two-dose immunisations (on days 0 and 28) at all doses (2 μg, 4 μg, and 8 μg) in two age groups (18–59 years and ≥60 years) induced neutralising antibodies in 100% of vaccine recipients. A phase 2 clinical trial of another inactivated Sinopharm vaccine in healthy adults aged 18–59 years showed a seroconversion rate of 97·6% at 14 days after a day 0 and 21 vaccination schedule. Additionally, a phase 2 study of another inactivated vaccine developed by the Institute of Medical Biology, Chinese Academy of Medical Sciences, showed that the vaccine was safe and induced neutralising antibody responses in adults aged 18–59 years. Several studies have shown neutralising antibody responses in older adults using other vaccine platforms, including two mRNA vaccines (Moderna and Pfizer/BioNTech, USA), one adenovirus type-5 vectored vaccine (CanSino Biological/Beijing Institute of Biotechnology, China), and one chimpanzee adenovirus-vectored vaccine (AstraZeneca, UK). We previously assessed CoronaVac, an inactivated vaccine developed by Sinovac Life Sciences, in adults aged 18–59 years, and showed that it was safe and well tolerated. Seroconversion rates ranged from 92% to 100% after two doses of CoronaVac (3 μg and 6 μg) with two immunisation schedules (on days 0 and 14, or on days 0 and 28).

Added value of this study

This is the first report of an inactivated SARS-CoV-2 vaccine, CoronaVac, tested in older adults (aged ≥60 years). We used a phase 1/2 study design to assess the safety of two different doses (3 μg and 6 μg) in a dose-escalation study with a two-dose vaccination schedule (days 0 and 28) before expanding the study to a larger cohort to explore immunogenicity in healthy older people. The neutralising antibody responses observed in those who received the 3 μg or 6 μg dose were higher than those in people who received the 1·5 μg dose, and were similar to the responses among adults aged 18–59 years who received the 3 μg or 6 μg dose.

Implications of all the available evidence

People older than 60 years have an increasing risk of severe illness and death from COVID-19, especially those with underlying chronic conditions. The response to vaccines is usually reduced in older adults due to immune senescence. Our findings indicate that CoronaVac is well tolerated and immunogenic in healthy adults aged 60 years and older, and neutralising antibody responses to live SARS-CoV-2 are not reduced in this population. Further studies of the effectiveness of this vaccine for prevention of COVID-19 in older adults are needed.

that individuals aged 60 years or older, and especially those with underlying chronic conditions, have an increased risk of severe illness and death compared with younger people, and that this risk increases with age.[2–4]

To control the pandemic and reduce the burden of COVID-19 worldwide, effective and safe COVID-19 vaccines are urgently needed. The response to vaccines is usually reduced in older adults because of immune senescence,[4–7] the age-related changes that affect many of the cellular and molecular elements of both the innate and adaptive immune systems. Therefore, testing the effectiveness of COVID-19 vaccines in this population is necessary.

Researchers around the world have been racing to develop COVID-19 vaccines since the outbreak began, with more than 64 candidate vaccines in the clinical evaluation stage and another 173 vaccines in preclinical evaluation as of Jan 15, 2021.[8] Studies have shown that the neutralising antibody responses can be induced in older adults with use of different vaccine platforms, including mRNA,[9,10] adenovirus vectors,[11,12] and inactivated virus.[13] The interim efficacy analyses from four phase 3 trials have shown different vaccines to be highly effective against COVID-19 in adults aged 16 years or older, including two mRNA vaccines with efficacies of 95%,[14,15] and two adenovirus-vectored vaccines with efficacies of 70%[16] and 91%.[17]

Purified inactivated viruses have traditionally been used for vaccine development, and currently eight inactivated COVID-19 candidate vaccines are in clinical evaluation.[8] Although the results of efficacy against COVID-19 are not yet available, several studies have shown that the inactivated vaccines can induce neutralising antibody responses and have good safety profiles.[13,18–20] CoronaVac is an inactivated SARS-CoV-2 vaccine developed by Sinovac Life Sciences (Beijing, China). The results of a preclinical study showed that CoronaVac induced good neutralising antibody responses in animals and provided partial or complete protection from severe interstitial pneumonia in macaques following SARS-CoV-2 challenge, without observable antibody-dependent enhancement of infection.[21] We previously reported the results of our phase 1/2 clinical trial of CoronaVac in participants aged 18–59 years, which showed that CoronaVac was well tolerated and induced humoral responses against SARS-CoV-2.[20] Here we report the safety, tolerability, and immunogenicity of CoronaVac among healthy adults aged 60 years and older.

Methods

Study design and participants

In our initial phase 1/2 trial of CoronaVac in participants aged 18–59 years old, doses of 3 μg and 6 μg were

evaluated,[20] and the preliminary safety results supported the expansion of the trial to older adults. We subsequently did a single-centre, randomised, double-blind, placebo-controlled, phase 1/2 trial to evaluate the safety, tolerability, and immunogenicity of CoronaVac in adults aged 60 years and older. Three different doses—1·5 μg, 3 μg, and 6 μg—were used in this study. Because the 1·5 μg dose was not evaluated in the initial human trial, and the number of participants in phase 1 of the current study was small, the dose of 1·5 μg was only given to participants in the phase 2 trial of those aged 60 years or older. This trial was run at Hebei Provincial Center for Disease Control and Prevention (CDC) in Renqiu (Hebei, China).

Phase 1 of the trial was a dose-escalation study of 72 participants. The first 36 participants (block 1) were randomly assigned to receive either 3 μg vaccine or placebo. After 7 days of follow-up for safety after the first dose, another 36 participants (block 2) were randomly assigned to receive either 6 μg vaccine or placebo. Phase 2 was initiated only after all the participants in phase 1 had finished and passed a 7-day safety observation period after the first dose, as confirmed by the data monitoring committee. The required safety criteria in both blocks were no life-threatening adverse events and no more than 15% of vaccinated participants reporting severe adverse events. In phase 2, vaccine doses of 1·5 μg, 3 μg, or 6 μg were compared with placebo.

Eligible participants were healthy adults aged 60 years or older. The key exclusion criteria included high-risk epidemiological history within 14 days before enrolment (eg, travel to or residence in Wuhan and surrounding areas or other communities with reports of COVID-19 cases, or contact with someone infected with SARS-CoV-2), history of severe acute respiratory syndrome or SARS-CoV-2 infection, axillary temperature of more than 37·0°C, or a history of allergy to any vaccine component. A complete list of exclusion criteria is provided in the protocol, which is available online.

Written informed consent was obtained from each participant before enrolment. The clinical trial protocol and informed consent form were approved by the Ethics Committee of Hebei CDC (IRB2020–006). The study was conducted in accordance with the requirements of Good Clinical Practice of China and the International Conference on Harmonisation.

Randomisation and masking

In phase 1, participants in block 1 and block 2 were randomly assigned (2:1) to receive either vaccine or placebo. In phase 2, participants were randomly assigned (2:2:2:1) to either 1·5 μg, 3 μg, or 6 μg of vaccine or placebo. The randomisation codes for phases 1 and 2 were generated by the randomisation statistician, using block randomisation and SAS software (version 9.4). The randomisation code was assigned to each participant in sequence in order of enrolment, and participants received the study vaccine or placebo labelled with the same code. The vaccine and placebo were completely identical in appearance, and all participants, investigators, and laboratory staff were masked to group allocation.
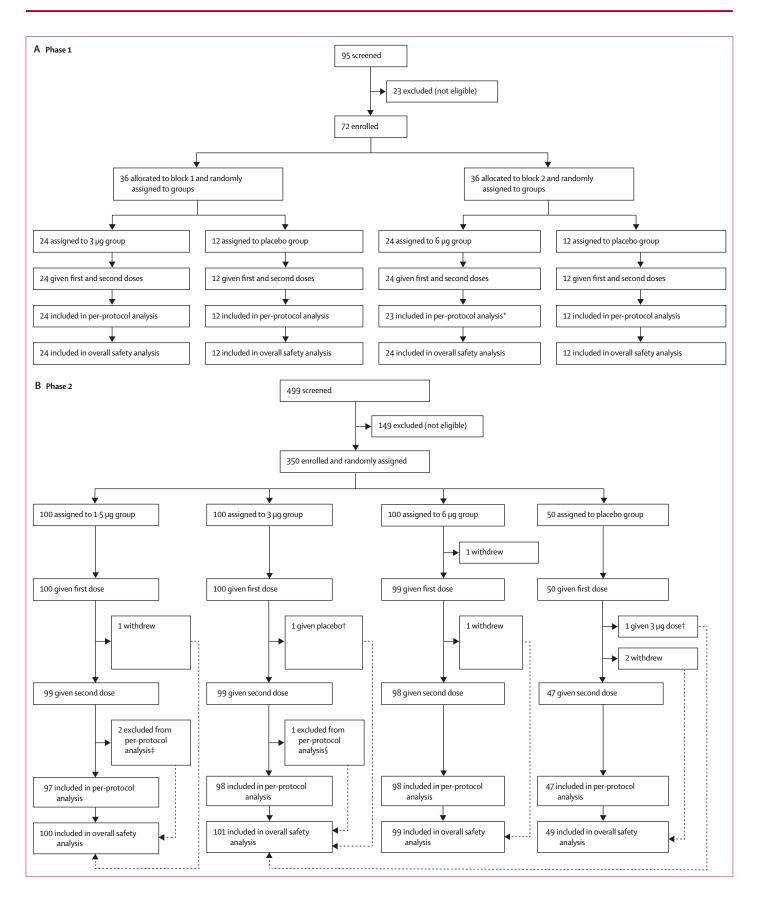
Procedures

CoronaVac is an inactivated vaccine candidate against COVID-19. To prepare the vaccine, SARS-CoV-2 (CN02 strain) was propagated in African green monkey kidney cells (WHO Vero 10-87 cells). At the end of the incubation period, the virus was harvested, inactivated with β-propiolactone, concentrated, purified, and finally adsorbed onto aluminium hydroxide. The aluminium hydroxide complex was then diluted in sodium chloride, phosphate-buffered saline, and water before being sterilised and filtered for injection. The placebo consisted only of the aluminium hydroxide solution with no virus. Both the vaccine and placebo were prepared in a Good Manufacturing Practice-accredited facility of Sinovac Life Sciences that is periodically inspected by the National Medical Products Administration committee for compliance. The production process of the vaccine in this trial was a highly automated bioreactor (ReadyToProcess WAVE 25; GE, Umea, Sweden), which was consistent with the production process of vaccine used in the phase 2 trial of adults aged 18–59 years.[20] Vaccine doses of 1·5 μg, 3 μg, or 6 μg in 0·5 mL of aluminium hydroxide solution per injection and placebo in ready-to-use syringes were administered intra-muscularly to participants on days 0 and 28.

For the first 7 days after each dose, participants were required to record injection site adverse events (eg, pain, swelling, or redness) and systemic adverse events (eg, allergic reaction, cough, or fever) on diary cards. On days 8 and 28, participants visited the study site for assessment by the study investigators (all medical practitioners) who conducted face-to-face interviews to confirm safety. Between visits, safety data were collected by spontaneous recording and reporting of adverse events by participants. The serious adverse events reported in this Article were collected from May 22 to Aug 28, 2020 and follow-up will continue until 12 months after the second dose. The reported adverse events were graded according to the China National Medical Products Administration guidelines.[22] The causal relationship between adverse events and vaccination was determined by the investigators.

Blood samples were collected on days 0, 28, and 56 from participants in phase 1, and on days 0 and 56 in phase 2 to evaluate the neutralising antibody titres. The neutralising antibody titres to live SARS-CoV-2 (virus strain SARS-CoV-2/human/CHN/CN1/2020, GenBank number MT407649.1) were quantified using a micro cytopathogenic effect assay.[23] Serum samples were inactivated at 56°C for 30 min and serially diluted with

A Phase 1

95 screened

→ 23 excluded (not eligible)

72 enrolled

36 allocated to block 1 and randomly assigned to groups

36 allocated to block 2 and randomly assigned to groups

24 assigned to 3 μg group

12 assigned to placebo group

24 assigned to 6 μg group

12 assigned to placebo group

24 given first and second doses

12 given first and second doses

24 given first and second doses

12 given first and second doses

24 included in per-protocol analysis

12 included in per-protocol analysis

23 included in per-protocol analysis*

12 included in per-protocol analysis

24 included in overall safety analysis

12 included in overall safety analysis

24 included in overall safety analysis

12 included in overall safety analysis

B Phase 2

499 screened

→ 149 excluded (not eligible)

350 enrolled and randomly assigned

100 assigned to 1·5 μg group

100 assigned to 3 μg group

100 assigned to 6 μg group

→ 1 withdrew

50 assigned to placebo group

100 given first dose

100 given first dose

99 given first dose

50 given first dose

→ 1 withdrew

→ 1 given placebo†

→ 1 withdrew

→ 1 given 3 μg dose†
→ 2 withdrew

99 given second dose

99 given second dose

98 given second dose

47 given second dose

→ 2 excluded from per-protocol analysis‡

→ 1 excluded from per-protocol analysis§

97 included in per-protocol analysis

98 included in per-protocol analysis

98 included in per-protocol analysis

47 included in per-protocol analysis

100 included in overall safety analysis

101 included in overall safety analysis

99 included in overall safety analysis

49 included in overall safety analysis

cell culture medium in two-fold steps. The diluted serum samples were incubated with equal volumes (50 μL) of live SARS-CoV-2 suspension, with a 50% cell culture infective dose of 100 for 2 h at 37·0°C. Vero cells ($1·0\times10^5$ to $2·0\times10^5$ cells per mL) were then added to the serum–virus suspensions in microplates in duplicate and incubated at 36·5°C for 5 days. Cytopathic effects were recorded under microscopes and the neutralising antibody titre was calculated by the dilution number of the 50% protective condition. Detection was done by the National Institute for Food and Drug Control. Further information on the method is provided in the appendix (p 1).

Outcomes

The primary safety endpoint was any vaccine-related adverse event (adverse reaction) within 28 days after the administration of each dose of vaccine or placebo. The primary immunogenicity endpoint was the sero-conversion rate of neutralising antibodies to live SARS-CoV-2 at day 28 after the second dose. Secondary endpoints were severe adverse events and geometric mean titre (GMT) of neutralising antibodies to live SARS-CoV-2, as well as seropositive rates and geometric mean increase. Seroconversion was defined as a change from seronegative at baseline to seropositive, or a four-fold titre increase if the participant was seropositive at baseline. The positive cutoff of the titre for neutralising antibodies to live SARS-CoV-2 was 1/8.

Statistical analysis

We assessed the safety endpoints in the safety population, which included all participants who received at least one dose of vaccine or placebo. We assessed the immunogenicity endpoints in the per-protocol population, which included all participants who had received the two doses of vaccine according to their random assignment, had antibody results available, and did not violate the trial protocol.

We did not determine the sample sizes on the basis of a statistical power calculation, but followed the requirements of the China National Medical Products Administration and Chinese Technical Guidelines for

	Phase 1			Phase 2			
	3 μg group (n=24)	6 μg group (n=24)	Placebo group (n=24)	1·5 μg group (n=100)	3 μg group (n=100)	6 μg group (n=99)	Placebo group (n=50)
Age, years							
Mean (SD)	65·6 (4·3)	67·5 (5·5)	64·2 (4·2)	66·8 (4·6)	66·5 (4·9)	66·2 (4·4)	67·4 (4·9)
60–64	12 (50%)	9 (38%)	18 (75%)	38 (38%)	39 (39%)	39 (39%)	16 (32%)
65–69	6 (25%)	8 (33%)	4 (17%)	35 (35%)	33 (33%)	40 (40%)	17 (34%)
≥70	6 (25%)	7 (29%)	2 (8%)	27 (27%)	28 (28%)	20 (20%)	17 (34%)
Sex							
Male	11 (46%)	13 (54%)	13 (54%)	49 (49%)	49 (49%)	44 (44%)	27 (54%)
Female	13 (54%)	11 (46%)	11 (46%)	51 (51%)	51 (51%)	55 (56%)	23 (46%)
Han ethnicity	24 (100%)	24 (100%)	24 (100%)	99 (99%)	100 (100%)	99 (100%)	50 (100%)
Height, m	1·6 (0·1)	1·7 (0·1)	1·6 (0·8)	1·6 (0·1)	1·6 (0·1)	1·6 (0·1)	1·6 (0·1)
Weight, kg	69·6 (7·5)	66·9 (9·0)	68·8 (7·0)	66·8 (10·2)	67·2 (11·2)	66·1 (9·8)	64·9 (11·5)

Data are mean (SD) or n (%).

Table 1: **Baseline demographic characteristics**

Clinical Trials of Vaccines—ie, recruitment of at least 20–30 participants in phase 1 and 300 participants in phase 2.

We used the Pearson χ² test or Fisher's exact test for the analysis of categorical outcomes. We calculated 95% CIs for all categorical outcomes using the Clopper-Pearson method. We calculated GMTs and corresponding 95% CIs on the basis of standard normal distribution of the log-transformation antibody titre. We used the ANOVA method to compare the log-transformed antibody titre. When the comparison among all groups showed a significant difference, we did pairwise comparisons. Hypothesis testing was two-sided and we considered p values of less than 0·05 to be significant.

An independent data monitoring committee consisting of one independent statistician, one clinician, and one epidemiologist was established before commencement of the study. Safety data were assessed and reviewed by the committee to ensure further proceeding of the study.

We used SAS (version 9.4) for all analyses. This trial is registered with ClinicalTrials.gov (NCT04383574).

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. All the authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Result

Between May 22 and June 1, 2020, 95 individuals were screened and 72 were enrolled in phase 1. Between June 12 and June 15, 2020, 499 individuals were screened and 350 were enrolled in phase 2. 421 (>99%) of 422 enrolled participants received at least one dose of

***Figure:* Trial profile**
*One participant was excluded from the per-protocol analysis because he received immunoglobulin within 7 days after the second dose. †One participant in the 3 μg group and one in the placebo group were mistakenly given each other's vaccine at the second dose. In the overall safety analysis, both participants were analysed as part of the 3 μg group. In the safety analysis of the second dose, each participant was analysed in the group corresponding to what they had actually received at the second dose. Both participants were excluded from the per-protocol immunogenicity evaluation. ‡Two participants in the 1·5 μg group were excluded from the per-protocol analysis (one did not have a blood sample taken 28 days after the second dose, and one was found not to meet the eligibility criteria after enrolment). §One participant in the 3 μg group was excluded from the per-protocol analysis because the second dose was given outside of the specified time window.

	1·5 µg group (n=100)	3 µg group (n=125)	6 µg group (n=123)	Placebo group (n=73)	p value*
Any adverse reaction	20 (20%)	25 (20%)	27 (22%)	15 (21%)	0·981
Grade 1	16 (16%)	24 (19%)	23 (19%)	13 (18%)	0·943
Grade 2	7 (7%)	4 (3%)	7 (6%)	4 (5%)	0·596
Local reactions	13 (13%)	15 (12%)	13 (11%)	3 (4%)	0·212
Pain	11 (11%)	14 (11%)	11 (9%)	3 (4%)	0·335
Erythema	2 (2%)	0	1 (1%)	1 (1%)	0·434
Pruritus	1 (1%)	1 (1%)	1 (1%)	0	1·000
Swelling	0	1 (1%)	1 (1%)	0	1·000
Systemic reactions	10 (10%)	13 (10%)	18 (15%)	12 (16%)	0·459
Fever	4 (4%)	4 (3%)	5 (4%)	1 (1%)	0·783
Fatigue	4 (4%)	4 (3%)	4 (3%)	1 (1%)	0·829
Diarrhoea	2 (2%)	2 (2%)	0	2 (3%)	0·323
Muscle pain	1 (1%)	2 (2%)	1 (1%)	2 (3%)	0·738
Nausea	1 (1%)	1 (1%)	0	3 (4%)	0·063
Headache	0	0	5 (4%)	0	0·0064
Mucocutaneous eruption	0	0	5 (4%)	0	0·0064
Cough	1 (1%)	1 (1%)	1 (1%)	1 (1%)	1·000
Anorexia	0	1 (1%)	2 (2%)	0	0·707
Hypoesthesia	0	0	0	2 (3%)	0·030
Dizziness	1 (1%)	0	0	1 (1%)	0·168
Abdominal distention	0	2 (2%)	0	0	0·341
Oral hypoesthesia	0	0	0	1 (1%)	0·173
Peripheral oedema	0	0	0	1 (1%)	0·173
Abdominal pain	0	0	0	1 (1%)	0·173
Vomiting	1 (1%)	0	0	0	0·411
Drowsiness	0	0	1 (1%)	0	0·703
Joint pains	0	0	0	1 (1%)	0·173
Rash	0	0	1 (1%)	0	0·703
Raised blood pressure	0	1 (1%)	0	0	1·000
Hypersensitivity	0	1 (1%)	0	0	1·000
Palpitation	0	0	0	1 (1%)	0·173

Data are n (%), representing the total number of participants who had adverse reactions (ie, adverse events related to vaccination). Results are broken down by phase and dose in the appendix (pp 3–9). *For differences across all groups.

Table 2: Adverse reactions reported within 28 days after the first and second doses of vaccine or placebo in phase 1 and phase 2

vaccine or placebo (72 in phase 1 and 349 in phase 2) and were included in the safety population (figure). 71 (99%) participants in phase 1 and 340 (97%) in phase 2 were eligible for the immunogenicity evaluation at day 28 after the second dose (per-protocol population; figure). The demographic characteristics of participants in the safety population were similar across treatment groups in terms of sex, mean age, height, weight, and ethnicity (table 1). The mean age of study participants in phase 1 was 65·8 years (SD 4·8), including 39 (54%) participants aged 60–64 years, 18 (25%) aged 65–69 years, and 15 (21%) aged 70 years or older. In phase 2, the mean age of the 349 treated participants was 66·6 years (SD 4·7), including 132 (38%) aged

60–64 years, 125 (36%) aged 65–69 years, and 92 (26%) aged 70 years or older.

The safety data of the phase 1 and phase 2 trial were combined for analysis because the same batches of vaccine and placebo and the same safety observation method were used. 87 (21%) of 421 participants reported at least one adverse reaction within 28 days of either vaccination, and the proportions of patients with any adverse reaction were similar across groups (table 2). All adverse reactions were either mild (grade 1) or moderate (grade 2) in severity. Most adverse reactions occurred within 7 days after vaccination and participants recovered within 48 h. The most common reactions were injection site pain (39 [9%] participants) and fever (14 [3%]). Except for a slightly higher incidence of headache and mucocutaneous eruption in the 6 µg group and a slightly higher incidence of hypoesthesia in the placebo group, there were no significant differences in the incidence of other injection site or systemic events among the four groups (table 2). As of Aug 28, 2020, eight serious adverse events have been reported by seven (2%) participants: four (4%) of 100 participants in the 1·5 µg group, one (1%) of 125 participants in the 3 µg group, two (2%) of 123 participants in the 6 µg group, and none of the 73 participants in the placebo group (p=0·240). All serious adverse events were considered to be unrelated to either the vaccine or the placebo (appendix p 10). The 6-month follow-up analysis is not yet complete, but no vaccine-related serious adverse events have been reported as of Jan 20, 2021.

In phase 1, none of the participants had any detectable neutralising antibody response against live SARS-CoV-2 at baseline (appendix p 11). The GMTs and sero-conversion rates of neutralising antibodies to live SARS-CoV-2 at day 28 showed no significant difference between the 3 µg group and 6 µg group after either the first vaccination (seroconversion 54·2% in the 3 µg group *vs* 62·5% in the 6 µg group) or second vaccination (100·0% *vs* 95·7%; table 3). Neutralising antibodies in all placebo recipients were negative after vaccination (appendix p 11). In an exploratory analysis by age, seroconversion rates at day 28 after the second dose of either 3 µg or 6 µg vaccine were higher than 88% in participants aged 60–64 years, 65–69 years, and 70 years or older, with the GMTs ranging from 33·3 to 89·1 (table 3, appendix p 13).

In phase 2, one participant in the 6 µg group was seropositive for SARS-CoV-2 neutralising antibody at baseline (appendix p 12). After the second dose of vaccine, there was no significant difference in seroconversion rate or GMT between the 3 µg group (seroconversion 98·0%) and the 6 µg group (99·0%; table 4). However, the seroconversion rates and GMTs of the 3 µg and 6 µg groups were significantly higher than those of the 1·5 µg group (table 4). All placebo recipients were negative for SARS-CoV-2 neutralising

	Day 28 after first dose			Day 28 after second dose		
	3 µg group	6 µg group	p value	3 µg group	6 µg group	p value
Seroconversion rate						
Total	13/24 (54·2% [32·8–74·5])	15/24 (62·5% [40·6–81·2])	0·558	24/24 (100·0% [85·8–100·0])	22/23 (95·7% [78·1–99·9])	0·489
60–64 years	8/12 (66·7% [34·9–90·1])	5/9 (55·6% [21·2–86·3])	0·673	12/12 (100·0% [73·5–100·0])	8/9 (88·9% [51·8–99·7])	0·429
65–69 years	3/6 (50·0% [11·8–88·2])	5/8 (62·5% [24·5–91·5])	1·000	6/6 (100·0% [54·1–100·0])	7/7 (100·0% [59·0–100·0])	1·000
≥70 years	2/6 (33·3% [4·3–77·7])	5/7 (71·4% [29·0–96·3])	0·286	6/6 (100·0% [54·1–100·0])	7/7 (100·0% [59·0–100·0])	1·000
Geometric mean titre						
Total	6·9 (4·6–10·2)	9·1 (6·4–13·0)	0·278	54·9 (38·6–78·2)	64·4 (41·5–99·7)	0·560
60–64 years	10·0 (5·7–17·8)	9·7 (4·9–19·4)	0·934	69·5 (38·9–124·2)	43·9 (15·9–120·7)	0·355
65–69 years	5·5 (2·3–13·1)	7·4 (3·2–17·4)	0·562	56·5 (35·7–89·6)	76·5 (32·5–178·4)	0·485
≥70 years	4·0 (1·6–10·0)	10·5 (6·0–18·4)	0·039	33·3 (13·4–82·8)	89·1 (57·6–137·8)	0·025

Seroconversion rates are n/N (% [95% CI]). Geometric mean titres are shown with 95% CIs.

Table 3: Neutralising antibody responses to live SARS-CoV-2 28 days after each dose in the phase 1 trial

	1·5 µg group	3 µg group	6 µg group	p value		
				1·5 µg vs 3 µg	1·5 µg vs 6 µg	3 µg vs 6 µg
Seroconversion rate						
Total	88/97 (90·7% [83·1–95·7])	96/98 (98·0% [92·8–99·8])	97/98 (99·0% [94·5–100·0])	0·029	0·010	1·000
60–64 years	34/36 (94·4% [81·3–99·3])	35/37 (94·6% [81·8–99·3])	38/38 (100·0% [90·8–100·0])	1·000	0·233	0·240
65–69 years	29/35 (82·9% [66·4–93·4])	33/33 (100·0% [89·4–100·0])	40/40 (100·0% [91·2–100·0])	0·025	0·0081	1·000
≥70 years	25/26 (96·2% [80·4–99·9])	28/28 (100·0% [87·7–100·0])	19/20 (95·0% [75·1–99·9])	0·482	1·000	0·417
Geometric mean titre						
Total	23·4 (19·4–28·3)	42·2 (35·2–50·6)	49·9 (42·2–58·9)	<0·0001	<0·0001	0·181
60–64 years	26·5 (20·2–34·7)	36·4 (26·2–50·6)	55·2 (43·4–70·1)	0·135	0·0001	0·041
65–69 years	21·1 (14·1–31·6)	44·5 (33·0–60·0)	50·4 (37·9–67·0)	0·0039	0·0005	0·545
≥70 years	22·7 (16·8–30·7)	48·2 (34·3–67·6)	40·2 (26·7–60·7)	0·0014	0·021	0·485

Seroconversion rates are n/N (% [95% CI]). Geometric mean titres are shown with 95% CIs.

Table 4: Neutralising antibody responses to live SARS-CoV-2 28 days after the second dose in the phase 2 trial

antibodies after vaccination (appendix p 12). In an exploratory analysis by age, seroconversion rates at day 28 after the second dose were higher than 94% in the 3 µg and 6 µg groups for participants aged 60–64 years, 65–69 years, and 70 years or older, with GMTs ranging from 36·4 to 55·2 (table 4; appendix p 13).

Discussion

We found that the two doses of CoronaVac were safe and well tolerated at doses of 1·5 µg, 3 µg, and 6 µg among adults aged 60 years and older. The incidence of adverse reactions in different dose groups was similar, indicating that there was no dose-related aggravation concern with regard to safety. Moreover, most adverse reactions were mild and transient, and injection site pain was the most reported symptom. The results were similar to our study of adults aged 18–59 years.[20] Our findings were also similar to the results of other inactivated COVID-19 vaccines in younger and older adults.[13,18,19]

None of the serious adverse events reported during the trial was related to vaccination. In our study, one case of pancreatitis was reported in the 3 µg group and was deemed to be unrelated to the receipt of the vaccine. Vaccine-related pancreatitis has been reported after the administration of other vaccines, such as vaccines against hepatitis A and hepatitis B (combined), hepatitis A, human papillomavirus (HPV), and measles, mumps, and rubella.[24,25] Among them, the combined hepatitis A and hepatitis B vaccine and the HPV vaccine contain an aluminium adjuvant. Bizjak and colleagues[24] pointed out that in conjunction with an aluminium adjuvant, the induction of immunity through molecular mimicry might culminate in the production of cytotoxic autoantibodies with a particular affinity for pancreatic acinar cells. Vaccine-induced pancreatitis is likely to be an underdiagnosed condition and can often be masked by the incidental presence of more commonly recognised causes, or it might simply be misdiagnosed as idiopathic pancreatitis.[24,25] We will carefully monitor the occurrence of pancreatitis in ongoing and future studies and through pharmacovigilance.

CoronaVac was immunogenic in adults aged 60 years and older. The neutralising antibody responses observed in the older adults who had received two vaccine doses of 3 µg or 6 µg were similar, and exceeded the response to the 1·5 µg dose. Phase 1 data showed that seroconversion rates and GMTs of neutralising antibodies were low before the second vaccination, which provides evidence for a two-dose immunisation schedule. In this study, the seroconversion rates in those who received 3 µg or 6 µg doses were over 95% after the two-dose vaccination, with GMTs ranging from 42·2 to 64·4—similar to the responses among adults aged 18–59 years who received 3 µg (seroconversion 97%; GMT 44·1) or 6 µg doses (100%; 65·4) of vaccine with the same immunisation schedule.[20] Thus, the preliminary results indicate that the responses to CoronaVac are not reduced in older adults.

In an exploratory analysis stratified by age, we did not observe significant differences in neutralising antibody responses after the second vaccination between age groups (60–64 years, 65–69 years, and ≥70 years) after the same doses of vaccine were given (appendix p 13). GMTs in phase 1 increased with age in recipients of the 3 µg dose, whereas they decreased with age in recipients of the 6 µg dose, although these trends were not statistically significant. By contrast, in phase 2, opposite trends in GMTs to those of phase 1 were observed (appendix p 13). In each age group, GMTs did not differ significantly between recipients of the 3 µg and 6 µg doses after the second injection, except in the group aged 70 years and older in phase 1 (p=0·025) and the group aged 60–64 years in phase 2 (p=0·041). Small sample sizes and large differences in immune responses to vaccination across older individuals might

account for these differences. We will assess the relationship between the immune response to CoronaVac and age in ongoing phase 3 trials (NCT004456959 and NCT04617483).

Although the correlates of protection have not yet been established for any COVID-19 vaccines in development, neutralising antibodies are evaluated in all clinical trials because of evidence of their association with protection against COVID-19 in animal challenge experiments.[21,26] Live virus neutralisation assays are laborious, time-consuming, and require biosafety level 3 conditions. Development of other assays to evaluate the antibody titres is necessary. In this study, we used only a neutralising antibody assay, which was a limitation of the study design. However, we assessed neutralising antibodies to live SARS-CoV-2 and anti-receptor-binding domain (anti-RBD) IgG antibodies in the study of adults aged 18–59 years, and a strong correlation between neutralising antibodies and anti-RBD IgG antibodies was found.[20]

This study has some further limitations. First, although much evidence supports the important role of a T cell response to COVID-19,[27] and such responses have been observed with use of mRNA vaccines and adenoviral-vectored vaccines,[9–12,28,29] those tests were not done in this study. However, we detected IFN-γ as an indicator of T-cell responses following vaccination in our phase 1 trial among adults aged 18–59 years, and the results showed that the responses induced by CoronaVac were low.[20] We will also assess the responses of type 1 and type 2 T-helper cells by CoronaVac in the ongoing phase 3 trial (NCT004456959). Second, at the time of the report, long-term immunogenicity and safety could not be evaluated, although the participants will be followed up for at least 1 year. Further results will be reported when data are available. Third, the study population were healthy older adults, and most of them were of Han ethnicity. Further studies are required to assess the efficacy of CoronaVac in various populations, including older people with chronic underlying diseases, and with ethnic and geographical diversity. Fourth, only a two-dose immunisation schedule with an interval of 28 days was used in this clinical trial. Antibody responses against viral infections such as SARS-CoV-2 infection, hepatitis A, and hepatitis B, could be induced within a relatively short time (1–2 weeks), which might be suitable for emergency use.[20,30] In our ongoing phase 3 clinical trial, a rapid immunisation schedule (with injections on days 0 and 14) is also being used in older adults to assess the efficacy of CoronaVac. Finally, the calculated p values presented in this study cannot support any powerful statistical conclusions, and are only for reference and should be interpreted with caution.

In conclusion, CoronaVac was well tolerated and induced humoral responses in adults aged 60 years and older, which supports the use of this vaccine in an older

population. Among the three doses evaluated, the neutralising antibody titres induced by the 3 μg dose were similar to those of the 6 μg dose, and higher than those of the 1·5 μg dose. Combined with the safety and production capacity, the 3 μg dose of CoronaVac with a two-dose immunisation schedule is being used in the ongoing phase 3 trials to assess protection against COVID-19.

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