Background document on the inactivated vaccine Sinovac-CoronaVac against COVID-19

Background document to the WHO Interim recommendations for use of the inactivated COVID-19 vaccine, CoronaVac, developed by Sinovac

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World Health Organization

Note. This background document was developed to inform the initial recommendation-making process. It will not be updated on a regular basis. The latest Grade and ETR tables can be obtained here: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-Sinovac-CoronaVac-GRADE-ETR

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Background

This background document was prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 Vaccines to inform the discussions of SAGE at its meeting on 29 April 2021, which resulted in the issuance of WHO interim recommendations for use of the inactivated COVID-19 vaccine, CoronaVac, developed by Sinovac. It is based on published data, data submitted to WHO for Emergency Use listing, and direct information shared by the company. Cut-off date of information included is 29 April 2021.

Recommendations, annexes the background document are available on the SAGE COVID-19 webpage: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials.

The Declarations of interests were collected from all external contributors and assessed for any conflicts of interest. Summaries of the reported interests can be found on the SAGE meeting webpage and SAGE Covid-19 Working Group webpage.

Context

Inactivated viral vaccines have been successfully used in immunization programmes for decades. Since they do not contain replicating virus, they are often a preferred product class for special populations, such as pregnant women and people who are immunocompromised. Inactivated vaccines frequently need to be given in multiple doses and often a booster dose is needed to maintain immunity.

Inactivated vaccines against SARS-CoV-2 are being developed by several vaccine manufacturers (1). The inactivated COVID-19 vaccine Sinovac-CoronaVac was developed by Sinovac. Sinovac-CoronaVac has been authorized as a 2-dose vaccine (3 μ per 0.5ml dose) for individuals aged 18 years and older. The proposed indication for emergency use listing (EUL) is a 2-dose schedule with a preferred interval of 14–28 days between doses. Sinovac-CoronaVac was granted conditional market authorization by the China National Medical Products Administration (NMPA) on 6 February 2021 and has since been granted emergency authorization in 32 countries or jurisdictions (at the time of writing). As of 21 April 2021, more than 260 million doses have been distributed to the public in China and elsewhere, and more than 160 million individuals have been vaccinated. The vaccine is currently being evaluated in several trials and is licensed under emergency use authorizations in several countries and territories (2):

- Conditional approval: China.
- Emergency use: Algeria, Benin, Botswana, Brazil, Cambodia, Chile, China (Hong Kong Special Administrative Region), Colombia, Djibouti, Dominica, Ecuador, El Salvador, Gabon, Georgia, Guinea, Guyana, Indonesia, Malaysia, Mexico, Morocco, Myanmar, Pakistan, Paraguay, Philippines, Thailand, Togo, Tunisia, Turkey, Ukraine, Uruguay, Zimbabwe.

All authorized indications are for individuals 18 years and older, with the exception of Colombia, El Salvador, Thailand and Tunisia (18–59 years), and Uruguay (18–70 years).

The following information is derived from the product information supplied in the context of the WHO Emergency Use Listing Process, Sinovac responses to questions from the SAGE Working Group, published articles and preprints, and other sources. Sinovac has given permission for unpublished data from the EUL process to be made public in this background paper.

Characteristics of Sinovac-CoronaVac vaccine against COVID-19

Sinovac-CoronaVac is a Vero cell-based, aluminium hydroxide-adjuvanted, β-propiolactone-inactivated vaccine based on the CZ02 strain. This strain of SARS-CoV-2 was isolated from the bronchoalveolar lavage of a hospitalized patient and is closely related to the 2019-nCoV-BetaCoV Wuhan/WIV04/2019 strain (3).

Composition

The final vaccine product in each 0.5 ml dose is composed of 3 μg of inactivated SARS-CoV-2 virus. The excipients are aluminium hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride, and water for injection (4). The vaccine does not contain preservatives.

None of the excipients are of animal or human origin. The excipients are well established for use in pharmaceutical products.

Stability

Of the nine finished product batches, three have completed long-term stability observation for six months; no significant change was found in any of the test items (4). The other six batches have completed long-term stability observation for 3 months; the antigen content of each batch of finished product of Sinovac-CoronaVac did not decrease significantly after dissociation.

Shelf-life

In line with the results of an accelerated stability study, the period of validity of the vaccine was tentatively determined by the China National Medical Products Administration (NMPA) to be 2 years at 2–8 °C, and by Agência Nacional de Vigilância Sanitária (ANVISA) to be 1 year at 2–8 °C (4). Each batch of finished product of Sinovac-CoronaVac will continue to be monitored in accordance with the stability study plan.

Drug product description

The dosage form of the vaccine is injectable liquid. Sinovac-CoronaVac is a milky-white suspension. Stratified precipitate may form, which can be dispersed by shaking. No clumps should be found on shaking. The vaccine is available in a single-dose vial or prefilled syringe.

Container

Each vial or prefilled syringe is packed in a single box.

Pharmacokinetics

As neither the delivery system nor the adjuvant used in the development or in the final formulation of Sinovac-CoronaVac is new, human pharmacokinetic studies were not performed.

Preclinical studies

Reproductive and developmental toxicity

The vaccine was injected intramuscularly in 336 Sprague-Dawley rats at doses of 1.5 µg and 6 µg during the period from before mating to the delivery of pup (4). The males were vaccinated before mating on days 1, 8, 15 and 28 and the females were vaccinated before mating on days 1, 8 and 15. Mating occurred one week after the last administration to male rats. Female rats were also vaccinated on gestational day 6 and postnatal day 7. Caesarean sections were performed on half of the pregnant females on gestational day 20 for embryo observation; the other females gave birth and suckled their pups until the end of the lactation period. No significant adverse effect was observed on the growth or fertility of parental female and male rates, or on gestation and lactation in female rats. No developmental toxicity and teratogenicity was seen in the embryos and fetuses, and no effect on the growth and development of F1 pups was observed. The no observed adverse effect level (NOAEL) of the vaccine on the fertility of parental male and female rats, pregnancy, and lactation of parental female rats, embryo-fetal developmental toxicity and teratogenicity, and physical and reflex development of F1 offspring was 6 µg.

Immunogenicity

Following the NMPA guidance for the safety evaluation (non-clinical studies) of pharmaceuticals, the following non-clinical studies of Sinovac-CoronaVac were completed: immunogenicity study and virus challenge studies to determine the possible dosage and schedule of the vaccine, as evidence for clinical application and preliminary evidence of efficacy; general safety evaluation, including single-dose toxicity, repeated-dose toxicity, active systemic anaphylaxis, local tolerance and reproductive toxicity studies, designed to evaluate both the efficacy and safety of the COVID-19 vaccine and to provide supportive evidence for developing clinical studies.

The immunogenicity of Sinovac-CoronaVac was assessed in BALB/c mice given two doses of 0, 1.5, 3 or 6 µg on a 0/7-day schedule (3). No adverse effect or inflammation was observed. Immunogenicity and protective efficacy were assessed in rhesus macaques. The animals were immunized on a 3-dose schedule at 0/7/14 days, with either 3 or 6 µg of vaccine, placebo (adjuvant) or saline. The vaccine was immunogenic at both doses. On day 22 (one week after the third vaccination), 106 $TCID_{50}$ of SARS-CoV-2 CN1 was inoculated intratracheally

into the macaques' lungs. By 3–7 days after inoculation, all control animals exhibited a high load (10^4 to 10^6/ml) of viral genomic RNA in the pharynx, rectum, and lung, as well as severe interstitial pneumonia. All vaccinated animals had mild and focal histopathological changes in a few lobes of lung. Viral RNA was detected in the vaccinated animals, but by day 7 after inoculation all four macaques that received the high dose had no detectable viral load in the pharynx, rectum, or lung. While viral RNA was detected in more animals in the lower-dose group, the load was about 95% lower than that seen in the group given saline. There was no evidence of antibody-dependent enhancement with the limited time interval between vaccination and challenge.

Clinical studies

The pivotal safety, efficacy and immunogenicity data informing registration of the vaccine are derived from several ongoing studies (see Table 1).

Table 1. Overview of clinical studies of Sinovac-CoronaVac (as of 4 March 2021).[a]

Study Name Trial Registration	**Sponsor**	**Phase (primary outcome)**	**Location(s)**	**No. of participants Eligible age groups**	**Dosing regimens**	**Study status**
Corona-01 NCT04352608	Sinovac Research and Development Co., Ltd.	Phase 1/2 (safety and immunogenicity)	China	Phase 1: 144 healthy participants 18–59 years	2 doses, 0/14 or 0/28 day schedule Medium dose: 3 µg per 0.5-ml dose High dose: 6 µg per 0.5-ml dose	Complete
				Phase 2: 600 healthy participants 18–59 years	2 or 3 doses, 0/14, 0/28 or 0/28/56 day schedule Medium dose: 3 µg per 0.5-ml dose High dose: 6 µg per 0.5-ml dose	
Corona-02 PRO-nCOV-1002 NCT04383574	Sinovac Research and Development Co., Ltd.	Phase 1/2 (safety and immunogenicity)	China	Phase 1: 72 healthy participants ≥60 years	2 doses 0/28 day schedule Medium dose: 3 µg per 0.5-ml dose High dose: 6 µg per 0.5-ml dose	Complete
				Phase 2: 350 healthy participants ≥60 years	2 doses, 0/28 day schedule Low dose: 1.5 µg per 0.5-ml dose Medium dose: 3 µg per 0.5-ml dose High dose: 6 µg per 0.5-ml dose	
Corona-03 PRO-nCOV-1003 NCT04551547	Sinovac Research and Development Co., Ltd.	Phase 1/2 (safety and immunogenicity)	China	522 healthy participants 3–17 years	2 doses, 0/28 day schedule Low dose: 1.5 µg per 0.5-ml dose Medium dose: 3 µg per 0.5-ml dose	Results pending
Corona-04 PRO-nCOV-3001 NCT04617483	Sinovac Research and Development Co., Ltd.	Phase 3 (immunobridge to commercial lot and immunobridge to elderly; single-arm)	China	1040 healthy participants ≥18 years 25% of participants ≥60 years	2 doses, 0/14 day schedule 3 µg per 0.5-ml dose	Complete
PROFISCOV NCT04456595	Butantan Institute	Phase 3 (vaccine efficacy and safety)	Brazil	12 688 healthy participants ≥18 years, health care workers who treat patients with COVID-19	2 doses, 0/14 day schedule 3 µg per 0.5-ml dose	Interim results available
CoV2-0320 NCT04508075	PT Bio Farma	Phase 3 (vaccine efficacy and lot-to-lot consistency)	Indonesia	1620 healthy participants 18–59 years	2-doses, 0/14 day schedule 3 µg per 0.5-ml dose	Interim results available
9026-ASI NCT04582344	Health Institutes of Turkey	Phase 3 (vaccine efficacy)	Turkey	13 000 healthy participants 18–59 years First cohort: health care workers in the high-risk group (K-1) Second cohort: people at normal risk (K-2)	2 doses, 0/14 day schedule 3 µg per 0.5-ml dose	Top line results available

Study Name Trial Registration	**Sponsor**	**Phase (primary outcome)**	**Location(s)**	**No. of participants** **Eligible age groups**	**Dosing regimens**	**Study status**
CoronaVac3CL NCT04651790	Pontificia Universidad Catolica de Chile	Phase 3 (safety and immunogenicity, comparing 2 schedules)	Chile	2300 healthy participants ≥18 years 40% of participants ≥60 years	2 doses, 0/14 and 0/28 day schedule 3 µg per 0.5-ml dose	Interim results available
COV-04-IB NCT04747821	Butantan Institute	Phase 4 (stepped-wedge cluster-randomized open-label vaccine effectiveness)	Brazil	30 000 healthy participants ≥18 years	2 doses 0/28 day schedule 3 µg per 0.5-ml dose	Active, not recruiting
NCT04756830	D'Or Institute for Research and Education	Phase 4 (single-group assignment, open label, safety and immunogenicity)	Brazil	1200 healthy participants ≥18 years	2 doses, 0/14 day schedule 3 µg per 0.5-ml dose	Not yet recruiting
NCT04754698	University of São Paulo General Hospital	Phase 4 (single-group assignment, open label, immunogenicity)	Brazil	2067 participants, persons with rheumatic diseases, persons living with HIV/AIDS and healthy controls ≥18 years	2 doses, 0/21–28 day schedule 3 µg per 0.5-ml dose	Recruiting
CHEMOCOVAC NCT04765215	Namik Kemal University	Phase 4 (single-group assignment, open label, immunogenicity)	Turkey	291 breast or lung cancer patients receiving active chemotherapy and healthy controls 18–90 years	2-doses schedule 3 µg per 0.5-ml dose	Not yet recruiting
NCT04751721 NCT04751695	Izmir Bakircay University	Phase 4 (single-group assignment, open label, oxidative stress)	Turkey	40 healthy participants 35–65 years (different trials for females and males)	2 doses, 0/24 day schedule 3 µg per 0.5-ml dose	Not yet recruiting
NCT04775069	Humanity & Health Medical Group Limited	Phase 4 (single-group assignment, open label, Sinovac-CoronaVac, BNT162b2 and AZD1222)	China (Hong Kong SAR)	900 participants with chronic liver disease ≥18 years	2 doses, 0/28 day schedule 3 µg per 0.5-ml dose	Not yet recruiting

[a] Studies were randomized controlled trials unless otherwise indicated.

During early clinical development, work was undertaken to evaluate both a 0/14 day emergency schedule and a 0/28 day routine schedule, the former of which was taken forward in efficacy trials. The clinical data package, available as of 21 April 2021, consists of assessments of safety and immunogenicity in three trials in China (participants ≥18 years of age), safety and efficacy in a phase 3 trial in health care workers treating COVID-19 patients in Brazil (immunogenicity pending), safety, immunogenicity and efficacy in a phase 3 trial in Indonesia, safety and immunogenicity in a phase 3 trial in Chile, and efficacy results from a phase 3 study in Turkey (Table 1, Appendix 1). A paediatric safety and immunogenicity phase 1/2 trial is ongoing in China. Two vaccine effectiveness assessments have been reported from Brazil and Chile, and a large phase 4 vaccine effectiveness stepped wedge study cluster-randomized trial is under way in Brazil. Other ongoing or planned clinical studies are assessing safety and immunogenicity in special populations, such as persons living with HIV/AIDS, rheumatic disease, chronic liver disease, and breast or lung cancer receiving active chemotherapy (Table 1).

The number of trial participants who received at least one dose of Sinovac-CoronaVac and contributed to the safety, immunogenicity, and efficacy analyses are shown in Table 2, stratified by age and whether the vaccine administered was of the authorized dose and schedule (0/14-28 days) or an alternative dose or schedule.

Table 2. Number of trial participants who received at least one dose of Sinovac-CoronaVac and are included in the clinical database available as of 21 April 2021 (from trials in Brazil, Chile, China, Indonesia and Turkey).

	Age group (years)	Authorized dose/schedule	Alternative dose/schedule	Total by age	Total all ages
Safety	18–59	7603	288	7891	8840
	≥60	726	223	949	
Immunogenicity	18–59	1589	288	1987	2608
	≥60	398	223	621	
Efficacy	18–59	12 098	0	12 098	12 310
	≥60	212	0	212	

Immunogenicity studies in humans

Clinical trials demonstrated that Sinovac-CoronaVac is immunogenic both in adults aged 18–59 years and in older adults ≥60 years. Initial indications are that titres decline by 3 months after dose 2. Geometric mean titres (GMTs) in different studies need to be interpreted in the context of the different labs performing the neutralization assays, vaccination schedule (0/14 days or 0/28 days) and the number of days post-vaccination that sera were collected.

Immunogenicity data are available from two clinical studies in China: Corona-01 (4, 5), a phase 1/2 study in individuals aged 18–59 years, and Corona-02 (4, 6), a phase 1/2 study in individuals ≥60 years of age. Data are also available from Corona-04 (4), a phase 3 immunobridging study in younger and older adults, the clinical study report from a phase 3 study in Indonesia (7), and a preliminary analysis from the phase 3 trial in Chile (8). The immunogenicity results, based on neutralizing antibody, are presented here.

Data are available up to 28 days after the second dose for most schedules and age groups, and for 3 months after the second dose from Indonesia. Across all age groups and studies, seroprotection/seroconversion was high, although neutralizing GMTs varied.

Corona-01 was a phase 1/2, randomized, double-blind placebo-controlled trial, involving SARS-CoV-2 antibody-negative, polymerized chain reaction (PCR)-negative healthy individuals aged 18–59 years (4, 5). A total of 144 healthy adults were enrolled in phase 1, which evaluated two doses (3 μg and 6 μg) and two vaccination schedules (an emergency vaccination schedule (day 0/14) and a routine vaccination schedule (day 0/28). Individuals were randomized 2:1 to receive Sinovac-CoronaVac or placebo. The primary endpoint of phase 1 was the incidence of adverse reactions following vaccination, with immunogenicity as secondary outcome. Phase 2 involved 600 healthy adults and evaluated two emergency schedules (day 0/14 and day 0/14/42), two routine schedules (day 0/28 and day 0/28/56), and two doses. For each vaccination schedule, participants were randomized 2:2:1 to receive 3 μg, 6 μg or placebo. The primary endpoints of phase 2 were the seroconversion rate of neutralizing antibody 14 days (emergency schedule) or 28 days (routine schedule) after the second vaccination, and the incidence of adverse reactions after each vaccination.

For the emergency schedule (0/14 days), in the small phase 1 study of 24 participants aged 18–58 years receiving 3 µg, seropositivity peaked 14 days after vaccination at 46% (95%CI 26 - 67); in the phase 2 study of 118 participants in the same age group, seropositivity was 92% (95%CI 86- 97) on the same day (Table 3) (4, 5). Neutralizing antibody titres were also significantly higher in the phase 2 trial (28, 95% CI 23- 34) compared with the small phase 1 trial (6, 95%CI 4- 9).

For the routine schedule (0/28 days), seropositivity peaked 28 days after the second dose, reaching 83% (95%CI 62- 95) in the phase 1 study and 97% (95%CI 93- 100) in the phase 2 study (Table 3) (4). Neutralizing antibody titres were comparable with those seen on the emergency schedule. With the exception of the small phase 1 trial results in participants vaccinated on days 0/14, immunogenicity was comparable across schedules. It is recognized that relatively few participants were vaccinated with the authorized dose.

The phase 3 trial in Indonesia, which was a lot-to-lot consistency trial of the authorized dose and also assessed efficacy, provided interim longer-term immunogenicity results in nearly 400 Sinovac-CoronaVac recipients aged 18–59 years (7). The dosing schedule was 0/14-21 days. Fourteen days after the second dose, 96% (95%CI 93-97) of participants were seropositive with a GMT of 16 (95%CI 15- 17), which is comparable to results from other trials. By 3 months after the second dose, 84% (95%CI 80- 87) of participants had detectable neutralizing antibodies with a GMT of 7 (95%CI 7- 8). Seropositivity over time and titre needed to determine longer-term protection is unknown and will need to be evaluated with further clinical data.

Table 3. Neutralizing antibody seropositivity (titre≥1:4) and GMTs available to date from clinical studies for the authorized 3 µg dose, by age group.

a) 0/14 day schedule

		18–59 years							Older adults ≥60 years	
		China Corona-01 Phase 1	China Corona-01 Phase 2	China Corona-04[a] Phase 3	China Corona-04[a] Phase 3	China Corona-04[a] Phase 3	Indonesia Phase 3	Chile Phase 3	China Corona-04 Phase 3	Chile Phase 3
Time point		**N=24**	**N=118**	**N=251**	**N=248**	**N=499**	**N=397**	**N=23**	**N=251**	**N=10**
Before vaccination	Seropositive (%) (95%CI)	0 (0–14)	0 (0–3)	0 (0–1)	0 (0– 1)	0 (0–1)	0 (0–1)	n.d	0 (0.00–1.46)	n.d.
	GMT (95%CI)	2 (2–2)	2 (2–2)	2 (2–2)	2 (2–2)	2 (2–2)	2 (2–2)	n.d	2 (2–2)	n.d
14 days after second dose	Seropositive (%) (95%CI)	46 (26–67)	92 (86–97)	93 (89–96)	91 (86–94)	92 (89–94)	96 (93–97)	94 (n.d.)	82 (77–87)	90 (n.d.)
	GMT (95%CI)	6 (4–9)	28 (23–34)	18 (16–20)	19 (16–21)	18 (17–20)	16 (15–17)	16 (10–26)	12 (11–13)	39 (10–163)
28 days after second dose	Seropositive (%) (95%CI)	25 (10–47)	94 (88–98)	n.d.	n.d.	n.d.	n.d.	96 (n.d.)	n.d.	100 (n.d.)
	GMT (95%CI)	5 (4–8)	24 (21–28)	n.d.	n.d.	n.d.	n.d.	18 (9–33)	n.d.	49 (22–106)
90 days after second dose	Seropositive (%) (95%CI)	n.d.	n.d.	n.d.	n.d.	n.d.	84 (80–87)	n.d	n.d.	n.d
	GMT (95%CI)	n.d.	n.d.	n.d.	n.d.	n.d.	7 (7–8)	n.d	n.d.	n.d

[a] The component of Corona-04 that compared the pilot scale to commercial scale comprised participants aged 26–45 years. The immunobridging component compared adults aged 18–59 years with those ≥60 years.

b) 0/28 day schedule

		18–59 years		Older adults ≥60 years	
		China Corona-01 Phase 1	China Corona-01 Phase 2	China Corona-02 Phase 1	China Corona-02 Phase 2
Time point		**N=24**	**N=118**	**N=24**	**N=98**
Before vaccination	Seropositive (%) (95%CI)	0 (0–14)	0 (0–3)	0 (0–14)	0 (0–4)
	GMT	2 (2–2)	2 (2–2)	2 (2–2)	2 (2–2)
14 days after second dose	Seropositive (%) (95%CI)	79 (58–93)	n.d.	n.d.	n.d.
	GMT (95%CI)	16 (10–25)	n.d.	n.d.	n.d.
28 days after second dose	Seropositive (%) (95%CI)	83 (63–95)	97 (93–100)	100 (86–100)	98 (93–100)
	GMT (95%CI)	19 (13–27)	44 (37–52)	55 (39–78)	42 (35–51)
90 days after second dose	Seropositive % (95%CI)	n.d.	n.d.	n.d.	n.d.
	GMT (95%CI)	n.d.	n.d.	n.d.	n.d.

Individuals aged ≥60 years

Immunogenicity data are currently available for participants aged ≥60 years receiving the authorized dose of Sinovac-CoronaVac (3 µg) in the phase 1/2 trial Corona-02 (0/28-day schedule) (4, 6), the phase 3 immunobridging study Corona-04 (0/14-day schedule) (4), and the phase 3 trial in Chile (0/14-day schedule) (8). Seropositivity in older adults was high in all studies, although GMTs in some studies were lower than those in younger adults aged 18–59 years.

Corona-02 was a phase 1/2, randomized, double-blind placebo-controlled trial, involving SARS-CoV-2 antibody-negative, PCR-negative healthy individuals aged ≥60 years (4, 6). A total of 72 healthy adults were enrolled in phase 1, which evaluated the administration of 3 µg of vaccine on the routine schedule (day 0/28). Individuals were randomized 2:1 to receive Sinovac-CoronaVac or placebo. The primary endpoint of phase 1 was the incidence of adverse reactions following vaccination, with immunogenicity as secondary outcome. Phase 2 involved 350 healthy older adults and evaluated three different doses (1.5 µg, 3 µg, and 6 µg) on a 0/28 day schedule. The primary endpoint of phase 2 was the seroconversion rate of neutralizing antibodies 28 days after the second vaccination.

In Corona-02, seropositivity and GMTs were similar in the ≥60-year age group across phase 1 and 2 (Table 2b), with GMTs of 54.9 (95%CI 38.6–78.2) and 42.2 (95%CI 35.2–50.6), respectively, 28 days after the second dose (4).

Corona-04 was a phase 3, randomized, immunobridging trial, comparing the immunogenicity of the pilot- and commercial-scale product, and immunobridging older adults to younger adults on the 0/14 day schedule (Table 3a) (9). The immunogenicity of the commercial-scale product was not inferior to that of the pilot-scale product. Immunogenicity in the elderly group did not meet non-inferiority criteria compared with the adult group. GMTs in older adults were notably lower in Corona-04 than in Corona-02, although it should be noted that Corona-04 had a 14-day interdose interval and immunogenicity was measured only 14 days after the second dose, while Corona-02 had a 28-day interdose interval and immunogenicity was measured 28 days after the second dose. Both these factors may have contributed to the difference seen. Neutralizing antibody was assessed in just 10 individuals ≥60 years in the interim analysis of the phase 3 study in Chile, but the results were consistent within the limitations of the small sample size (8).

Efficacy

The most complete analysis of vaccine efficacy of Sinovac-CoronaVac is based on interim data from PROFISCOV, conducted by Instituto Butantan (10). Interim vaccine efficacy estimates have also been provided from phase 3 trials in Indonesia (conducted by PT Bio Farma) (7) and Turkey (conducted by Health Institutes of Turkey) (11).

PROFISCOV is a multicentre, randomized, double-blind, placebo-controlled and endpoint-driven phase 3 clinical trial (10). The study was conducted in 16 clinical research centres in Brazil. The participants were healthy, non-pregnant, non-breastfeeding health care professionals aged ≥18 years, who worked in direct contact with suspected or confirmed cases of COVID-19 in their daily work and were fully exposed to the risk of infection by SARS-CoV-2. Prior history of COVID-19 disease or positive test result was not an exclusion criterion. This study enrolled 12 408 participants, of whom approximately 5% were aged ≥60 years. Trial participants were randomly assigned to vaccine or placebo group on a 1:1 ratio to receive two doses of Sinovac-CoronaVac (3 μg/0.5 ml) or placebo on a 0/14-day schedule. Visits were scheduled for days 1, 14, 28, 56, 91, 182, 273, and 364 after the first dose.

The primary objectives of PROFISCOV were as follows.

1. To evaluate the efficacy of two doses of Sinovac-CoronaVac against virologically confirmed COVID-19, two weeks after the second vaccination, among participants aged 18 years or older who worked as health care professionals in direct contact with people with possible or confirmed COVID-19.

2. To describe the occurrence of adverse reactions associated with the administration of each of two doses of Sinovac-CoronaVac up to one week after vaccination in adults (18–59 years of age) and elderly participants (≥60 years) working as health care professionals in direct contact with people with possible or confirmed COVID-19.

Confirmed COVID-19 cases for the primary outcome were defined in line with the NMPA recommendation: (1) at least two consecutive days with one or more specific symptoms (cough, newly developed taste or smell disorders, shortness of breath or dyspnoea); or (2) with two or more nonspecific symptoms (fever (axillary temperature ≥37.5 ℃), chills, sore throat, fatigue, nasal congestion or runny nose, body pain, muscle pain, headache, nausea or vomiting, or diarrhoea); or (3) imaging features of COVID-19; and (4) detection of SARS-CoV-2 nucleic acid in respiratory swab by PCR. The original protocol definition was any COVID-19 symptom lasting for more than 2 days and detection of SARS-16 CoV-2 nucleic acid in respiratory swab by PCR.

Box 1. Case definition used in the study: severe case[a]

The **case definition for a severe COVID-19** case used in the study was a laboratory-confirmed case of SARS-CoV-2 infection with one or more of the following conditions:

- clinical signs at rest indicating severe systemic disease (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, oxygen saturation ≤ 93% at room temperature at sea level or PaO2/FiO2 <300 mm Hg);
- respiratory failure (defined as the need for high-flow supplemental oxygen, non-invasive ventilation, mechanical ventilation or extracorporeal oxygenation);
- evidence of shock (systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or need for vasopressors);
- major acute renal, hepatic or neurological dysfunction;
- admission to the intensive care unit;
- death.

[a] The case definitions used were developed by the manufacturer and differ from WHO standard definitions of COVID-19 disease severity which can be found in: COVID-19 Clinical management: living guidance (https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1, accessed 16 March 2021).

Clinical progression scale for SARS-CoV-2 infection

All cases of SARS-CoV-2 infection were classified according to the scale of clinical progression proposed by the World Health Organization (12). Hospitalized cases (score 4 or higher) were evaluated daily until the symptoms resolved. For non-hospitalized cases, the maximum score and duration of symptoms were recorded (score 1–3).

A Clinical Endpoint Adjudication Committee (CEAC), comprising experts in the field of COVID-19 vaccine research, was constituted to evaluate primary endpoint events and to make sure that each event included in the analysis met the definition of the clinical trial protocol. Committee members did not participate as principal or co-investigators, and their review was intended to ensure that the reports were adequate and unbiased, and that clinical endpoints were reviewed in a blinded manner. The primary function of the CEAC was to review in detail each case reported by the investigator as a possible study endpoint and to determine whether the case met the definition in the clinical trial protocol or the definition finally determined by the CEAC.

Cox proportional risk regression was used to generate efficacy estimates, with group and age stratification (18–59 years and ≥60 years) as fixed effect to evaluate vaccine efficacy. Point estimates of vaccine efficacy (VE) were calculated using the formula 100 × (1 – HR), where HR is the risk ratio; the bounds of confidence intervals were similarly converted.

Results of the PROFISCOV phase 3 VE study among Brazilian health care workers

In the PROFISCOV clinical trial, a total of 12 396 subjects were included in the intention-to-treat analysis set, including 11 764 aged 18–59 years and 632 aged ≥60 years (10). The subjects were divided into two groups: 6195 received the vaccine and 6201 placebo. The mean age of participants was 39.5 years, and 5.1% were aged ≥60 years; 36% of participants were male. There was no significant difference in demographic and other baseline characteristics between the vaccine group and placebo group.

The median follow-up time to date is 73 days after the second dose (11). A total of 253 cases were reported up to the time of data cut-off: 85 cases in the Sinovac-CoronaVac group (incidence density 11.0/100 person-years) and 168 cases in the placebo group (incidence density 22.3/100 person-years). The per-protocol estimate of vaccine efficacy against COVID-19 of any severity was 50.7% (95%CI 35.9, 62.0) (Table 4).

Table 4. Vaccine efficacy in health professionals in direct contact with COVID-19 patients, interim per protocol analysis, PROFISCOV trial (NCT04456595)

	Vaccine group		Placebo group		Vaccine efficacy (%) (95% CI)
Group/subgroup	**No. at risk**	**No. of cases**	**No. at risk**	**No. of cases**	
Overall	4953	85	4870	168	50.7 (35.9–62.0)
Hospitalization (grade 4+)	4953	0	4870	10	100.0 (56.4–100.0)
Severe	4953	0	4870	6	100.0 (16.9–100.0)
Sex					
Male	1806	33	1698	52	41.9 (10.1–62.4)
Female	3147	52	3172	116	54.7 (37.2–67.3)
Age group					
18–59 years	4741	83	4663	164	50.7 (35.8–62.1)
≥60 years	212	2	207	4	51.1 (–166.9–91.0)
Interdose interval					
<21 days	4184	77	4148	149	49.1 (33.0–61.4)
21–28 days	769	8	722	19	62.3 (13.9–83.5)
Comorbidity[a]					
Any	2731	44	2730	86	48.9 (26.6–64.5)
Cardiovascular disease	621	6	608	10	39.5 (–66.4–78.0)

	Vaccine group		Placebo group		Vaccine efficacy (%)
Group/subgroup	**No. at risk**	**No. of cases**	**No. at risk**	**No. of cases**	**(95% CI)**
Hypertension	335	0	330	7	100.0 (28.4–100.0)
Obesity	1099	13	1112	50	74.9 (53.7–86.4)
Type 2 diabetes mellitus	175	3	159	5	48.6 (–115.3–87.7)
Baseline exposure to SARS-CoV-2					
Unexposed	3637	67	3587	133	50.5 (33.6–63.1)
Exposed	401	3	408	6	49.5 (–101.8–87.4)

[a] Comorbidities for which there were too few data to evaluate were asthma, cancer, chronic kidney disease, chronic obstructive pulmonary disorder (COPD), HIV infection, immunocompromised, liver disease, and neurological conditions.

Subgroups

Adults aged 60 years and above. A total of 632 participants were aged 60 years or above, 419 of whom were in per protocol set. To date, six COVID-19 cases have occurred in this age group, for an overall vaccine efficacy against COVID-19 of any severity of 51.1% (95%CI –166.9, 91.0) (10). Only one case of severe COVID-19 occurred in this age group, in the placebo arm, and thus there were too few cases to assess protection against severe disease in this age group (9).

Hospitalized and severe disease. The vaccine was efficacious against hospitalization for COVID-19 (WHO severity score ≥4) at 100.0% (95%CI 16.9, 100.0), with 10 cases in the placebo group and none in the vaccine group (10). Vaccine efficacy against severe COVID-19 as per the trial case definition was 100.0% (95%CI 16.9, 100.0), with no cases in the vaccine group and six in the placebo group. In this study, one COVID-19 death occurred in the placebo group.

Comorbidities. Vaccine efficacy was similar among participants with any comorbidity (VE=48.9%, 95%CI 26.6, 64.5). Vaccine efficacy against COVID-19 was demonstrated in participants with hypertension (VE=100.0%, 95%CI 28.4,100.0) (9) and obesity (VE=74.9%, 95%CI 53.7, 86.4) (10). The number of cases was too small to allow vaccine efficacy to be assessed among participants with comorbidities within age groups.

Asymptomatic infection. Asymptomatic infection was not assessed. Seroconversion could be used in the future as a proxy for asymptomatic infection.

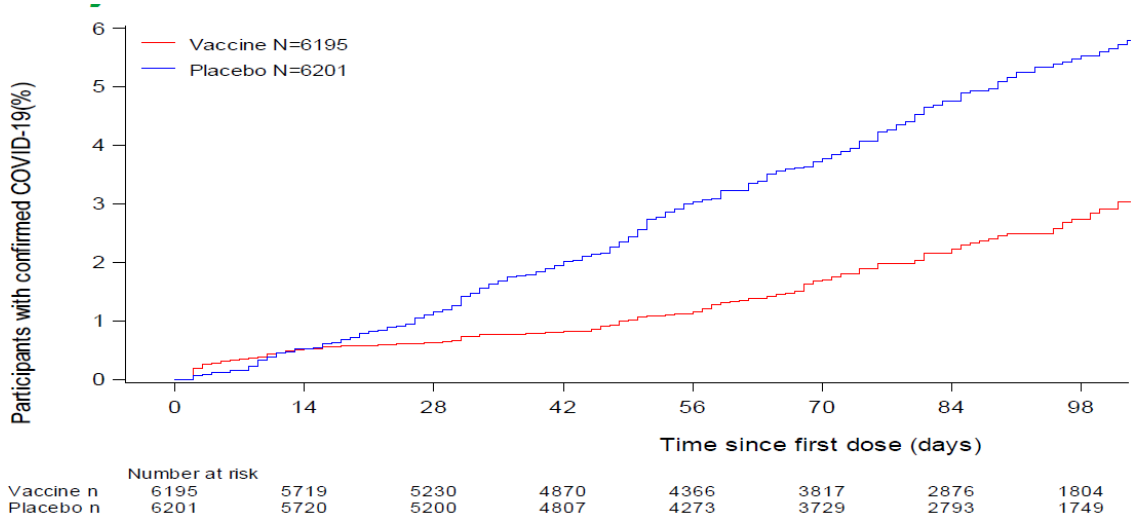
Interdose interval. Although the protocol schedule was 0/14 days, some participants received their second dose later. There was a suggestion that vaccine efficacy may be higher with a vaccination interval of at least 21 days (VE=62.3%, 95%CI: 13.9, 83.5) compared with an interval of less than 21 days (49.1%, 95%CI: 33.0, 61.4) (10). Additional data will be needed to determine whether there is a true difference in efficacy with increased dose interval.

Prior exposure to SARS-CoV-2. A total of 8033 participants (81.8%) had baseline nucleic acid detection or serum antibody test results. The nucleic acid detection and serum antibody test results of 7224 participants (89.9%) were negative (i.e. they were unexposed) before immunization, and those of 809 subjects (10.1%) were positive (exposed) before immunization (10). Vaccine efficacy in unexposed participants was 50.5% (95% CI: 33.6, 63.1) and in exposed participants 49.5% (95% CI: –101.8, 87.4).

Consistency and duration of protection

Figure 1 shows the cumulative incidence curve for PCR-confirmed COVID-19 disease among trial participants by trial arm. During the 14 days after the first dose, there was one additional case in the vaccine group than in the placebo group for a vaccine efficacy of -3.3% (95% CI: –4.8, –1.9) (10). An increased risk in the 14 days after the first dose was also detected in a post-licensure vaccine effectiveness study in Brazil (described in the section Vaccine effectiveness) (13). Data from other Phase 3 trials in Indonesia and Turkey will be important to give support to or refute this interim finding.

Figure 1. Cumulative incidence curve for PCR-confirmed SARS-CoV-2 symptomatic infection among vaccine and placebo recipients by time since first dose (data cut-off 16 December 2020)[a]



[a] Reproduced from ref. 10. By permission.

Figure 1 also suggests a variable rate of disease acquisition in the vaccine group relative to the placebo group over the duration of follow up. Cumulative vaccine efficacy after the first dose peaked at 60.4% (95%CI: 56.5, 63.9) within 56 days after the first dose, then gradually decreased with extended follow up to 52.5% (95%CI: 51.9, 53.1) within 98 days after the first dose (10). This may be an indication of waning immunity that will require further monitoring to evaluate and determine whether a booster dose may be necessary.

Results from other phase 3 studies

Top line, interim results are available for other phase 3 studies in Indonesia (7) and Turkey (11). The characteristics of these are given in Table 5. Vaccine efficacy against COVID of any severity was 83.5% (95%CI 65.4, 92.1) in Turkey (11) and 65.3% (95%CI 20.0, 85.1) in Indonesia (7) (Table 5). There were no cases of hospitalized grade 4+ COVID-19 in the vaccine arm of any trial.

Each trial had important features that may influence the vaccine efficacy estimate, including risk of disease among participants, case detection particularly of mild cases, and circulation of variants of concern that may reduce efficacy. Table 6 highlights some key differences between the studies. Notably, participants in the trial in Brazil were frontline health care workers who were treating patients with COVID-19, and whose exposure to SARS-CoV-2 may have been high. Additionally, it has been suggested that health care workers are more likely to be tested for SARS-CoV-2 with known exposure or very mild symptoms, leading to a higher ascertainment of mild cases. This effect is suggested by the proportion of all cases that were grade 4 and above in the Brazil trial (6%) compared with those in Indonesia (0%) and Turkey (19%); the Indonesian trial was also much smaller (9). The higher capture of mild cases in Brazil and Indonesia probably lowers the efficacy point estimate against COVID-19 of any severity. The P.1. variant was not circulating at any of the Brazil trial sites and so is not a current hypothesis to explain differences in efficacy (10).

Table 5. Comparison of phase 3 clinical trials with efficacy estimates currently available (7, 9-11).

Country	Population	Mean age (standard deviation)	Proportion with comorbidity	Incidence in placebo group per 100 person-years	Proportion of grade 4+ COVID-19 in placebo group	Variants of concern in circulation	Case definition for primary analysis	Median follow-up time	VE against symptomatic COVID-19	VE against grade 4+ COVID-19
Brazil	Health care workers treating patients with COVID-19	39.50 (10.75)	56%	22.34	6%	Limited	Case definition 1[a]	73 days	Vaccine: 85/4953 Placebo: 168/4870 VE: 51% (95%CI 36–62)	Vaccine: 0/5717 Placebo: 10/5714 VE: 100% (95%CI 56–100)
Turkey	Medical staff (10%) General population (90%)	Not available	Not available	19.22	19%	Limited	Case definition 3[b]	Not available	Vaccine: 9/6659 Placebo: 32/3471 VE: 84% (95%CI 65–92)	Vaccine: 0/6550 Placebo: 6/3445 VE: 100% (95%CI 20–100)
Indonesia	General population	35.82 (11.4)	Not available	11.25	0%	Limited	National case definition[c]	~2.5 months	Vaccine: 7/798 Placebo: 18/804 VE: 65% (95%CI 20–85)	Vaccine: 0/798 Placebo: 0/804 VE (95%CI): NE

[a] Individuals with at least two type A symptoms, or at least one type B symptom, or radiological characteristics of COVID-19 infection *plus* positive PCR test of COVID-19 (including saliva sample).

Type A symptoms (for at least 2 days): fever (axillary temperature ≥37.5 ºC), chills, sore throat, fatigue, nasal congestion or runny nose, muscle pain, headache, nausea or vomiting, diarrhoea.

Type B symptoms: cough (for at least 2 days), loss of smell or taste (for at least 2 days), shortness of breath or difficulty breathing.

Radiological characteristics of COVID-19: in the early stage, multiple small patches and interstitial changes, especially in the extrapulmonary zone, developing into multiple ground glass shadows and infiltrating shadows in both lungs. In severe cases, lung consolidation may occur, and rarely pleural effusion.

[b] At least one of the following symptoms for at least two days, and nucleic acid positive test for SARS-CoV-2 (excluding nucleic acid positive test of saliva sample).

Fever or cold, cough, shortness of breath or difficulty breathing, fatigue, muscle or physical pain, headache, loss of smell or taste, sore throat, stuffy or runny nose, nausea or vomiting, diarrhoea.

[c] Clinically confirmed or suspected COVID-19 case (referring to the case definition of the national guidelines for the diagnosis and treatment of COVID-19).

Summary

Vaccine efficacy against COVID-19 of any severity has been demonstrated across multiple populations and geographical areas. There is some variability in efficacy estimates, which may reflect study characteristics, such as population, testing rate/capture of milder cases, interdose interval, and force of infection. In other settings circulation of variants of concern may affect clinical protection, but that does not appear to be a relevant factor in the data available to date. Across trials, there were no hospitalized COVID-19 cases in the vaccine groups, suggesting good protection against severe disease. Data on vaccine efficacy in adults ≥60 years of age remain limited in clinical trials. Initial data suggest the vaccine may protect better with an interdose interval greater than 21 days. Evidence from vaccine effectiveness studies is summarized in the section Vaccine effectiveness; data available to date are consistent with the clinical trial results (Table 6) and provide evidence of protection in subpopulations.

Table 6. Vaccine efficacy and effectiveness estimates (with 95% confidence intervals) for Sinovac-CoronaVac (ordered by highest to lowest protection against symptomatic disease).

Study location	Population size	Schedule (days)	Design / measure of effect	Circulation of VOCs	Protection against symptomatic disease	Protection against hospitalization
Turkey	13 000	0, 14	RCT / Efficacy	Limited	84% (65–92)	100% (20–100)
Chile	10.5 million	0, 28	Cohort / Effectiveness	P.1, B.1.1.7	67% (65–69)	85% (83–97)
Indonesia	1620	0, 14	RCT / Efficacy	Limited	65% (20–85)	Not estimated[a]
Brazil	12 688	0, 14	RCT / Efficacy	Limited	51% (36–62)	100% (56–100)
Brazil	393 case–control pairs	0, 14[b]	TND / Effectiveness	P.1	50% (11–71)	Not reported

[a] No cases in either group.
[b] Analysis based on receiving ≥1 dose.
RCT: randomized controlled trial; TND: test negative design.

Safety

A total of 8840 individuals have been vaccinated in trials for which safety data are available with any dose of Sinovac-CoronaVac. Of these, 8329 (94%) were vaccinated with the authorized dose on either a 0/14 or a 0/28 day schedule (2). The largest safety database to date comes from the phase 3 trial in Brazil (10). The data available to date indicate that Sinovac-CoronaVac is generally well tolerated and consistent with the safety profile of other licensed, alum-adjuvanted inactivated vaccines. The incidence rate of grade 4 solicited or unsolicited adverse events (regardless of relatedness to vaccine/placebo) in the 28 days following immunization was listed in Table 7. In the 28 days following the second dose, the only adverse reactions (determined to be related to vaccination/placebo) that occurred at a higher frequency in the vaccine group than the placebo group were local adverse reactions, such as injection site pain, swelling, pruritus, redness, and induration. Aside from COVID-19, which was more frequent in the placebo group, serious adverse events occurred at the same frequency between vaccine and placebo groups and were distributed across organ classes. The following sections break down safety results by age group.

Table 7. Percentage of participants experiencing an adverse event or adverse reaction in the 28 days post-vaccination in the phase 3 trial in Brazil (14).

		18–59-year age group				≥60-year age group			
		≤7 days after dose 1		≤7 days after dose 2		≤7 days after dose 1		≤7 days after dose 2	
Parameter	**Severity**	**Vaccine (n=5880)**	**Placebo (n=5884)**	**Vaccine (n=5235)**	**Placebo (n=5209)**	**Vaccine (n=316)**	**Placebo (n=316)**	**Vaccine (n=246)**	**Placebo (n=244)**
General solicited adverse events	**Any**	72.11	64.82	68.52	56.73	50.32	50.63	54.47	45.49
	Grade 4	0.20	0.32	0.55	0.48	0.63	0.00	0.81	1.23
	Grade 3	1.67	1.75	2.14	2.50	0.00	0.32	1.22	1.64
	Grade 2	23.13	23.06	24.97	23.73	11.08	9.81	12.20	16.39
	Grade 1	68.10	59.65	64.53	51.83	47.47	48.10	51.62	41.80
Solicited local adverse reactions	**Any**	46.39	24.69	47.26	20.39	24.68	12.66	31.71	18.44
	Grade 4	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Grade 3	0.00	0.02	0.08	0.00	0.00	0.00	0.00	0.00
	Grade 2	2.16	0.85	3.61	0.98	1.58	0.00	0.41	1.23
	Grade 1	44.86	24.12	45.12	19.75	23.42	12.66	31.30	17.21
Solicited systemic adverse reactions	**Any**	40.20	39.34	26.57	25.38	24.05	28.80	25.61	20.90
	Grade 4	0.02	0.02	0.02	0.02	0.00	0.00	0.00	0.00
	Grade 3	0.68	0.63	0.46	0.65	0.00	0.00	0.00	0.00
	Grade 2	12.21	13.15	8.46	8.91	3.16	5.06	4.88	5.33
	Grade 1	35.43	33.84	22.37	20.77	22.78	25.32	23.58	20.08
Unsolicited adverse reactions	**Any**	25.19	24.46	24.05	22.77	15.51	16.77	17.89	17.62
	Grade 4	0.03	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Grade 3	0.34	0.49	0.44	0.77	0.00	0.32	0.00	0.41
	Grade 2	7.16	6.90	8.12	7.76	3.16	3.80	2.85	4.10
	Grade 1	21.34	21.13	20.40	19.43	13.92	15.51	17.48	15.16

Adverse event: any event regardless of relatedness to vaccination/placebo

Adverse reaction: event determined to be related to vaccination/placebo

Safety in the adult population aged 18–59 years

Most adverse reactions were grade 1 and fewer than 1% of participants experienced a grade 3 adverse event. In the 7 days following dose 1, 54.9% of participants who received Sinovac-CoronaVac experienced a solicited AE compared with 45% of participants who received placebo (Table 7) (14).

Approximately 40% of vaccinees experienced a solicited local adverse reaction after either dose of Sinovac-CoronaVac, approximately double the proportion in the placebo group (14). The most common solicited local

adverse reaction was pain at the injection site, experienced by 39.6% of vaccinees after dose 1 and 42.7% of vaccinees after dose 2. Solicited systemic adverse reactions were reported in 35.6% of vaccinees after dose 1 and 24.1% after dose 2; these rates were similar to those in the placebo group. The most common systemic adverse events reported were headache (24.2% after dose 1 in vaccinees compared with 24.6% in the placebo group), fatigue and myalgia. Aside from injection-site reactions, adverse reactions tended to be less frequent with the second dose.

Allergic reactions were observed after the first dose of the vaccine in 0.3% of participants in the vaccine group and 0.2% of those in the placebo group (14). Among vaccinees, 0.2% presented a grade 1 allergic reaction and 0.2% grade 2. Among those who received placebo, 0.2% presented a grade 1 allergic reaction and 0.1% grade 2.

During the 28-day follow up, 5 subjects reported grade 4 adverse events: cough and dyspnoea (reported as asthma); ulcerative colitis (determined to be possibly unrelated); headache; fatigue and arthralgia; and headache, myalgia and fatigue (9).

Unsolicited adverse reactions were reported in 14% of vaccinees after dose 1 and 9.2% after dose 2, compared with 12.2% and 7.4% of placebo recipients after dose 1 and 2, respectively (14).

Safety was also assessed in the phase 1 and 2 trials in China comparing multiple dosages. The safety results from these small studies are consistent with those from the phase 3 trial. Among participants who received the authorized dose, pain at the injection site was the most common adverse event, reported in 4 of 24 (17%) participants in phase 1 and 25 of 120 (21%) participants in phase 2 (4, 5, 15). Most adverse reactions were mild (grade 1) in severity and participants recovered within 48 hours. There was one case of acute hypersensitivity with manifestation of urticaria 48 hours after the first dose of the vaccine in the high-dose group (4%), which was classified as severe and possibly related to vaccination (14). Another case of acute hypersensitivity, classified as grade 1, occurred after the first dose of the medium-dose vaccine. No serious vaccine-related adverse events were observed within 28 days after vaccination. No significant increase in serum inflammatory factors was detected on day 7 after each dose.

Similarly, the phase 3 trial in Chile found the most common solicited adverse event to be pain at the injection site, with 56% of vaccinees reporting pain compared with 40% of those given placebo (8). In Indonesia, the most commonly reported adverse events were pain at the injection site (approximately 33% of vaccinees after either dose) and myalgia (approximately 20–25% of vaccinees after either dose) (7). Only one subject experienced a grade 3 hypersensitivity reaction (urticaria). Of 405 vaccinees, 30 experienced a severe adverse event, the type of which was distributed across multiple organ groups.

Safety in the population aged ≥60 years

Over 900 older adults ≥60 years have been vaccinated with Sinovac-CoronaVac in clinical trials for which safety data are available; most were vaccinated with the authorized 3 µg dose. These trials include phase 1 and 2 studies in China (4, 6, 15), the phase 3 bridging trial in China (4, 15), the phase 3 efficacy trial in Brazil (10), and the phase 3 trial in Chile (8). Some of these studies (e.g. Chile) have so far contributed only low numbers of participants in this age group based on the interim results.

In the phase 3 trial in Brazil, in the 7 days following vaccination there were generally fewer reported adverse events in those ≥60 years than in younger adults (aged 18–59 years) (Table 7) (14). There were no grade 4 solicited or unsolicited adverse reactions in the 7 days following immunization. The only grade 3 events were unsolicited (0.1%), and most adverse reactions were grade 1. In the 7 days following dose 1, 29% of participants who received Sinovac-CoronaVac experienced a solicited AE compared with 23% of participants who received placebo.

In the older adult group, 18% of vaccinees experienced a solicited local adverse reaction after dose 1 of Sinovac-CoronaVac, compared with 10% in the placebo group; this increased to 28.7% with the second dose and 16.2% after the second dose of placebo (14). The most common solicited local adverse reaction was pain at the injection site, experienced by 17% of vaccinees after dose 1 and 28% after dose 2. Solicited systemic adverse reactions were reported by 17.7% of vaccinees after dose 1 and 21.1% of vaccinees after dose 2; these figures were similar to those in the placebo group. The most common systemic adverse event reported was headache (9.5% after dose 1 in vaccinees, 9.3% in the placebo group). Grade 1 allergic reactions were observed in 0.5% of vaccinated participants. Unsolicited adverse reactions were reported in 10.9% of vaccinees after dose 1 and 8.1% after dose 2, compared with 8.7% and 7.4% of placebo recipients.

Safety was also assessed in a dedicated phase 1/2 trial in China, in which 348 individuals aged ≥60 years received vaccine (three different doses) and 73 received placebo, all on a 0/28 day schedule (Tables 8, 9). The incidence rate of vaccination-related adverse events was 20.7% (87/421): 20.0% (20/100) in the low-dose group, 20.0%

(25/125) in the medium-dose group (the authorized dose), 21.0% (27/123) in the high-dose group and 20.6% (15/73) in the placebo group (6). All adverse reactions were grade 1 or 2. The most frequent adverse reaction was pain at the vaccination site, which occurred in 11% of vaccinees in the authorized dose group. All other adverse reactions were reported by less than 5.0% of participants. The most common systemic adverse reactions were fever (3%) and fatigue (3%), followed by diarrhoea (2%), muscle pain (2%), and muscle distention (2%) (6).

The phase 3 bridging trial in China enrolled 260 older adults ≥60 years of age on a 0/14 day schedule. Adverse events were generally less frequent in the older adult age group; the overall frequency of adverse events reported in the older adult age group was about half that in the younger age group (Tables 8, 9) (15). The frequency of adverse events in older adults on the 0/14 day schedule also seemed to be lower than that seen in the phase 1/2 study in older adults on the 0/28 day schedule, possibly suggesting that less reactogenicity is associated with lower immunogenicity, as seen in the phase 1/2 trials in younger adults.

The safety evaluation from the phase 3 trial in Chile also found a lower rate of solicited adverse events, including pain and headache, in the older adult population compared with the younger adult population (8).

Table 8. Adverse events reported in phase 1/2 trial conducted in older adults ≥60 years and in the phase 3 bridging trial (4, 15).

	Phase 1/2 trial (≥60 years)				**Phase 3 bridging trial**				
	Vaccine (authorized dose) (N=125)		**Placebo (N=73)**		**≥60 years group (N=260)**		**18–59 years (N=519)**		
	No. of events	**No. of subjects (%)**	**No. of events**	**No. of subjects (%)**	**No. of events**	**No. of subjects (%)**	**No. of events**	**No. of subjects (%)**	***P-value***
Overall AEs	69	38 (30)	38	24 (33)	35	25 (10)	163	103 (20)	0.0002
Related AEs	37	25 (20)	23	15 (21)	23	15 (6)	111	67 (13)	0.0019
Local AEs	19	13 (10)	19	12 (16)	7	7 (3)	31	28 (5)	0.0996
Systemic AEs	18	15 (12)	4	3 (4)	16	10 (4)	80	48 (9)	0.0058
Solicited AEs	33	24 (19)	14	12 (16)	21	13 (5)	97	63 (12)	0.0013
Unsolicited AEs	4	3 (2)	9	5 (7)	2	2 (1)	14	10 (2)	0.3551
Within 30 min	6	5 (4)	4	2 (3)	1	1 (<1)	14	12 (2)	0.0709
Days 0–7	36	25 (20)	22	14 (19)	23	15 (6)	111	67 (13)	0.0019
Days 8–28	Not reported				0	0 (0)	0	0 (0)	1
First dose	27	18 (15)	18	11 (15)	12	11 (4)	79	49 (9)	0.01
Second dose	10	10 (8)	5	5 (7)	11	4 (2)	32	25 (5)	0.0258

Table 9. Adverse reactions in phase 1/2 and phase 3b bridging clinical trials (4, 15).

	18–59 years				≥60 years		
Schedule	**0/14 days**		**0/28 days**		**0/14 days**	**0/28 days**	
	Vaccine (N=923) n (%)	**Placebo (N=84) n (%)**	**Vaccine (N=144) n (%)**	**Placebo (N=83) n (%)**	**Vaccine (N=260) n (%)**	**Vaccine (N=125) n (%)**	**Placebo (N=73) n (%)**
Overall adverse reactions	**159 (17)**	**15 (18)**	**26 (18)**	**14 (17)**	**15(6)**	**25 (20)**	**15 (21)**
Solicited adverse reactions	**152 (16)**	**15 (18)**	**26 (18)**	**13 (16)**	**13 (5)**	**24 (19)**	**12 (16)**
Systemic adverse reaction	**93 (10)**	**10 (12)**	**16 (11)**	**7 (8)**	**8 (3)**	**12 (10)**	**9 (12)**
Fatigue	25 (3)	7 (8)	10 (7)	2 (2)	2 (1)	4 (3)	1 (1)
Fever	28 (3)	1 (1)	4 (3)	2 (2)	3 (1)	4 (3)	1 (1)
Myalgia	14 (2)	1 (1)	2 (1)	3 (4)	0 (0)	2 (2)	2 (3)
Diarrhoea	19 (2)	1 (1)	2 (1)	1 (1)	4 (2)	1 (1)	1 (1)
Headache	13 (1)	1 (1)	3 (2)	0 (0)	1 (<1)	0 (0)	0 (0)
Cough	11 (1)	0 (0)	3 (2)	0 (0)	1 (<1)	1 (1)	1 (1)
Nausea	7 (1)	0 (0)	2 (1)	0 (0)	0 (0)	1 (1)	3 (4)
Abnormal skin and mucous membrane	4 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Anorexia	2 (0<1)	0 (0)	0 (0)	0 (0)	2 (1)	1 (1)	0 (0)
Vomiting	2(<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Acute allergic reaction	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)
Local adverse reactions	**77 (8)**	**7 (8)**	**15 (10)**	**9 (11)**	**7 (3)**	**15 (12)**	**3 (4)**
Pain	71 (8)	7 (8)	15 (10)	9 (11)	6 (2)	15 (12)	3 (4)
Pruritus	6 (1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
Swelling	6 (1)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)
Redness	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Induration	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unsolicited adverse reactions	16 (2)	0 (0)	0 (0)	2 (2)	2 (1)	3 (2)	5 (7)

Serious adverse events

In the PROFISCOV trial, two non-COVID-19 deaths were reported among trial participants, one in the vaccine group and one in the placebo group. The causes of death were cardiopulmonary arrest (placebo arm) and suicide (vaccine arm); both were determined to be unrelated to vaccination. The overall fatality rate was 0.02%.

Throughout the study, 64 participants reported 67 serious adverse events: 34 in the vaccine group and 33 in the placebo group (10). Overall, 0.5% (64/12 396) of participants had a serious adverse event, 0.5% (33/6202) in the vaccine group and 0.5% (31/6194) in the placebo group. The only statistically significant difference between vaccine and placebo group was the incidence of COVID-19 (0.0% and 0.2%). In the vaccine group, the SAEs

were balanced in different organ groups without a clear signal (Table 10). All SAEs were classified as unrelated or unlikely to be related to vaccination. There was one case of deep vein thrombosis diagnosed in the vaccine group.

In the Chile phase 3 study, no SAEs or adverse events of special interest were reported in either arm (8). In the Indonesia phase 3 study, a total of nine SAEs were reported (numbers specific to trial arm not yet available) (7). Of the nine SAEs, two were COVID-19 diagnoses, four were determined to be "not related", and three were determined to be "less likely" to be causally related. Of these last three, there was one sudden death that occurred over two months after the intervention.

Table 10. Occurrence of serious adverse events after vaccination by system organ class in phase 3 trial in Brazil (10).

	Vaccine group (N=6202) No. (%)	Placebo group (N=6194) No. (%)	*P* value[a]
Overall SAE	33 (0.53)	31 (0.50)	0.9004
Infections	13 (0.21)	13 (0.21)	1.0000
COVID-19	2 (0.03)	9 (0.15)	0.0384
Appendicitis	5 (0.08)	1 (0.02)	0.2186
Pyelonephritis	2 (0.03)	2 (0.03)	1.0000
Severe acute respiratory syndrome (SARS)	0 (0.00)	1 (0.02)	0.49997
Vestibular neuronitis	1 (0.02)	0 (0.00)	1.0000
Urinary tract infection	1 (0.02)	0 (0.00)	1.0000
Diverticulitis	1 (0.02)	0 (0.00)	1.0000
Pelvic inflammatory disease	1 (0.02)	0 (0.00)	1.0000
Nasal abscess	0 (0.00)	1 (0.02)	0.49997
Injury, poisoning and procedural complications	4 (0.06)	5 (0.08)	0.7537
Psychiatric disorders	3 (0.05)	2 (0.03)	1.0000
Pregnancy, puerperium and perinatal conditions	1 (0.02)	3 (0.05)	0.3746
General disorders and administration site conditions	3 (0.05)	0 (0.00)	0.2499
Musculoskeletal and connective tissue disorders	2 (0.03)	1 (0.02)	1.0000
Respiratory, thoracic and mediastinal disorders	3 (0.05)	0 (0.00)	0.2499
Nervous system disorders	1 (0.02)	1 (0.02)	1.0000
Renal and urinary disorders	0 (0.00)	2 (0.03)	0.2497
Gastrointestinal disorders	1 (0.02)	1 (0.02)	1.0000
Vascular disorders	2 (0.03)	0 (0.00)	0.5000
Deep vein thrombosis	1 (0.02)	0 (0.00)	1.0000
Hypertension	1 (0.02)	0 (0.00)	1.0000
Metabolism and nutrition disorders	0 (0.00)	1 (0.02)	0.49997
Cardiac disorders	0 (0.00)	1 (0.02)	0.49997
Reproductive system and breast disorders	0 (0.00)	1 (0.02)	0.49997
Skin and subcutaneous tissue disorders	1 (0.02)	0 (0.00)	1.0000
Hepatobiliary disorders	0 (0.00)	1 (0.02)	0.49997

[a] *Calculated using Fisher's exact test.*

Special considerations

Pregnancy and lactation

Pregnant and lactating women have been excluded from clinical trials so far. Sinovac is planning a retrospective study of safety in pregnant and lactating women, including data on abortion, teratogenesis, arrested fetal development, pregnancy and childbirth complications, and COVID-related outcomes (2).

In the phase 3 trial in Brazil, a total of 52 female subjects reported pregnancy to date over the course of the trial, 23 from the vaccine group and 29 from the placebo group (16). All those women became pregnant after having received 1st or 2nd dose of the vaccine. They are currently being followed up. During emergency use in China, 12 female vaccine recipients reported a pregnancy to Sinovac. Three of the 12 subjects elected to have a termination. Available medical records for the nine other pregnant vaccine recipients suggested that all indicators were in the normal range. According to their own reports, there have been no adverse events. Sinovac has indicated they will continue to follow up pregnant women and newborns to obtain relevant safety data.

Paediatric population

The phase 1/2 safety and immunogenicity study Corona-03 will provide data on children aged 3–17 years.

Immunosuppression

There is no information on persons with immunosuppression, since this group was excluded from clinical trials.

Safety related to vaccine interactions

Concomitant use with other vaccines. No clinical study has been carried out to evaluate the effect on the immune response of other vaccines given before, after or at the same time. A coadministration study with 23-valent pneumococcal polysaccharide vaccine and inactivated influenza vaccine is planned.

Concomitant use with other drugs. No data are yet available. Immunosuppressive drugs, including chemotherapy drugs, antimetabolic drugs, alkylating agents, cytotoxic drugs and corticosteroids, may reduce the immune response to this product.

Considerations for vaccinating older adults

The available data from clinical trials suggest that Sinovac-CoronaVac is safe and immunogenic in people ≥60 years of age. With small numbers of older adults and few cases of COVID-19 in this group in the available efficacy trial, clinical efficacy has not been established. Supportive data for clinical protection in adults ≥60 years are now available through post-authorization effectiveness studies (see Vaccine effectiveness).

Interdose interval

Both immunogenicity and efficacy data suggest possible improved protection with an interdose interval of approximately 21–28 days rather than 14–21 days. Additional data are needed to confirm this.

Emerging virus variants of concern

In a recent preprint (17), two P.1 variants (P.1/12 and P.1/30) were isolated from nasopharyngeal and bronchoalveolar lavage samples of patients in Manaus, Brazil. These were assessed in vitro for neutralization with plasma from 19 blood donors who had recently had COVID-19 and from 8 Sinovac-CoronaVac recipients. Plasma was collected from the individuals vaccinated with Sinovac-CoronaVac during the phase 3 trial in Brazil, 153–159 days after the second vaccine dose was given on a 0/14 day schedule. The plasma was incubated with the two P.1 variants and an isolate of SARS-CoV-2 lineage B (isolate SARS.CoV2/SP02.2020).

COVID-19 convalescent plasma produced GMTs of 40 and 35 against the P.1 isolates, compared with a GMT of 240 against the B lineage isolate, representing a 6-fold lower neutralization capacity for the P.1 isolates. The GMT of all plasma samples from the eight Sinovac-CoronaVac-vaccinated individuals against both P.1 isolates was below the limit of detection (<20), whereas the GMT for the B lineage isolate was 25 (interquartile range <20–30). The failure to neutralize P.1 isolates suggests that P.1 virus could escape Sinovac-CoronaVac-induced antibodies. The lower GMT against the B lineage in Sinovac-CoronaVac vaccinees compared with COVID-19 convalescent patients is also worth noting. In the phase 3 trial in Brazil, a subset of serum samples from 45 vaccinees was used to determine neutralization titres against SARS-CoV-2 wild-type variants: B.1.128, P.1 and

P.2 (10). Among the vaccinees, 71% seroconverted for B.1.1.28, 68.9% for P.1, and 80.0% for P.2. GMTs across the three variants were not significantly different.

Two recent vaccine effectiveness studies conducted in the presence of circulating variants of concern are described under Vaccine effectiveness.

Post-licensure experience

As of 21 April 2021, more than 260 million doses have been distributed to the public in China and elsewhere, and more than 160 million individuals have been vaccinated (2).

Risk management plan

No important risks have been identified (2). Important potential risks include vaccine-associated enhanced disease (including vaccine-associated enhanced respiratory disease).

The following studies are ongoing or planned as part of the clinical development program and the Risk Management Plan (2):

- Follow up of existing clinical trial participants:
  - 6 months follow up: Phase 1/2 trials, Phase 3 in Indonesia
  - 1 year follow up: Phase 3 trials in Brazil and Turkey
- Pediatric immunogenicity and safety in China
- Phase 4 vaccine effectiveness stepped wedge cluster-randomized trial in Brazil
- Other clinical studies assessing safety/immunogenicity in special populations such as persons living with HIV/AIDS, rheumatic disease, chronic liver disease, and breast and lung cancer receiving active chemotherapy
- Retrospective study of safety in pregnant and lactating women, including data on abortion, teratogenesis, arrested fetal development, pregnancy and childbirth complications, and COVID-related outcomes
- Coadministration study with 23-valent pneumococcal polysaccharide vaccine and inactivated influenza vaccine
- Large-scale observational of safety in the target population and special populations, monitoring select individuals for adverse events of special interest including vaccine-associated enhanced disease

In addition, several studies in special populations are planned or under way by partners (Table 1).

Areas of emphasis in the post-marketing risk management plan include safety monitoring among the target population of large-scale vaccination programmes, and further collection and evaluation of safety information, especially for rare and very rare adverse reactions (2). A special focus will be put on monitoring and timely assessment of potential vaccine-enhanced disease risks, as well as safety risks for special populations (including elderly patients with chronic disease, pregnant and lactating women, people with vital organ damage and people with immunodeficiency or immune weakness), while also paying attention to the occurrence of abnormal laboratory indicators. Both passive and active monitoring systems will focus on monitoring, timely assessment and reporting of potential antibody dependent enhancement/ vaccine enhanced disease risks (focusing on COVID-19 hospitalizations and deaths) and safety information related to immune diseases, neurological diseases, adverse events of special interest, and other SAEs.

Post-licensure safety monitoring

According to company information, as of 14 March 2021, based on 35.8 million doses administered, 6638 adverse events following immunization (AEFIs) had been reported through routine AEFI surveillance in China (2), for an overall reporting rate of 18.5 AEFI/100,000 doses administered. Sixty-four percent were defined as general reactions, 14% as abnormal reactions, 13% as coincidental, 5% as psychogenic and 4% undetermined. Of the 5427 AEFIs for which causality with Sinovac-CoronaVac cannot be ruled out, symptoms and diagnosis were available for severity determination for 4990. A total of 49 cases (0.9%) were classified as serious.

Of the serious adverse reactions, there were 6 cases of anaphylactic shock, 5 cases of Henoch-Schönlein purpura, 4 cases of facial paralysis, 3 cases of laryngeal oedema, 3 cases of demyelination, 3 cases of cerebral haemorrhage, 2 cases of Guillain-Barré syndrome, and one case each of thrombocytopenic purpura, peripheral neuropathy, intracranial haemorrhage, syncope, septic shock, meningitis, sensation of foreign body (laryngeal), multiorgan dysfunction syndrome, autonomic nervous system imbalance, sudden hearing loss, haemorrhagic disorder, conversion disorder, nephrotic syndrome, tubulointerstitial nephritis, and subacute thyroiditis (2).

The total number of serious blood and lymphatic system disorders as defined in MedDRA reported as of 14 March 2021 was 4 from mainland China (reporting rate 0,01/100 000 doses administered) and 6 globally (reporting rate 0.002/ 100 000). In addition, as of the data cut-off point, there had been 6 deaths, of which 4 were determined to be coincidental ; the cause of death in the other two cases was not yet clear. No signals of concern were identified by Sinovac.

AEFIs have been reported from Brazil and Indonesia, with a total of 2686 cases of known adverse reactions. Outside of China, a total of 162 serious AEFI have been reported exclusively from Brazil and Indonesia. The level of monitoring of AEFIs varies greatly from country to country. Of the 115 individuals with reported AEFIs (both serious and non-serious) where causality to Sinovac-CoronaVac could not be ruled out, the most common were fever (16), dyspnoea (13), death (10), headache (9), discomfort (8), nausea (8), vomiting (7), fatigue (7), facial paralysis (6), diarrhoea (6), cardiorespiratory arrest (6), seizure (5), cough (5), myalgia (5). Among the vascular AEFIs reported, there were 3 cases of hypotension, 2 of thrombocytopenic purpura, 2 of pallor, 1 of arterial thrombosis and 1 of autoimmune haemolytic anaemia.

Post-authorization safety was recently assessed by the National Centre for Pharmacovigilance of the National Institute of Public Health (NIPH) of Chile through a vaccine adverse event passive reporting system (18). A total of 3 378 552 doses of Sinovac-CoronaVac have been administered to date. Ninety serious adverse events have been reported following vaccination with Sinovac-CoronaVac, giving an SAE reporting rate of 2.7 per 100 000 doses. Sixty-four percent of SAEs were among older adults over 65 years of age, which was the initial target group for vaccination. The most frequent adverse event reported was clinical symptoms of anaphylaxis. A total of 49 notifications of anaphylaxis were reported, a reporting rate of 1.69 per 100 000 doses administered.

Vaccine effectiveness

Brazil

Vaccine effectiveness was assessed among health care workers in Manaus, Brazil, using a matched test-negative design (13). Data were collected at the beginning of 2021, as the epidemic was declining from its peak in late December 2020. At this time, SARS-CoV-2 P.1 variant was identified in 75% of isolates genotyped through surveillance. In the context of significant P.1 transmission, adjusted vaccine effectiveness against symptomatic COVID-19 disease with at least one dose of Sinovac-CoronaVac was 49.6% (95%CI 11.3, 71.4). The authors relate this effectiveness estimate most closely to vaccine efficacy with a moderate clinical endpoint in the trial (VE=78%, 95%CI 46.2, 90.4). When asymptomatic cases were included, adjusted vaccine effectiveness against SARS-CoV-2 infection was 35.1% (95%CI –6.6, 60.5). An increased risk of symptomatic COVID-19 disease was detected in the first 13 days after receiving the first dose (adjusted odds ratio (OR) 1.69, 95%CI 1.09, 2.64), a phenomenon also observed in the phase 3 clinical trial in Brazil and discussed in the section Vaccine efficacy.

There were limitations to this study. Because of the declining outbreak, most cases occurred before a second dose was received. Earlier, the region had been affected by a large outbreak that is estimated to have infected 76% of the population (19). Thus, these results may not be generalizable to a largely unexposed population. Indeed, a prior positive SARS-CoV-2 test was associated with lower odds of symptomatic COVID-19 (adjusted OR 0.38, 95%CI 0.17, 0.87), as was female sex (adjusted OR 0.50, 95%CI 0.38, 0.81). Only 5 case isolates were genotyped), 4 of which were the P.1 variant.

Another preprint report of a vaccine effectiveness evaluation in São Paulo, Brazil, estimated the number of cases expected in a population of health care workers in the month following vaccination, based on COVID-19 cases in the prior 6 months and the case and mobility trends in the general population for that period (20). Observed case numbers were compared with expected case numbers. The authors estimated vaccine effectiveness at 51% (95%CI 22, 63) during the third week after vaccination, moving up to 74% (95%CI 57, 85) in the sixth week after vaccination. However, such an analysis is challenging in view of the multiple assumptions about comparability between health care workers and non-health care workers and disease trends and predictions. The total case numbers during the observation period among health care workers did not decrease following vaccination, but this was in the context of a significant increase in cases in São Paulo.

Chile

In Chile, a vaccine effectiveness study of about 2 months following vaccination was conducted through programme rollout on a 0/28 day schedule (21). Over 10 million individuals receiving health care through the Fondo Nacional de Salud (FONASA) were included in the surveillance population. Because the national rollout targeted older adults first, the majority of the over 2.5 million people under surveillance above 60 years of age were vaccinated. Over 30% of the population had one or more comorbidities. Although information on genotype

was not uniformly available, evidence from select hospitals in Chile suggest broad circulation of P.1 and B.1.1.7. The incidence of COVID-19, including disease of any severity, hospitalization, admission to ICU, and death was compared between vaccinated and unvaccinated populations. Vaccine effectiveness was adjusted for age, sex, region of residence, income, and nationality. Vaccine effectiveness was assessed in fully immunized individuals (≥14 days after the second dose) and partially immunized individuals (≥14 days after the first dose). After adjusting for several factors, including age, region/nationality, sex, and comorbidities, vaccine effectiveness estimates were similar to previously reported estimates of efficacy and effectiveness, with the lowest estimate being against COVID of any severity (Table 11). Across all ages, vaccine effectiveness was 67% (95%CI 65, 69) against symptomatic COVID-19, 85% (95%CI 83, 97) against hospital admission, 89% (95%CI 84, 92) against ICU admission and 80% (95%CI 73, 86) against death. Vaccine effectiveness was similar when limited to the age group ≥60 years of age (Rafael Araos, personal communication). Vaccination with only a single dose was significantly less effective against all endpoints, suggesting that completion of the 2-dose schedule is critical to achieving sufficient protection.

Although it cannot be excluded that some bias may have been introduced by individuals targeted for vaccination who chose not to receive it, these data suggest strong vaccine effectiveness including in adults ≥60 years of age. The clinical trials did not determine efficacy in this group because of the small numbers of participants.

Table 11. Adjusted vaccine effectiveness estimates from post-authorization use in Chile. [a]

	All ages		Adults ≥60 years	
	Partial immunization	**Full immunization**	**Partial immunization**	**Full immunization**
COVID-19 of any severity	16% (14–18)	67% (65–69)	14% (11–17)	67% (65–70)
Hospitalization	37% (32–39)	85% (83–87)	36% (32–40)	83% (80–86)
ICU admission	43% (37–43)	89% (84–92)	44% (38–51)	88% (83–91)
Death	40% (33–47)	80% (73–86)	41% (33–48)	83% (76–88)

Partial immunization ≥14 days after the first dose; full immunization ≥14 days after the second dose.

[a] Source: Ref. 20 and R Araos, personal communication.

Appendix 1. Summary of available evidence from trial participants vaccinated with Sinovac-CoronaVac for SAGE review.

Because of the way in which data are becoming available for review, SAGE has considered data in preprints and presentations that have not gone through a formal peer review process. These inputs are reflected in the data below and the numbers should be considered in that context.

Table A1.1 Number of trial participants who were included in the safety clinical database reviewed by SAGE. [a]

Age group	Study	Number receiving authorized 3-µg dose on 2-dose schedule		Number receiving alternative dose	
		0/14 day schedule	0/28 day schedule	0/14 day schedule	0/28 day schedule
18–59 years	Corona-01 phase 1	24	24	24	24
	Corona-01 phase 2	120	120	120	120
	Corona-05 (bridging trial)	779	-----	-----	-----
	PROFISCOV (phase 3, Brazil)	5886	-----	-----	-----
	CoV2-0321 (phase 3, Indonesia)	405	-----	-----	-----
	Phase 3 Chile	245	-----	-----	-----
	TOTAL	**7459**	**144**	**144**	**144**
≥60 years	Corona-02 phase 1	-----	24	-----	24
	Corona-02 phase 2	-----	101	-----	199
	Corona-05 (bridging trial)	260	-----	-----	-----
	PROFISCOV (phase 3, Brazil)	316	-----	-----	-----
	Phase 3 Chile	25	-----	-----	
	TOTAL	**601**	**125**	**0**	**223**

[a] Safety data from the phase 3 trial in Turkey are pending.

Table A1.2. Number of trial participants who were included in the immunogenicity clinical database reviewed by SAGE. [a]

Age group	Study	Number receiving authorized 3 µg dose on 2-dose schedule		Number receiving alternative dose	
		0/14 day schedule	0/28 day schedule	0/14 day schedule	0/28 day schedule
18–59 years	Corona-01 phase 1	24	24	24	24
	Corona-01 phase 2	120	120	120	120
	Corona-05 (bridging trial)	779	-----	-----	-----
	CoV2-0321 (phase 3, Indonesia)	390	-----	-----	-----
	Phase 3 Chile	132	-----	-----	-----
	TOTAL	**1445**	**144**	**144**	**144**
≥60 years	Corona-02 phase 1	-----	24	-----	24
	Corona-02 phase 2	-----	100	-----	199
	Corona-05 (bridging trial)	260	-----	-----	-----
	Phase 3 Chile	14	-----	-----	-----
	TOTAL	**274**	**124**	**0**	**223**

[a] Immunogenicity data are pending for the PROFISCOV phase 3 trial in Brazil (≥18 years) and the phase 3 trial in Turkey (18–59 years).

Table A1.3. Number of trial participants who were included in the efficacy clinical database reviewed by SAGE.

Age Group	Study	Number receiving authorized 3 µg dose on 2-dose 0/14 day schedule	Number receiving alternative dose
18-59	PROFISCOV (phase 3, Brazil)	4741	0
	CoV2-0321 (phase 3, Indonesia)	798	0
	9026-ASI (phase 3, Turkey)	6559	0
	TOTAL	**12 098**	**0**
≥60Y	PROFISCOV (phase 3, Brazil)	212	0

References

1. World Health Organization. Draft landscape and tracker of COVID-19 candidate vaccines. Geneva, Switzerland2021 (https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines, accessed February 26).
2. Sinovac. Responses to the SAGE Working Group on Covid-19 Vaccines - Submitted 21 April 2021.
3. Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science. 2020;369:77-81. doi: doi: 10.1126/science.abc1932.
4. Sinovac. Common Technical Document submitted to WHO Emergency Use Listing. 2021.
5. Zhang Y, Zeng G, Pan H, Li C, Hu Y, Chu K, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis. 2021;21:181-92. doi: https://doi.org/10.1016/S1473-3099(20)30843-4.
6. Wu Z, Hu Y, Xu M, Chen Z, Yang W, Jiang Z, et al. 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. Lancet Infect Dis. 2021. doi: https://doi.org/10.1016/S1473-3099(20)30987-7.
7. Farma PB. Clinical Trial Report Interim II: A Phase III, Observer-blind, Randomized, Placebo-controlled Study of the Efficacy, Safety and Immunogenicity of SARS-CoV-2 Inactivated Vaccine in Healthy Adults Aged 18-59 Years in Indonesia. 2021
8. Bueno S, Abarca K, González PA, Gálvez NMS, Soto JA, Duarte LF, et al. Interim Report: Safety and immunogenicityof an inactivated vaccine aginst SARS-CoV-2 in health Chilean adult in a Phase 3 clinical trial. medRxiv preprint. 2021.
9. Sinovac. Responses to the SAGE Working Group on Covid-19 Vaccines - Submitted 16 March 2021.
10. Palacios R, Batista AP, Nascimento Albuquerque CS, Patiño EG, do Prado Santos J, Pessoa Conde MTR, et al. Efficacy and safety of a COVID-19 inactivated vaccine in healthcare 2 professionals in Brazil: The PROFISCOV study. SSRN. 2021.
11. Sinovac. COVID-19 Vaccine (Vero cell), inactivated. In: Proceedings. SAGE Meeting March 23, 2021, Virtual Meeting.
12. WHO Working Group on the Clinical Characterization and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis. 2020;20:E192-E7. doi: https://doi.org/10.1016/S1473-3099(20)30483-7.
13. Hitchings M, Ranzani OT, Torres MSS, de Oliveira SB, Almiron M, Said R, et al. Effectiveness of CoronaVac in the setting of high SARS-CoV-2 P.1 variant transmission in Brazil: A test-negative case-control study. medRxiv preprint. 2021.
14. ANVISA. Public Opinion for evaluation of request for temporary authorization for emergency use, on an experimental basis, of the adsorbed vaccine covid-19 (inactivated) - Instituto Butantan. 2021.
15. Sinovac. Responses to the SAGE Working Group on Covid-19 Vaccines - Submitted 12 March 2021.
16. Sinovac. Responses to the SAGE Working Group on Covid-19 Vaccines - Submitted 25 February 2021.
17. Souza W, Amorim MR, Sesti-Costa R, Coimbra LD, Toledo-Teixeira DA, Parise PL, et al. Levels of SARS-CoV-2 lineage P.1 neutralization by antibodies elicited after natural infection and vaccination. Pre-print SSRN. 2021.
18. National Centre for Pharmacovigilance Chile. Serious Adverse Events associated with the administration of vaccines against SARS-CoV-2 in Chile, 24 December 2020 to 02 March 2021: Third Statistical Report. 2021.
19. Buss L, Prete Jr CA, Abrahim CMM, Mendrone Jr A, Salomon T, de Almeida-Neto C, et al. Three-quarters attack rate of SARS-CoV-2 in the Brazilian Amazon during a largely unmitigated epidemic. Scince. 2021;15. doi: 10.1126/science.abe9728. .

20. de Faria E, Guedes AR, Oliveira MS, de Godoy Moreira MV, Maia FL, et al. . Performance of vaccination with CoronaVac in a cohort of healthcare workers (HCW) - preliminary report. medRxiv preprint. 2021.

21. Araos R. Effectivness of the inactivated CoronaVac vaccine against SARS-CoV-2 in Chile: Preliminary Report. 2021.

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