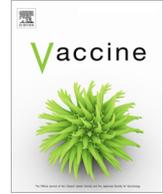**ELSEVIER**

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Safety, immunogenicity, and immune persistence of two inactivated COVID-19 vaccines replacement vaccination in China: An observational cohort study

Xiaoqi Wang [a,1], Yao Deng [b,1], Li Zhao [b,1], Lei Wang [c,1], Zhenwang Fu [d,1], Lin Tang [a], Fei Ye [b], Qianqian Liu [a], Wenling Wang [b], Siquan Wang [c], Bo Hu [e], Xuhua Guan [c], Zhuling Han [f], Yeqing Tong [c], Lance E. Rodewald [a], Zundong Yin [a], Wenjie Tan [b], Fuzhen Wang [a,*], Baoying Huang [b,*]

[a] National Immunization Program, Chinese Center for Disease Control and Prevention, Beijing, China
[b] NHC Key Laboratory of Biosafety, Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China
[c] Hubei Provincial Center for Disease Control and Prevention, Wuhan, China
[d] Hainan Provincial Center for Disease Control and Prevention, China
[e] Danzhou Center for Disease Control and Prevention, China
[f] Wenchang Center for Disease Control and Prevention, China

ARTICLE INFO

ABSTRACT

Background: To mitigate a national shortage of WIBP-CorV COVID-19 vaccine, China's regulator approved administering BBIBP-CorV after WIBP-CorV for completion of a primary series. In a pragmatic observational study, we compared immunogenicity and safety of a primary series of WIBP-CorV followed by BBIBP-CorV with a primary series of two doses of BBIBP-CorV.

Methods: We invited healthy 18–59-years-old adults who had already received either WIBP-CorV or BBIBP-CorV as their first dose in a primary series to participate in this observational cohort study. Subjects who had received WIBP-CorV as their first dose became the observation group; subjects who had received BBIBP-CorV as their first dose became the control group. All participants received BBIBP-CorV as their second dose. We obtained sera 1, 2, and 6 months after second doses for nAb titer measurement by micro-neutralization cytopathic effect assay with SARS-CoV-2 strain HB01, standardized with WHO International Standard for anti-SARS-CoV-2 immunoglobulin. Safety was assessed for the 7 days after administration of second doses.

Results: Between March and December 2021, 275 subjects were included in the observation group and 133 in the control group. Neutralizing seropositivity (≥1:4) rates were 98.91 % and 99.25 % at 1 month and 53.16 % and 70.69 % at 6 months. One-month geometric mean titers (GMTs) were 21.33 and 22.45; one-month geometric mean concentrations (GMCs) were 227.71 IU/mL and 273.27 IU/mL. One to two months after vaccination, observation group seropositivity rates and titers were not significantly different to the control group's. Adverse reaction rates were 11.27 % and 18.80 %, all mild or moderate in severity.

Conclusions: Both primary series were immunogenic; immunogenicity of WIBP-CorV followed by BBIBP-CorV was not different than immunogenicity following two doses of BBIBP-CorV for two months after vaccination; safety profiles were acceptable for both regimens. BBIBP-CorV can be used to complete a primary series that started with WIBP-CorV.

© 2022 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Through July 2022, there have been more than 575 million cases and 6 million COVID-19 deaths reported to the World Health Organization [1]. Vaccines are powerful weapons for epidemic prevention and control; 67 % of the world's population has received at least one dose of a COVID-19 vaccine, but only 19.9 % of people in

---

low-income countries have received a dose [2]. Vaccine shortages and disruptions or delays in the supply chain due to production or transportation problems have occurred frequently since COVID-19 vaccines were approved.

There are seven vaccines approved conditionally or for emergency use in China: five inactivated vaccines, one adenovirus vectored vaccine, and one recombinant protein vaccine. Safety, immunogenicity, and protective efficacy of these vaccines have been shown in clinical trials [3–11]. In December 2020, during the early stage of COVID-19 vaccine approval, Hubei and Hainan provinces used the inactivated vaccine WIBP-CorV, developed by the Wuhan Institute of Biological Products Co, Ltd, to vaccinate people at high risk of SARS-CoV-2 exposure in a two-dose primary series with an inter-dose interval of 3–8 weeks. However, due to insufficient supplies of WIBP-CorV, and to avoid delays in vaccination, another inactivated vaccine, BBIBP-CorV, developed by the Beijing Institute of Biological Products Co, Ltd, was approved to complete a primary series that started with WIBP-CorV. Both manufacturers belong to the China National Biotec Group Company Limited.

The interruption of supply of WIBP-CorV provided an opportunity to conduct a pragmatic observational cohort study to assess the safety, immunogenicity, and immune persistence of a primary series of WIBP-CorV followed by BBIBP-CorV compared with a primary series of two doses of BBIBP-CorV. We report results of our study.

2. Methods

2.1. Setting and subjects

The study was set in Hubei and Hainan provinces and was conducted from March 2021 to December 2021, during which time there was almost no transmission of SARS-CoV-2 in the mainland of China due implementation of public health and social measures (PHSM) that prevent transmission. A population-based serological survey in Hubei and six other provinces in China following initial containment of SARS-CoV-2 showed population seroprevalence to be 0.44 % in Hubei-ex-Wuhan and <0.1 % outside of Hubei [12]. There were no SARS-CoV-2 outbreaks in the study areas during the study period.

Hubei and Hainan provincial centers for disease prevention and control (CDCs) invited healthy adults, 18–59-years-old, who were already in the process of receiving a primary series with either WIBP-CorV or BBIBP-CorV inactivated COVID-19 vaccine, to participate in the study. Exclusion criteria were history of SARS-CoV-2 infection, history of using blood products or immunosuppressive drugs, and history of severe adverse reaction following any vaccine. Withdrawal and discontinuation criteria included moving away, inability to complete follow-up sample collection due to health conditions or serious adverse reaction, or requesting to withdraw or discontinue the study for any reason.

2.2. Vaccines

The study vaccines were WIBP-CorV, developed by Wuhan Institute of Biological Products Co, Ltd., and BBIBP-CorV, developed by Beijing Institute of Biological Products Co, Ltd. Both vaccines are ancestral strain, whole-virus, β-propiolactone-inactivated, aluminum hydroxide adjuvanted, liquid COVID-19 vaccines. BBIBP-CorV was made using the 19nCoV-CDC-Tan-HB02 strain of SARS-CoV-2 and WIBP-CorV was made using the WIV04 strain. Both vaccines had been conditionally approved for individuals 18 years and older by the National Medical Products Administration (NMPA), the vaccine regulatory authority of China, prior to the start of the

study, and both were in widespread use in China during the study period.

2.3. Design

Fig. 1 shows the study flow diagram. Due to insufficient supply of WIBP-CorV, individuals who received one dose of either WIBP-CorV or BBIBP-CorV vaccine to start their 2-dose primary series had to complete their primary series with BBIBP-CorV. Consenting, eligible adults who had received one dose of WIBP-CorV or one dose of BBIBP-CorV were recruited into this cohort study before receiving primary-series dose two. We observed the subjects during the process of receiving dose two (always BBIBP-CorV), obtained demographic information with a questionnaire, and observed for adverse reactions occurring 0–7 days after dose two. Thus, there were two study groups – one group received WIBP-CorV as their first dose (observation group) and the other received BBIBP-CorV as their first dose (control group) – both groups received BBIBP-CorV as their second dose.

For the control group, we based the sample sizes target using α = 0.05, β = 0.10, dropout rate λ = 0.2, two-sided tests, with expected seropositive by time since vaccination of 100 % at 1 month [5], and effect sizes of 3.5 percentage point differences from expected values. The required sample size was 133. The target sample size of the observation group was set at 266, twice that of the control group.

Three mL samples of venous blood were drawn from participants at 1 month, 2 months, and 6 months after administration of the second dose. Specimens were processed the same day and frozen until laboratory analysis.

2.4. Laboratory testing and standardization

In a BSL-3 laboratory, serum neutralizing antibody (nAb) responses were assessed by the reduction of cytopathic effect (CPE) method in Vero cells using infectious SARS-CoV-2 strain 19nCoV-CDC-Tan-HB01 (HB01 is an ancestral strain isolated from a patient during the initial outbreak in Wuhan in early 2020). Briefly, serum was inactivated at 56℃ for 30 min and successively diluted from 1:4 to the required concentration in 2-fold series. An equal volume of challenge virus solution containing 100 $CCID_{50}$ virus was added. After neutralization in a 37℃ incubator for 2 h, a 1.5–2.5 $\times$ 10^5/mL cell suspension was added to the wells; cytopathic effect was assessed 4 days after infection. Neutralization titers (NT_{50}) were expressed as the reciprocal of the highest dilution protecting 50 % of the cells from the virus challenge. $NT_{50} \geq 4$ were considered positive.

To facilitate comparison of SARS-CoV-2 neutralization assay data from multiple assay formats and vaccines, we used the WHO international standard (IS) and an internal neutralization standard. The WHO 1st IS for antisera to SARS-CoV-2 (NIBSC code 20/136) was obtained from National Institute for Biological Standards and Control (NIBSC). The internal neutralization standard 'R1' was generated in-house by Beijing Minhai Biotechnology Co., Ltd. by pooling a selection of SARS-CoV-2 RBD protein immunized goat sera. All neutralization standardizations were run in triplicate on the SARS-CoV-2 neutralizing assay described above. The internal reference was calibrated according to the WHO 1st IS for anti-SARS-CoV-2 immunoglobulin; test samples compared to the IS can be expressed in IU/mL by the calculation: GMT of test samples / (GMT of SARS-CoV-2 IS/1000) = IU/mL. The calibrated potency of internal standard 'R1' was 16,734 IU/mL. The internal reference was included in every experiment and used for correction of tested sample results. To convert sample neutralization titers into international units, the neutralization dilution values of the sample were divided by the neutralization of the internal standard run
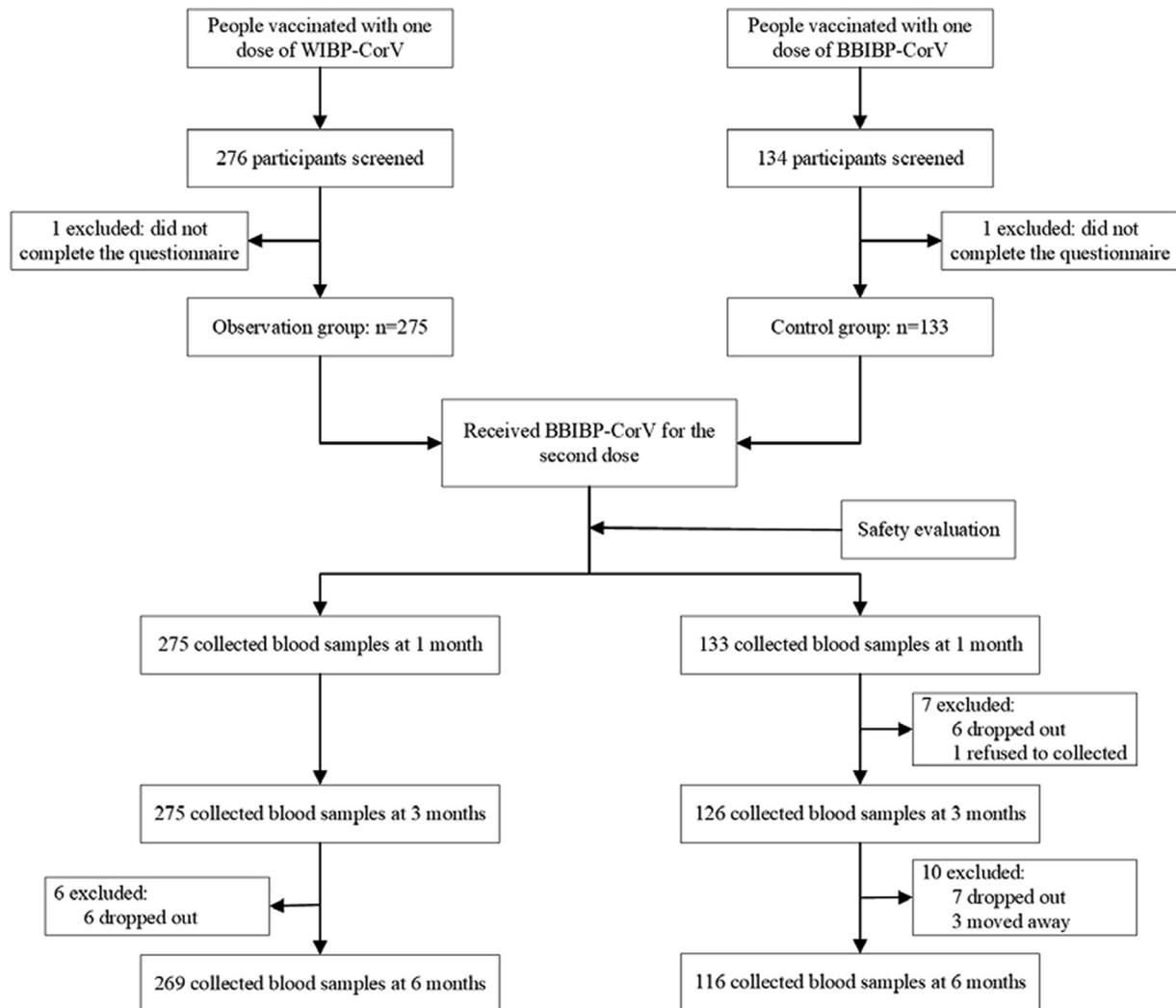
Fig. 1. Study flow diagram.

during the same experiment and then multiplied by the calibrated potency of the respective internal standards in international units. Use of the reference standard sera allowed neutralization assay outputs to be converted to international units per milliliter (IU/mL).

2.5. Safety

As is standard practice for vaccinations in China, participants were requested to stay in the clinic for 30 min of observation after vaccination. Adverse events during the clinic stay were recorded. Participants were requested to record any injection site–specific adverse reactions (e.g., pain, redness, swelling) and systemic adverse reactions (e.g., fever, headache, fatigue) on diary cards through 7 days after dose two (BBIBP-CorV). Unsolicited symptoms and signs were recorded during follow-up. Subjects turned in diary cards at the 1-month blood draw visit. Adverse events were graded according to the guiding principles for grading standard of adverse events in clinical trials of vaccines (No. 102 in 2019), issued by NMPA [13].

2.6. Statistical analysis

Two trained postgraduate students independently entered data in EpiData software version 3.1 with double entry verification. All analyses were performed with R version 4.1.0. We used mean ± standard deviation (SD) and composition ratio (%) to describe sociodemographic information. Immunogenicity was expressed by nAb seroconversion percentage (NT_{50} positive rates), geometric mean titers (GMT), and geometric mean concentrations (GMC, IU/mL) referenced to WHO, with associated 95 % confidence intervals (CI). Any serologic values below the lower limit of quantification were set to 0.5 times the lower limit of quantification. Decrease of nAb titers was calculated by: (GMT at 1 month - GMT at 12 months)/GMT at 1 month * 100 %, and a decreasing trend was tested for by linear regression. Safety end points included the incidence of injection site and systemic adverse reactions within 30 min and through 7 days after vaccination. T tests, Chi square tests, or Fisher exact tests and Mann-Whitney U tests were used for comparisons. Chi square trend analyses and linear regression models were used for trend tests. All tests were 2-tailed, with P values of 0.05 or less considered statistically significant.

3. Results

3.1. Participants

Four hundred and ten eligible participants were recruited into the study. With the exception of two individuals who did not complete the questionnaire, 408 participants were successfully enrolled: 275 had received WIBP-CorV for their first dose and

became the observation group and 133 had received BBIBP-CorV for their first dose and became the control group. Subjects in both groups received BBIBP-CorV for their second dose. Table 1 shows participant characteristics by study group. Demographic and clinical characteristics were similar. The most common comorbidity was hypertension. The average inter-dose interval in the control group was four days longer than in the observation group (30.5 vs 26.3 days), a statistically significant difference.

3.2. Neutralizing antibody responses to vaccination

Neutralizing antibody responses declined over time for both observation group and control group subjects. In the WIBP-CorV-first observation group, NT_{50} positive rates declined from 98.91 % at 1 month to 53.16 % at 6 months (trend χ^2 = 199.54, $P < 0.001$), and corresponding nAb titers decreased by 83.31 % (t = −30.98, $P < 0.001$); nAb concentrations declined from 227.71 [95 %CI: 209.06–248.03] to 13.34 [95 %CI: 12.34–14.41] (IU/mL). In the BBIBP-CorV-first control group, NT_{50} positive rates declined from 99.25 % to 70.69 % in 6 months (trend χ^2 = 55.68, $P < 0.001$) and corresponding GMTs decreased by 76.12 % (t = −17.41, $P < 0.001$); GMC declined from 273.27 [95 %CI: 243.93–306.13] to 25.08 [95 %CI: 21.23–29.64] (IU/mL) (Figs. 2 and 3).

Based on NT_{50} positive rate and GMT, the neutralizing antibody response of the observation group was not significantly different from that in the control group for the first 2 months after vaccina-

Table 1
Socio-demographic characteristics of study participants (N = 408).

Variable	Observation Group (WIBP-CorV + BBIBP-CorV) n(%)	Control Group (BBIBP-CorV + BBIBP-CorV) n(%)	t/χ^2	P
Age (years)				
Mean (SD)	37.94(9.88)	37.84(9.41)	0.095	0.924
Gender				
Male	113(41.09)	45(33.83)	1.695	0.193
Female	162(58.91)	88(66.17)		
Obesity (BMI ≥ 28 kg/m²)				
Yes	14(5.09)	7(5.26)	0.000	1.000
No	261(94.91)	126(94.74)		
Comorbidities[a]				
Yes	17(6.23)	8(6.02)	0.000	1.000
No	256(93.77)	125(93.98)		
Inter-dose interval (days)				
Mean(SD)	30.50(4.59)	26.32(5.03)	8.110	**<0.001**
Median(range)	30(21–53)	28(15–33)		
15–27	62(22.55)	66(49.62)	29.285	**<0.001**
28–53	213(77.45)	67(50.38)		
Total	275(100.00)	133(100.00)		

[a] Two individuals lacked comorbidity data and were excluded, making 406 subjects for comorbidity description.
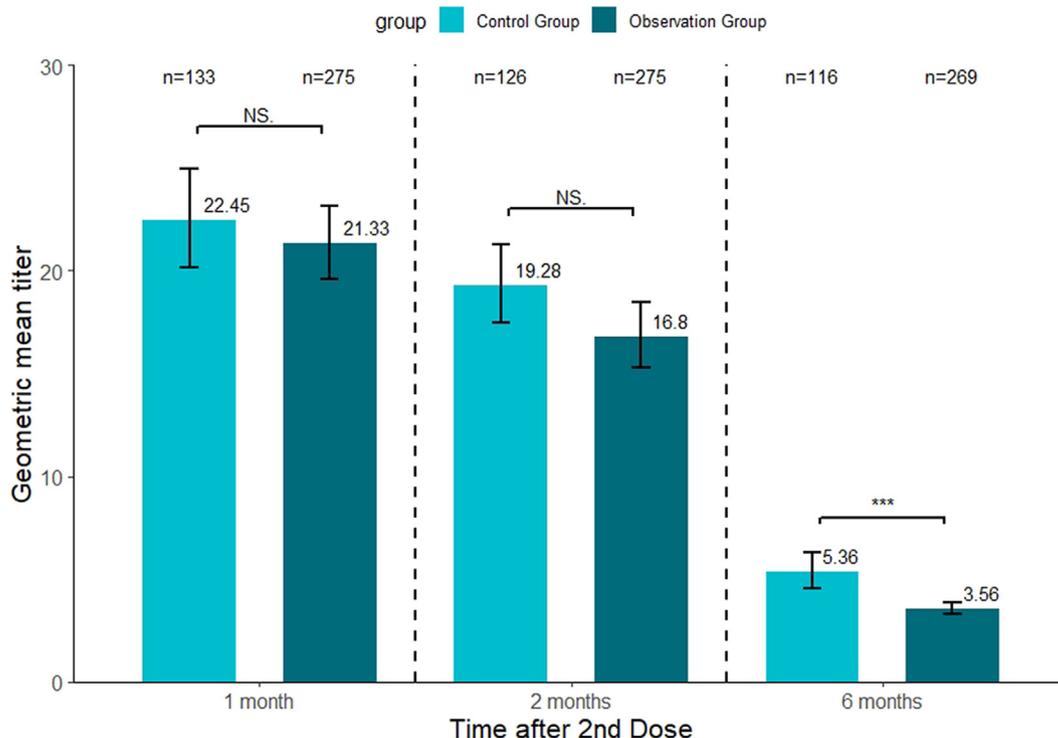
Mann-Whitney U test was used in GMT test.
n represented the sample size of each group included in analysis.

Fig. 2. Neutralizing antibody titer after the administration of 2 doses of inactivated COVID-19 vaccine.
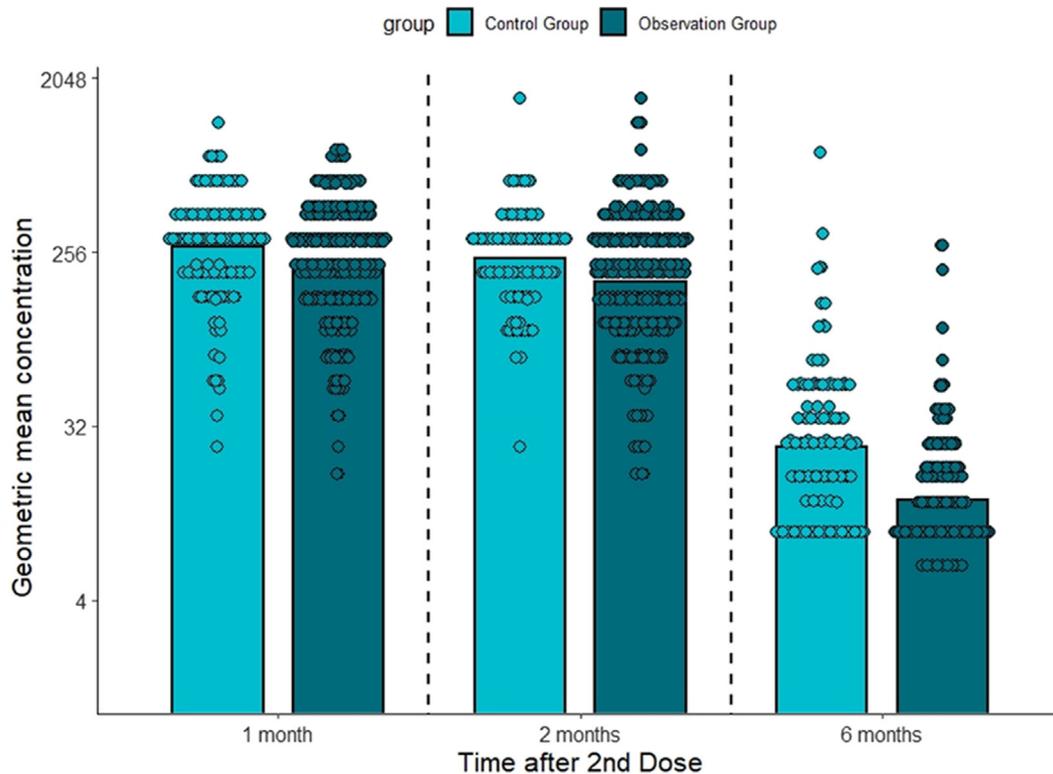
Fig. 3. Geometric mean concentrations of neutralizing antibody after the administration of 2 doses of inactivated COVID-19 vaccine.

tion (NT_{50} positive rate: $P = 0.114$; GMT: $P = 0.241$ at 2 months) but was lower at 6 months (NT_{50} positive rate: $P = 0.002$; GMT: $P < 0.001$). The control group had statistically greater GMCs than the observation group at all time points (Table 2).

3.3. Adverse reactions and events

Systemic and injection site adverse reactions are shown in Table 3 and Fig. 4. Adverse reactions within 7 days after the second dose were reported by 31 participants (11.27 %) in the observation group and 25 participants (18.80 %) in the control group. During the 30-minute observation period, at least one adverse reaction occurred in 12 (4.36 %) of 275 observation group subjects and 13 (9.77 %) of 133 control group subjects ($P = 0.055$). The most common injection site adverse reaction within 30 min was pain, which was reported in 11 (4.00 %) observation group subjects and 12 (9.02 %) control group subjects ($P = 0.067$). One participant in the control group reported dizziness; there were no other systemic adverse reactions reported during the 30-minute observation period. The most common adverse reaction during the 7-day reporting

period was pain, which was reported by 24 (8.73 %) of 275 observation group subjects, compared with 12 (9.02 %) of 133 control group subjects. Additional injection site adverse reactions included redness (1 [0.75 %] in the control group), swelling (2 [1.50 %] in the control group) and induration (2 [0.73 %] vs 2 [1.50 %]). Systematic adverse reactions within 7 days in the observation group were weakness (1 [0.36 %]) and chills (1 [0.36 %]), and in the control group 1 (0.75 %) reported dizziness. All adverse reactions were mild in severity (grade 1 or 2) and were transient and self-limiting, without need of treatment. There were no notable differences in adverse events between groups. No other unsolicited symptoms or signs were reported.

4. Discussion

In this observational cohort study of adults, we compared the safety, immunogenicity, and immune persistence of a primary series of one dose of WIBP-CorV followed by one dose of BBIBP-CorV with a primary series of two doses of BBIBP-CorV. Our study showed that during the first 2 months after completing the pri-

Table 2
Neutralizing antibody responses to inactivated COVID-19 vaccine.

	Time after 2nd Dose	Observation Group (WIBP-CorV + BBIBP-CorV)	Control Group (BBIBP-CorV + BBIBP-CorV)	χ^2/W	P value
Seroconversion rate (%)	1 month	98.91 (97.67–100.00)	99.25 (97.76–100.00)	–[a]	1.000
	2 months	96.00 (93.67–98.33)	99.21 (97.64–100.00)	–[a]	0.114
	6 months	53.16 (47.16–59.16)	70.69 (62.28–79.10)	9.546	**0.002**
GMT(1:) (95 %CI)	1 month	21.33 (19.62–23.18)	22.45 (20.16–24.99)	17,653	0.564
	2 months	16.80 (15.28–18.47)	19.28 (17.48–21.25)	16,076	0.241
	6 months	3.56 (3.28–3.86)	5.36 (4.56–6.31)	11,246	**<0.001**
GMC[IU/mL] (95 %CI)	1 month	227.71 (209.06–248.03)	273.27 (243.93–306.13)	15,362	**0.008**
	2 months	179.35 (162.34–198.13)	236.71 (213.81–262.07)	14,012	**0.002**
	6 months	13.34 (12.34–14.41)	25.08 (21.23–29.64)	8685	**<0.001**

[a] Fisher's test was used for statistical analysis.

Table 3
Adverse reactions within 30 min and through 7 days after the second dose.

	Observation Group (WIBP-CorV + BBIBP-CorV) N = 275	Control Group (BBIBP-CorV + BBIBP-CorV) N = 133	χ^2	*P* value
Adverse reactions within 0–7 days				
Any	31(11.27 %)	25(18.80 %)	3.674	0.055
Injection site adverse reactions within 30 min				
Any	12(4.36 %)	13(9.77 %)	3.671	0.055
Pain	11(4.00 %)	12(9.02 %)	3.359	0.067
Redness	9(3.27 %)	8(6.02 %)	1.071	0.301
Swelling	8(2.91 %)	10(7.52 %)	3.490	0.062
Induration	8(2.91 %)	9(6.77 %)	2.445	0.118
Rash	8(2.91 %)	8(6.02 %)	1.545	0.214
Other	4(1.45 %)	0(0.00 %)	–[a]	0.309
Systemic adverse reactions within 30 min				
Any	0(0.00 %)	1(0.75 %)	–[a]	0.326
Fever	0(0.00 %)	0(0.00 %)	–[a]	1.000
Dizzy	0(0.00 %)	1(0.75 %)	–[a]	0.326
Injection site adverse reactions within 7 days				
Any	24(8.73 %)	13(9.77 %)	0.026	0.872
Pain	24(8.73 %)	12(9.02 %)	0.000	1.000
Redness	0(0.00 %)	1(0.75 %)	–[a]	0.326
Swelling	0(0.00 %)	2(1.50 %)	–[a]	0.106
Induration	2(0.73 %)	2(1.50 %)	–[a]	0.599
Systemic adverse reactions within 7 days				
Any	2(0.73 %)	1(0.75 %)	–[a]	1.000
Weakness	1(0.36 %)	0(0.00 %)	–[a]	1.000
Chills	1(0.36 %)	0(0.00 %)	–[a]	1.000
Dizzy	0(0.00 %)	1(0.75 %)	–[a]	0.326

[a] Fisher's test was used for statistical analysis.
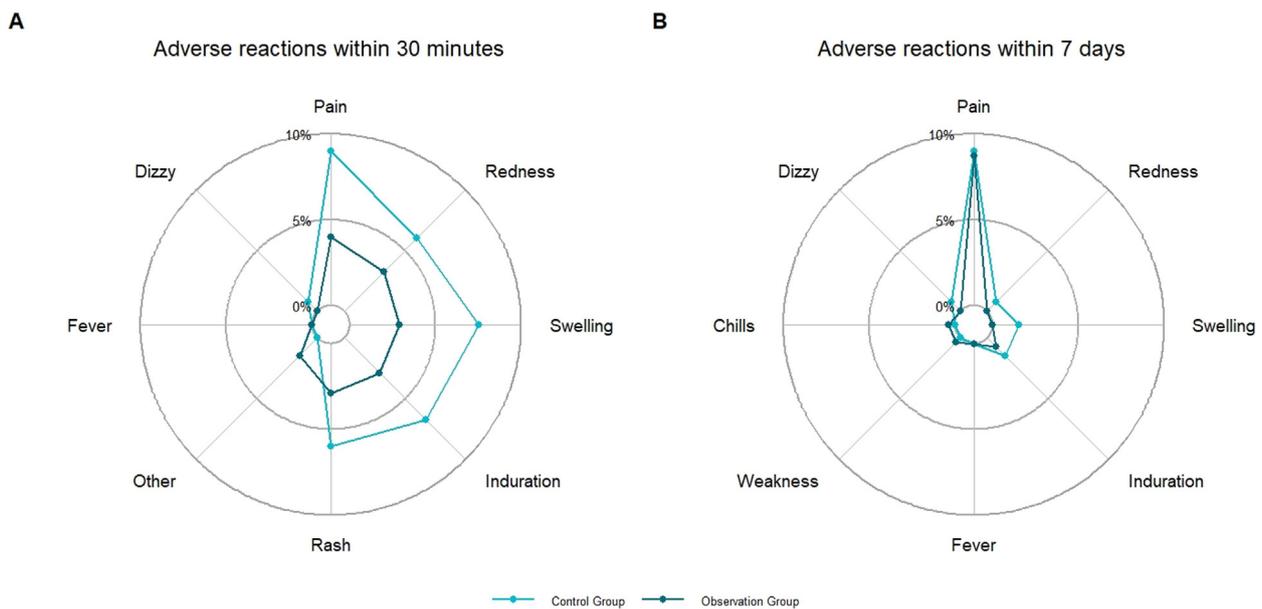
Fig. 4. Adverse reactions within 30 min and through 7 days after the administration of 2 doses of inactivated COVID-19 vaccine.

mary series, NT_{50} positive rates and GMTs of the two primary series regimens were not significantly different. All adverse reactions were mild and there were no significant differences in adverse reaction rates between the two regimens. Primary series that start with WIBP-CorV can be completed with BBIBP-CorV vaccine.

Completing COVID-19 vaccination with vaccines produced by different manufacturers has been widely used worldwide to mitigate insufficient vaccine supplies, avoid rare adverse reactions, or

further enhance immunogenicity [14–16]. Heterologous booster vaccination has been approved in many countries including China [17–19]. In the early stage of COVID-19 vaccine approval in China, Hubei and Hainan provinces used two different vaccine products made by the same technical route in primary series schedules. Because of insufficient supply of WIBP-CorV, individuals who started their primary series with WIBP-CorV had to complete their primary series with a regulator-approved second dose of BBIBP-

CorV. Our study found that this vaccination schedule had an acceptable safety profile and non-inferior immunogenicity for the first two months after primary series completion.

A single-blind, randomized, phase 2, non-inferiority trial in the UK showed non-inferiority of mRNA-1273 after a dose of BNT162b2 (GMC of live virus neutralizing antibody, normalized NT_{80}: 3252, 95 %CI: 2416–4376) to 2 doses of BNT162b2 (GMC: 3216, 95 %CI: 2336–4427), demonstrating the similar immunogenicity of two different manufactures' COVID-19 vaccines made by the same technical route [20]. Many studies have established that heterologous booster vaccination with vaccines made by different technical routes induces stronger immune response than homologous booster vaccination [14,16,21].

Serum neutralizing antibody monitoring over 6 months in our study showed that the humoral immune response produced in both study groups declined over time, and with similar downward trends. Immunogenicity and protective efficacy of COVID-19 vaccine waning over time has been found in many studies, regardless of vaccine type [22–24]. For example, Zeng and colleagues found that neutralizing seropositivity decreased from 100 % to 35 % for people aged 18–59 six months after 2 doses of CoronaVac, while GMT decreased from 45.9 to 6.8 [25]. GMTs from Pfizer/BioNTech BNT162b2 decreased from 557.1 to 119.4 six months after immunization according to Levin and colleagues' study [22].

In terms of safety and reactogenicity, the most common adverse reactions within 30 min and 7 days of combined vaccination were pain, redness, and swelling at the injection site. There were no serious adverse reactions in either group, and there were no differences in adverse reaction incidence. In clinical trials of BBIBP-CorV, incidences of adverse reactions within the first 7 days were 33 % (8/24) in phase 1, and 12 %–18 % (10/84 and 15/84 for 0–21-day group and 0–28-day group, respectively) in phase 2 in a 4 μg dose group of participants aged 18–59 years [5]. In clinical trials of WIBP-CorV, 7-day adverse reactions rates were 16.7 % (4/24) in phase 1 and 19.0 % (16/84) in phase 2 for a 5 μg dose group [3]. Our safety and reactogenicity results were similar to findings from clinical trials of both vaccines and to other studies of inactivated vaccines [4,6], with reactogenicity somewhat lower than seen with mRNA or adenovirus vectored vaccines [26–29]. However, a cross-sectional study for the side effects of CoronaVac in Turkish healthcare workers reported a higher incidence of side effects following inactivated vaccine administration (62.5 %, 487/780) than what we found in our study or in clinical trials. This may be because healthcare workers have a high level of health literacy and scientific interest, making it easier to conduct self-assessments [30].

There are many methods being used for neutralizing antibody detection, and different methods, laboratories, and testing personnel may give different results. In December 2020, the WHO Expert Committee on Biological Standardization formulated the WHO international standard for anti-SARS-CoV-2 immunoglobulin (NIBSC code 20/136) to promote standardized evaluation of COVID-19 vaccines [31]. In our study, we used the first WHO IS, NIBSC code 20/136 to facilitate comparison of SARS-CoV-2 neutralization assay data from multiple assay formats and vaccine candidates. A study on Oxford/AstraZeneca's vaccine AZD1222 also corrected the neutralizing antibody titer using the WHO international standard. The results showed that when the protective effect of AZD1222 against symptomatic infection of Alpha variant was 80 %, the standardized GMC was 247 (95 % CI: 101-NC) IU/mL [32], which was similar to our findings at 1 month for WIBP-CorV followed by BBIBP-CorV (227.71, 95 %CI: 209.06–248.03 IU/mL), but slightly higher than that at 2 months (179.35, 95 %CI: 162.34–198.13 IU/mL). A predictive model study of immune protection and in vitro neutralization levels found that a 50 % protective neutralization level was equivalent to a measured in vitro neutralization titer of between 1:10 and 1:30 in most assays, or

approximately 54 IU/mL (95 %CI: 30–96 IU/mL) - indicating that the heterologous primary series in our study induced a good humoral immune response [33].

Our study has limitations. First, we only assessed live virus neutralizing antibody levels and did not test individual antigens or cellular immune responses. The effect of such combined vaccination regimens on cellular immune response is not clear and needs further study. Earlier basic immunity studies have shown that both of the two inactivated vaccines we studied can induce cellular immunity. Second, there may be underreporting of adverse reactions. However, that our safety and immunogenicity findings are similar to other studies of the same vaccines provides some confidence in our safety/reactogenicity results. Third, the interval between primary series doses in our study was slightly longer in the heterologous primary series group than the homologous group, which may lead to a slight overestimation of neutralizing antibody GMT in the observation group. Several studies have shown that increasing the primary series dose interval will increase antibody responses [6,34].

In conclusion, we found that after a first dose of WIBP-CorV COVID-19 vaccine, completing the primary series with BBIBP-CorV induced a good humoral immune response and had an acceptable safety profile compared with a primary series consisting of two doses of BBIBP-CorV. Therefore, BBIBP-CorV is an appropriate vaccine for completing a primary series that started with WIBP-CorV.

Author contributions

The study was conceived and designed by WJ Tan and ZD Yin. Data analyses were performed by XQ Wang, FZ Wang, and L Tang. BY Huang, Y Deng, L Zhao, F Ye, WL Wang conducted laboratory testing. L Wang, ZW Fu, SQ Wang, B Hu, XH Guan, ZL Han, and YQ Tong were responsible for data collection. XQ Wang and QQ Liu wrote the first draft of the manuscript; FZ Wang, BY Huang and Lance Rodewald contributed to the final version of the paper.

Ethical approval

The study protocol and informed consent form were approved by the Medical Ethics Committee of the Chinese Center for Disease Control and Prevention (Approval notice: 202101). Written informed consent was obtained from all study participants.

Data availability

Data will be made available on request.

Declaration of Competing Interest

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

References

[1] World Health Organization. WHO coronavirus (COVID-19) dashboard. 2022-02-15. Available from: https://covid19.who.int/.

[2] OWI Data. Coronavirus (COVID-19) vaccinations; 2022. Available from: https://ourworldindata.org/covid-vaccinations.

[3] Xia S, Duan K, Zhang Y, Zhao D, Zhang H, Xie Z, et al. Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes. JAMA 2020;324(10):951.

[4] Al Kaabi N, Zhang Y, Xia S, Yang Y, Al Qahtani MM, Abdulrazzaq N, et al. Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults. JAMA 2021;326(1):35.

[5] Xia S, Zhang Y, Wang Y, Wang H, Yang Y, Gao GF, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. Lancet Infect Dis 2021;21(1):39–51.

[6] 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(2):181–92.

[7] Tanriover MD, Doğanay HL, Akova M, Güner HR, Azap A, Akhan S, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. The Lancet 2021;398(10296):213–22.

[8] Che Y, Liu X, Pu Yi, Zhou M, Zhao Z, Jiang R, et al. Randomized, double-blinded, placebo-controlled phase 2 trial of an inactivated severe acute respiratory syndrome coronavirus 2 vaccine in healthy adults. Clin Infect Dis 2021;73(11): e3949–55.

[9] Pan H-X, Liu J-K, Huang B-Y, Li G-F, Chang X-Y, Liu Y-F, et al. Immunogenicity and safety of a severe acute respiratory syndrome coronavirus 2 inactivated vaccine in healthy adults: randomized, double-blind, and placebo-controlled phase 1 and phase 2 clinical trials. Chin Med J 2021;134(11):1289–98.

[10] Zhu F-C, Guan X-H, Li Y-H, Huang J-Y, Jiang T, Hou L-H, et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet 2020;396(10249):479–88.

[11] Yang S, Li Y, Dai L, Wang J, He P, Li C, et al. Safety and immunogenicity of a recombinant tandem-repeat dimeric RBD-based protein subunit vaccine (ZF2001) against COVID-19 in adults: two randomised, double-blind, placebo-controlled, phase 1 and 2 trials. Lancet Infect Dis 2021;21 (8):1107–19.

[12] Li Z, Guan X, Mao N, Luo H, Qin Y, He Na, et al. Antibody seroprevalence in the epicenter Wuhan, Hubei, and six selected provinces after containment of the first epidemic wave of COVID-19 in China. Lancet Reg Health West Pac 2021;8:100094.

[13] NMP Administration. Circular of national medical products administration on issuing guidelines for grading criteria of adverse events in clinical trials of vaccines (No. 102 of 2019). 2019-12-31. Available from: https://www.nmpa.gov.cn/xxgk/ggtg/qtggtg/20191231111901460.html.

[14] Shaw RH, Stuart A, Greenland M, Liu X, Nguyen Van-Tam JS, Snape MD. Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data. The Lancet 2021;397(10289):2043–6.

[15] Barros-Martins J, Hammerschmidt SI, Cossmann A, Odak I, Stankov MV, Morillas Ramos G, et al. Immune responses against SARS-CoV-2 variants after heterologous and homologous ChAdOx1 nCoV-19/BNT162b2 vaccination. Nat Med 2021;27(9):1525–9.

[16] Liu X, Shaw RH, Stuart ASV, Greenland M, Aley PK, Andrews NJ, et al. Safety and immunogenicity of heterologous versus homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine (Com-COV): a single-blind, randomised, non-inferiority trial. The Lancet 2021;398 (10303):856–69.

[17] China NHCOTPSRO. China widens choices for COVID-19 booster shots. 2022-02-21. Available from: http://en.nhc.gov.cn/2022-02/21/c_85855.htm.

[18] Prevention CFDCA. COVID-19 vaccine booster shots. 2022-02-2. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/booster-shot.html.

[19] Control ECFDPA. Overview of the implementation of COVID-19 vaccination strategies and deployment plans in the EU/EEA. 2022-01-31.

[20] Stuart ASV, Shaw RH, Liu X, Greenland M, Aley PK, Andrews NJ, et al. Immunogenicity, safety, and reactogenicity of heterologous COVID-19 primary vaccination incorporating mRNA, viral-vector, and protein-adjuvant vaccines in the UK (Com-COV2): a single-blind, randomised, phase 2, non-inferiority trial. Lancet (London, England) 2022;399(10319):36–49.

[21] Tenbusch M, Schumacher S, Vogel E, Priller A, Held J, Steininger P, et al. Heterologous prime-boost vaccination with ChAdOx1 nCoV-19 and BNT162b2. Lancet Infect Dis 2021;21(9):1212–3.

[22] Levin EG, Lustig Y, Cohen C, et al. Waning immune humoral response to BNT162b2 Covid-19 vaccine over 6 months. N Engl J Med 2021;385(24):e84.

[23] Pegu AOCS, Schmidt SD, et al. Durability of mRNA-1273 vaccine-induced antibodies against SARS-CoV-2 variants. Science 2021;373(6561):1372–7.

[24] Barouch DH, Stephenson KE, Sadoff J, et al. Durable humoral and cellular immune responses 8 months after Ad26.COV2.S vaccination. N Engl J Med 2021;385(10):951–3.

[25] Zeng G, Wu Q, Pan H, Li M, Yang J, Wang L, et al. Immunogenicity and safety of a third dose of CoronaVac, and immune persistence of a two-dose schedule, in healthy adults: interim results from two single-centre, double-blind, randomised, placebo-controlled phase 2 clinical trials. Lancet Infect Dis 2022;22(4):483–95.

[26] Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA vaccine against SARS-CoV-2 — preliminary report. N Engl J Med 2020;383(20):1920–31.

[27] El Sahly HM, Baden LR, Essink B, Doblecki-Lewis S, Martin JM, Anderson EJ, et al. Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. N Engl J Med 2021;385(19):1774–85.

[28] Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature 2020;586 (7830):589–93.

[29] Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet (London, England) 2020;396(10249):467–78.

[30] Riad A, Sağıroğlu D, Üstün B, Pokorná A, Klugarová J, Attia S, et al. Prevalence and risk factors of CoronaVac side effects: an independent cross-sectional study among Healthcare Workers in Turkey. J Clin Med 2021;10(12):2629.

[31] Control NIFBSA. First WHO International Standard for anti-SARS-CoV-2 immunoglobulin, human (NIBSC code: 20/136). 2020-12-17. Available from: https://www.nibsc.org/science_and_research/idd/cfar/covid-19_reagents.aspx.

[32] Feng S, Phillips DJ, White T, Sayal H, Aley PK, Bibi S, et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. Nat Med 2021;27(11):2032–40.

[33] Khoury DA-O, Cromer DA-O, Reynaldi AA-O, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med 1546-170X (Electronic)).

[34] Voysey M, Costa Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. The Lancet 2021;397 (10277):881–91.