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Immunogenicity and safety of an inactivated SARS-CoV-2 vaccine (Sinopharm BBIBP-CorV) coadministered with quadrivalent split-virion inactivated influenza vaccine and 23-valent pneumococcal polysaccharide vaccine in China: A multicentre, non-inferiority, open-label, randomised, controlled, phase 4 trial

Haiping Chen [a,1], Zhuoying Huang [b,1], Shaoying Chang [c,1], Mei Hu [d,1], Qingbin Lu [e,1], Yuntao Zhang [a], Hui Wang [c], Yanhui Xiao [a], Hui Wang [f], Yonghong Ge [g], Yong Zou [h], Fuqiang Cui [e], Shasha Han [a], Min Zhang [a], Shengyi Wang [a], Xiaoping Zhu [d], Biao Zhang [i], Zhi Li [b], Jia Ren [b], Xiao Chen [c], Rui Ma [f], Lei Zhang [g], Xue Guo [h], Linyun Luo [a], Xiaodong Sun [b,*], Xiaoming Yang [a,j,*]

[a] China National Biotec Group Company Limited, Beijing, China
[b] Shanghai Municipal Center for Disease Control and Prevention, Shanghai, China
[c] Shanxi Provincial Center for Disease Control and Prevention, Taiyuan, China
[d] Sichuan Center for Disease Control and Prevention, Chengdu, China
[e] Department of Laboratorial Science and Technology & Vaccine Research Center, School of Public Health, Peking University, Beijing, China
[f] Beijing Institute of Biological Products Company Limited, Beijing, China
[g] Chengdu Institute of Biological Products Company Limited, Chengdu, China
[h] Changchun Institute of Biological Products Company Limited, Changchun, China
[i] Santai County Center for Disease Control and Prevention, Mianyang, China
[j] National Engineering Technology Research Center for Combined Vaccines, Wuhan Institute of Biological Products Company Limited, Wuhan, China

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ABSTRACT

Background: The safety and immunogenicity of the coadministration of an inactivated SARS-CoV-2 vaccine (Sinopharm BBIBP-CorV), quadrivalent split-virion inactivated influenza vaccine (IIV4), and 23-valent pneumococcal polysaccharide vaccine (PPV23) in adults in China is unknown.

Methods: In this open-label, non-inferiority, randomised controlled trial, participants aged ≥ 18 years were recruited from the community. Individuals were eligible if they had no history of SARS-CoV-2 vaccine or any pneumonia vaccine and had not received an influenza vaccine during the 2020–21 influenza season. Eligible participants were randomly assigned (1:1:1), using block randomization stratified, to either: SARS-CoV-2 vaccine and IIV4 followed by SARS-CoV-2 vaccine and PPV23 (SARS-CoV-2 + IIV4/PPV23 group); two doses of SARS-CoV-2 vaccine (SARS-CoV-2 vaccine group); or IIV4 followed by PPV23 (IIV4/PPV23 group). Vaccines were administered 28 days apart, with blood samples taken on day 0 and day 28 before vaccination, and on day 56.

Results: Between March 10 and March 15, 2021, 1152 participants were recruited and randomly assigned to three groups (384 per group). 1132 participants were included in the per-protocol population (375 in the SARS-CoV-2 + IIV4/PPV23 group, 380 in the SARS-CoV-2 vaccine group, and 377 in the IIV4/PPV23 group). The seroconversion rate (100 % vs 100 %) and GMT (159.13 vs 173.20; GMT ratio of 0.92 [95 % CI 0.83 to 1.02]) of SARS-CoV-2 neutralising antibodies in the SARS-CoV-2 + IIV4/PPV23 group was not inferior to those in the SARS-CoV-2 vaccine group. The SARS-CoV-2 + IIV4/PPV23 group was not inferior to the IIV4/PPV23 group in terms of seroconversion rates and GMT of influenza virus antibodies for all strains except for the seroconversion rate for the B/Yamagata strain. The SARS-CoV-2 + IIV4/PPV23 group

* Corresponding authors at: China National Biotec Group Company Limited, No.2, Shuangqiao Street, Chaoyang District, Beijing 100024, China (X. Yang). Shanghai Municipal Disease Prevention and Control Center, No.1380, Zhongshanxi Street, Changning District, Shanghai 200336, China (X. Sun).
E-mail addresses: sunxiaodong@scdc.sh.cn (X. Sun), yangxiaoming@sinopharm.com (X. Yang).
[1] Equal contributors to this manuscript.

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was not inferior to the IIV4/PPV23 group regarding seroconversion rates and GMC of *Streptococcus pneumoniae* IgG antibodies specific to all serotypes. All vaccines were well tolerated.
Conclusions: The coadministration of the inactivated SARS-CoV-2 vaccine and IIV4/PPV23 is safe with satisfactory immunogenicity.
This study is registered with ClinicalTrials.gov, NCT04790851.

1. Introduction

The COVID-19 pandemic has severely affected global public health, societies, and economies, causing more than 571 million infections and more than 6.38 million deaths as of Jul 29, 2022 [1]. Multiple SARS-CoV-2 vaccines with proven efficacy, including inactivated vaccines, are being administered globally and have substantially reduced the burden of disease and mortality, especially for severe cases [2,3]. More than 50 % of vaccine efficacy against the Delta variant (B.1.617.2) has been observed in individuals who have received two doses of vaccine [4–6]. Real-world studies indicated that two or three dose schedules of SARS-CoV-2 vaccines still offered strong protection against severe disease and death caused by infection with Omicron variant [7–9]. Thus, SARS-CoV-2 vaccination is the most effective measure for disease control.

Public health measures implemented during the early stages of the COVID-19 pandemic to reduce the spread of SARS-CoV-2, including wearing facemasks, public education, and restrictions on large gatherings, also effectively reduced the transmission of other viruses and bacteria that cause respiratory diseases, such as influenza virus and Streptococcus pneumonia [10,11]. However, increased incidences of infections with influenza virus and other respiratory viruses were associated with the lifting of public health measures in late 2020 [10,12]. In China, influenza virus and *S pneumoniae* are the leading viral and bacterial pathogens that cause acute respiratory diseases [13], leading to substantial public health and socioeconomic challenges. The annual influenza-associated excess influenza-like-illness outpatient consultations, severe acute respiratory infections hospitalizations and excess respiratory deaths were 3 million, 2.34 million, 0.09 million in China from 2006 to 2019 [14]. Wahl, et al. estimated that China still had approximately 7400 pneumococcal deaths in children aged 1–59 months in 2015 [15], and there was little information about the burden of pneumococcus in adult and the older. However, there was low influenza vaccine and the 23-valent pneumococcal polysaccharide vaccine (PPV23) coverage in China, influenza vaccine coverage was only 1.5–2.2 % [16], and for PPV23 was only about 2.98 %–22.8 % [17,18]. While the governments of some cities have made great efforts in pushing forward influenza or PPV23 vaccination coverage, for example, cities such as Beijing, Shenzhen and Guangzhou provided free influenza vaccination to local elderly and school children, and cities such as Shanghai and Chengdu provided free PPV23 for the elderly, the coverage was much lower than that of developed countries [16,18,19].

The quadrivalent split-virion inactivated influenza vaccine (IIV4) has been found to be a more cost-effective means of reducing the influenza virus burden than the trivalent influenza vaccine [20], and the PPV23 has been widely used and is highly effective in preventing invasive pneumococcal disease[21]. Maintaining high coverage of influenza vaccines and PPV23 has the potential to both reduce the burden of the targeted diseases and reduce COVID-19-associated morbidity and mortality among older people[22].

Previous studies have shown that the coadministration of IIV4 and PPV23 can protect against influenza and pneumococcal disease with an acceptable reactogenicity and safety profile, as well as improve the uptake of both vaccines, and is associated with socioeconomic benefits[21,23,24]. Inactivated SARS-CoV-2 vaccines have been dominantly administered throughout China, and have been approved for use in many countries and regions. We hypothesised that the coadministration of IIV4, PPV23, and an inactivated SARS-CoV-2 vaccine, Sinopharm BBIBP-CorV, could reduce health-care expenditures and increase socioeconomic benefits. During the COVID-19 pandemic, the willingness to receive IIV4 and PPV23 increased in adults in China [25,26], which creates an unprecedented opportunity to improve vaccine coverage and reduce the burden of diseases caused by SARS-CoV-2, influenza virus, and *S pneumoniae*. Therefore, in the absence of relevant evidence, we need to determine the immunogenicity and safety profile of the coadministration of an inactivated SARS-CoV-2 vaccine with IIV4 and PPV23 compared with the administration of only an inactivated SARS-CoV-2 vaccine and sequential administration of IIV4 and PPV23.

2. Methods

2.1. Study design and participants

This multicentre, open-label, non-inferiority, randomised, controlled, phase 4 trial was conducted in Shanghai, Shanxi, and Sichuan provinces, China. The provincial Centers for Disease Control and Prevention (CDC) in Shanghai city, Shanxi province, and Sichuan province acted as cooperative institutions to recruit participants from the community. This trial was registered with ClinicalTrials.gov (NCT04790851).

Individuals aged 18 years or older who lived in the province or city were eligible for recruitment. Individuals were eligible for inclusion if they had no history of SARS-CoV-2 vaccine or any pneumonia vaccine ever and did not receive an influenza vaccination during the 2020–21 influenza season, and had a body temperature of 37·0°C or lower. Exclusion criteria at the time of first dose were previous SARS-CoV-2 infection; family or individual history of allergy to a previous vaccination, convulsions, epilepsy, cerebral disease, or mental diseases; current or previous severe allergy or contraindication to any vaccination; hypoimmunity or receipt of blood products or immunosuppressive therapy within the past month; and receipt of any vaccines within the past 2 weeks. Exclusion criteria at the time of the second dose were the occurrence of any serious adverse events associated with the study vaccination protocol and any new event meeting the exclusion criteria for the first dose. A complete list of eligibility criteria is available in the protocol (Supplemental Materials p 35–36).

Written informed consent was obtained from all participants before receipt of any study treatment. The study protocol was approved by the Ethical Review Committee of Shanghai CDC (2021–7), Shanxi CDC (SXCDCIRBYJ2021058001), and Sichuan CDC (SC-0820211301).

2.2. Randomisation and masking

Participants were randomly assigned (1:1:1) to either SARS-CoV-2 and IIV4 followed by SARS-CoV-2 and PPV23 (SARS-COV-2

+ IIV4/PPV23 group); two doses of SARS-CoV-2 vaccine (SARS-CoV-2 vaccine group); or IIV4 followed by PPV23 (IIV4/PPV23 group). Randomisation was done by an independent statistician (QL) using block randomisation (block size of six) and stratified by age (18–59 years vs $\geq$ 60 years) and study site (Shanghai, Shanxi and Sichuan). The statistician generated sequential random numbers and all eligible participants were assigned a random number by envelop that was used to identify all procedures to be done after the participants had been randomly grouped. Once a random number had been assigned to one participant, it could not be reassigned to another participant. Although participants and assessors were not masked to study group assignment, the laboratory technicians were masked to which vaccines were administered to each of the three groups.

2.3. Procedures

After enrolment, the baseline demographic for each participant, including their date of birth, sex, education, weight, and height was obtained using a uniform questionnaire completed by the study physician. The vaccines used in the present study were domestically produced and authorised for human use in the general population.

The IIV4 vaccine was produced by the Changchun Institute of Biological Products (containing 15 μg of each haemagglutinin; lot number Q20200925, Changchun, China) and was composed of haemagglutinin from A/Guangdong - Maonan / SWL1536 / 2019, A/HongKong/2671/2019, B/Washington/02/2019, and B/Phuket/3073/2013 viruses. The IIV4 vaccine was approved for adults and children older than 3 years with a schedule of one dose. The PPV23 vaccine was produced by Chengdu Insititute of Biological Products (lot number 20200734, Chengdu, China) and contained 25 μg of the purified pneumococcal capsular polysaccharides for each of 1, 2, 3, 4, 5, 6B, 7F, 8, 9 N, 9 V, 10A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F. It was approved in China for adults and children older than 2 years with a schedule of one dose. The inactivated SARS-CoV-2 vaccine, Sinopharm BBIBP-CorV, was produced by Beijing Institute of Biological Products (lot number 202011177, Beijing, China), and contained 6.5 U of the inactivated SARS-CoV-2 antigen based on the 19nCov-CDC-Tan-HB02 strain and approved for a schedule of two doses with an interval of 28 days among people aged 18 years and older in many countries.

All vaccines were administered intramuscularly. The SARS-COV-2 + IIV4/PPV23 group received one dose of the SARS-CoV-2 vaccine and one dose of IIV4 on day 0, followed by one dose of SARS-CoV-2 vaccine and one dose of PPV23 on day 28, with each dose at each visit being administered in a different arm. The SARS-CoV-2 vaccine group received two doses of SARS-CoV-2 vaccine, one on day 0 and the other on day 28. The IIV4/PPV23 group received one dose of IIV4 on day 0, followed by one dose of PPV23 on day 28. For each of the three groups, each vaccination could be done within 5 days of the prespecified window.

Three blood samples were collected from each participant: one before immunisation on day 0, one before second immunisation on day 28, and one on day 56. Final blood samples could be collected up to 5 days after day 56. The first sample on day 0 was used to measure the baseline vaccine-related antibodies, and the second sample on day 28 was used to measure the SARS-CoV-2 neutralising antibodies (from the first dose) or influenza virus antibodies. The third sample on day 56 was used to measure SARS-CoV-2 neutralising antibodies or PPV23 IgG antibodies.

The SARS-CoV-2 neutralising antibody titre was measured using a plaque reduction neutralisation test [27]. The neutralisation assay was done at the National Institute for Viral Disease Control and Prevention (China CDC, Beijing, China; details are in the Supplemental Materials p 3). SARS-CoV-2 neutralising antibody seroconversion was defined as a fourfold increase in the post-vaccination titre [27]. The IIV4 antibody titre was detected using a haemagglutination inhibition test [28] (Supplemental Materials p 3). Seroconversion of IIV4 antibodies was defined as an influenza antibody titre after vaccination of 1:40 or higher if<1:10 at baseline, or at least a fourfold increase after vaccination compared with baseline if titre was 1:10 or higher at baseline. Seropositivity for IIV4 antibodies was defined as an influenza antibody titre of 1:40 or higher. Four types of influenza virus antibody were assessed: A/H1N1, A/H3N2, B/Victoria and B/Yamagata. The PPV23 IgG antibody concentration was determined using an in-house ELISA[29]. IgG antibody seroconversion of 23 serotypes of *S pneumoniae* was defined as a minimum twofold increase in the post-vaccination IgG antibody concentration compared with baseline.

Adverse events after immunisation were monitored based on the WHO global manual on surveillance of adverse events following immunisation, 2nd edition [30]. Adverse events after immunisations were recorded by participants using a diary card for 30 min immediately after each vaccination. Any other local or systemic reactogenicity events that occurred within 28 days after vaccination in conjunction with any medications and other vaccinations that had been administered were also recorded in the diary cards every day, and adverse events up to 6 months after full immunisation were collected by the investigators using a surveillance system on adverse events following immunisation run by the China CDC. Solicited adverse events within 7 days of immunisation were assumed to be related to the vaccine; whether adverse events outside of this period and unsolicited adverse events were related to immunisation was determined by the investigators. Local solicited reactions included injection-site pain, redness, swelling, induration, rash, and pruritus. Systemic solicited reactions included fever, dizziness, headache, cough, feeble, nausea, vomiting, chest tightness, diarrhoea, somnolence, acute allergic reaction, myalgia, facial neuritis, and arthralgia. Grading of post-immunisation systemic and local reactions were done in accordance with the Guidelines for Classification of Adverse Events in Clinical Trials of Preventive Vaccines (2019 edition) by National Medical Products Administration; more information regarding this grading is in the protocol (Supplemental Materials p 25–44).

All participants were offered, and voluntarily received, any vaccines they had not received as part of the study after the end of the 56 days follow-up period.

2.4. Outcomes

The primary outcome was the non-inferiority of the seroconversion rate and neutralising antibody level against SARS-CoV-2 on day 28 and day 56 between the SARS-COV-2 + IIV4/PPV23 group and the SARS-CoV-2 vaccine group and influenza virus on day 28 and *S pneumoniae* on day 56 between the SARS-COV-2 + IIV4/PPV23 group and the IIV4/PPV23 group. The secondary outcome was the incidence of reported vaccine-related adverse events within 28 days of each immunization.

2.5. Statistical analysis

We used the seroconversion rates after immunisation with each vaccine as the main index for assessing vaccine immunogenicity, and we estimated the minimum sample size required for a non-inferiority test using PASS (2021; NCSS, Kaysville, UT, USA). According to the seroconversion rate of each antibody serotype obtained from clinical trials of SARS-CoV-2, IIV4, and PPV23, the lowest seroconversion rate of influenza virus B/Victoria antibody was 74 % among people aged 18–59 years (Supplemental Materials p 3). Therefore, we used a seroconversion rate of 70 % to calculate the sample size. Assuming a potential loss to follow-up of 15 %, we

estimated at least a sample size of 380 participants per group would provide a power of 80 %, a one-sided α of 0.025, and a non-inferiority margin of –10 % [28]. Finally, a sample size of 384 was determined according to the multicentre design.

The primary outcome was assessed in the per-protocol population, which included all participants randomly assigned to treatment who completed the entire vaccination process with no major deviations in the protocol, and the secondary outcome was assessed in all participants who received at least one dose of study vaccine. We report baseline characteristics using descriptive statistics and summarise continuous variables using median (IQR) and categorical variables using n (%). To determine differences between groups, we used the $\chi 2$ test, Fisher's exact test, or the *Mann–Whitney U* test where appropriate. An antibody titre below the detection limit was calculated as half of the detection limit (limit of detection was 1:4 against SARS-CoV-2 and 1:10 against influenza virus). We calculated two-sided 95 % CIs using the Clopper-Pearson method and provide them for both the seropositive and seroconversion rates. The SARS-COV-2 + IIV4/PPV23 group was determined to be non-inferior to the SARS-CoV-2 vaccine group and the IIV4/PPV23 group if the between group difference of the lower limit of the 95 % CI was –10 % or higher. We converted the antibody titres or concentrations using $\log_{10}$ transformations and present them as a geometric mean titre (GMT) or geometric mean concentration (GMC) with a 95 % CI. The SARS-COV-2 + IIV4/PPV23 group was determined to be non-inferior to the SARS-CoV-2 vaccine group and the IIV4/PPV23 group if the lower limit of 95 % CI of GMT ratio or GMC ratio was 0.67 or higher. All the non-inferiority comparisons for seroconversion rate and GMT or GMC between the SARS-COV-2 + IIV4/PPV23 group and the SARS-CoV-2 vaccine group, and between the SARS-COV-2 + IIV4/PPV23 group and the IIV4/PPV23 group were determined to be significant if the associated one-sided p value was<0.025.

Subgroup exploratory analyses were done for the primary outcome by age group (18–59 years and $\geq$ 60 years). The level of significance for the comparison was two-sided at 0.05.

The safety dataset included all participants who received at least one dose of any one vaccine in this study. Safety outcomes are presented descriptively as n (%) for local and systemic vaccine-related adverse events (ie, reported within 28 days of each immunisation), and we compared these using the $\chi 2$ test or Fisher's exact test as appropriate. We also assessed local adverse events by site (ie, arm) of injection. We also compared the incidence of adverse events between the second dose and the first dose.

We did all analyses using STATA 17, unless otherwise stated.

3. Results

Between March 10 and March 15, 2021, 1152 individuals were assessed for eligibility, including 384 individuals in Shanghai, 384 individuals in Shanxi and 384 individuals in Sichuan. All were found to be eligible and randomly assigned to either the SARS-COV-2 + IIV4/PPV23 group (n = 384), SARS-CoV-2 vaccine group (n = 384), or the IIV4/PPV23 group (n = 384). All participants received their first dose of vaccine and 1132 were included in the per-protocol population (Fig. 1). In the per-protocol population, the median age was 59 years (IQR 37–70), 537 (47 %) participants were female and 595 (53 %) were male. Participants in each group were well balanced in terms of age, sex, education, and body-mass index (Table 1), and all participants were of Asian race, of whom 1129 (greater than99 %) were of Han Chinese ethnicity and three (<1%) were of non-Han Chinese ethnicity.

For the SARS-COV-2 + IIV4/PPV23 group and SARS-CoV-2 vaccine group, 28 days after the first SARS-CoV-2 vaccination, the seroconversion rate of SARS-CoV-2 neutralising antibodies was 97 % (362 of 375 participants; 95 % CI 94–98) in the SARS-COV-2 + IIV4/PPV23 group, which was non-inferior to the seroconversion rate in the SARS-CoV-2 vaccine group (99 % [376 of 380 participants; 95 % CI 97 to 100; lower limit of 95 % CI difference of –2% [95 % CI –5 to 0]; Fig. 2; Supplemental Materials p 6). The seroconversion rate increased to 100 % (374 of 375; 95 % CI 99 to 100) in the SARS-COV-2 + IIV4/PPV23 group and 100 % (380 of 380; 95 % CI 99 to 100) in the SARS-CoV-2 vaccine group on day 56, indicating non-inferiority (lower limit of 95 % CI difference of 0 % [95 % CI –1 to 0]; Fig. 2; Supplemental Materials p 6). In exploratory subgroup analyses, similar results in the SARS-CoV-2 neutralising antibody seroconversion rates were observed among the participants aged 18–59 years and 60 years and older (Fig. 2; Supplemental Materials p 6).

The GMT of the SARS-CoV-2 neutralising antibodies was 31.57 (95 % CI 29.07–34.28) in the SARS-COV-2 + IIV4/PPV23 group and 35.27 (32.66–38.09) in the SARS-CoV-2 vaccine group on day 28 after first dose of SARS-CoV-2 vaccination, which increased to 159.13 (148.06–171.04) and 173.20 (160.71–186.66) on day 56; exceeding the margins for non-inferiority (GMT ratio 0.90 [95 % CI 0.80–1.00] on day 28 and 0.92 [95 % CI 0.83–1.02] on day 56; Fig. 2; Supplemental Materials p 7) among all participants. Similar results were found among the participants aged 18–59 years and 60 years and older. Moreover, participants aged 18–59 years had a higher GMT than those aged 60 years and older on day 28 after both first and second dose of SARS-CoV-2 vaccine.

On day 28 after the vaccination, SARS-COV-2 + IIV4/PPV23 group was non-inferior to IIV4/PPV23 group in terms of seroconversion of influenza virus antibodies for all strains, except for B/Yamagata (Fig. 3; Supplemental Materials p 8). We found similar findings when assessing the seroconversion rates by age groups (Supplemental Materials p 9). Among those aged 60 years and older, seropositive rates were slightly lower in the SARS-COV-2 + IIV4/PPV23 group than in the IIV4/PPV23 group for B/Victoria (57 % [105 of 191; 95 % CI 50–64] vs 62 % [116 of 189; 95 % CI 54–69]) and B/Yamagata (82 % [151 of 191; 95 % CI 76–87] vs 89 % [168 of 189; 95 % CI 84–93]; Supplemental Materials p 9). By contrast, participants aged 18–59 years in the SARS-COV-2 + I IV4/PPV23 group had a higher seropositive rate of B/Yamagata antibodies than did those in the IIV4/PPV23 group (100 % [190 of 191; 95 % CI 97–100] vs 96 % [182 of 189; 95 % CI 93–99]; Supplemental Materials p 9).

Non-inferiority was met for the GMT of influenza virus antibodies in the SARS-COV-2 + IIV4/PPV23 group compared with the IIV4/PPV23 group on day 28 after first vaccination (Fig. 3; Supplemental Materials p 10). The GMT of A/H3N2 was higher in the SARS-COV-2 + IIV4/PPV23 group than in the IIV4/PPV23 group (603.24 [95 % CI 543.75–669.25] vs 435.81 [95 % CI 390.14–486.82]). No differences in GMT of A/H1N1, B/Victoria, and B/Yamagata were observed between the SARS-COV-2 + IIV4/PPV23 group and the IIV4/PPV23 group in either of the age groups (Supplemental Materials p 11).

On day 56, SARS-COV-2 + IIV4/PPV23 group was found to be non-inferior to IIV4/PPV23 group regarding the seroconversion rates and GMC of *S pneumoniae* IgG antibody differences for all serotypes (Fig. 4; Supplemental Materials p 12–14). Among participants aged 18–59 years, the seroconversion rates and the GMC of the *S pneumoniae* serotypes in the SARS-COV-2 + IIV4/PPV23 group were similar to those observed in the IIV4/PPV23 group on day 28 after the PPV23 vaccination, except for GMCs of serotypes 1 and 22F antibodies, which were significantly higher in the SARS-COV-2 + IIV4/PPV23 group (Supplemental Materials p 15–17). Among the participants aged 60 years and older, seroconversion rates of all serotypes in the SARS-COV-2 + IIV4/PPV23 group were similar to those in the IIV4/PPV23 group (Supplemental Materials p 18). Only the GMCs of eight antibody serotypes (9N, 11A, 14, 18C,

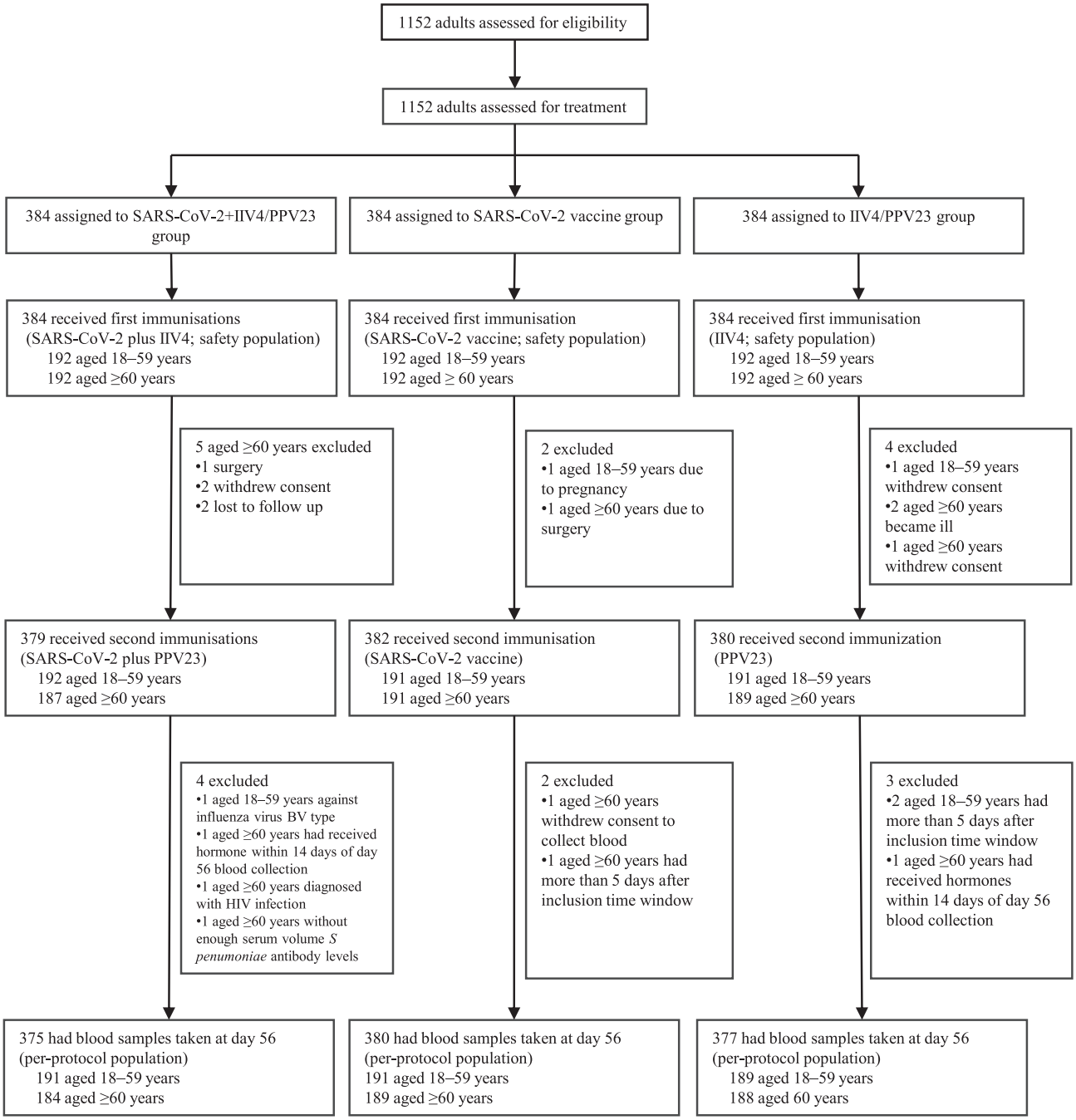

Fig. 1. Trial profile. IIV4 = quadrivalent split-virion inactivated influenza vaccine. PPV23 = 23-valent pneumococcal polysaccharide vaccine. S pneumoniae = Streptococcus pneumoniae.

19A, 19F, 23F, and 33F) were slightly lower in the SARS-COV-2 + IIV4/PPV23 group than in the IIV4/PPV23 group among the participants aged 60 years and older (Supplemental Materials p 19–20).

All vaccines administered during the study were well tolerated, and no deaths or severe adverse events were observed in any of the participants as of data cutoff (Aug 15, 2021; Table 2; Supplemental Materials p 21–23). All observed adverse events were temporary, with pain at the injection site being the most commonly reported adverse event. No significant differences were observed between the SARS-COV-2 + IIV4/PPV23 group and the IIV4/PPV23 group (Table 2). The SARS-COV-2 + IIV4/PPV23 group had a significantly higher incidence of adverse events than did the SARS-CoV-2 vaccine group, which were mainly local reactions including pain, redness, swelling, and induration (Table 2). When local adverse events were classified by type of vaccine, according to the arm in which the vaccine was administered, the differences between groups were reduced; however, the frequency of pain in the SARS-COV-2 + IIV4/PPV23 group remained significantly higher than in the SARS-CoV-2 vaccine group (Supplemental Materials p 23). Fewer adverse events occurred after the second dose than after the first dose (Supplemental Materials p 21–22). Three cases of serious adverse events (SAEs) were observed in the SARS-COV-2 + IIV4/P

Table 1
Characteristics of the participants in the study.

Characteristics	SARS-CoV-2 + IIV4/PPV23 (Group A, n = 375)	SARS-CoV-2 vaccine (Group B, n = 380)	IIV4/PPV23 (Group C, n = 377)
Age, years, median (IQR)	58 (37–70)	59 (38–71)	59 (38–71)
Sex, n (%)			
Male	194 (52)	202 (53)	199 (53)
Female	181 (48)	178 (47)	178 (47)
Education, n (%)			
Middle school and below	189 (50)	195 (52)	208 (55)
High school	92 (25)	108 (28)	84 (22)
Bachelor or above	94 (25)	76 (20)	85 (23)
BMI, kg/m^2, median (IQR)	24.2 (21.9–26.4)	24.5 (22.2–26.6)	24.2 (22.1–26.6)
Area			
Shanghai City	126 (34)	126 (33)	127 (34)
Shanxi Province	123 (32)	127 (34)	124 (33)
Sichuan Province	126 (34)	127 (33)	126 (33)

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IIV4, quadrivalent split-virion inactivated influenza vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine; IQR, interquartile range. There was 1 participant unknown for the variable of education in the SARS-CoV-2 vaccine group.

PV23 group, two cases in the SARS-CoV-2 vaccine group, and four cases in the IIV4/PPV23 group. Neither of the SAEs or lost were related to the vaccination.

4. Discussion

In addition to SARS-CoV-2, the control and prevention of influenza and pneumococcal infections is critical during the COVID-19 pandemic. No studies have reported the safety and immunogenicity associated with the coadministration of three vaccines against these pathogens. We found that an inactivated SARS-CoV-2 vaccine coadministered with IIV4 and PPV23 was safe and immunogenic in adults aged 18 years and older. We found non-inferiority of this vaccination schedule in terms of immunogenicity against SARS-CoV-2, influenza virus (A/H1N1, A/H3N2, and B/Victoria), and *S pneumoniae* (23 serotypes) compared with two doses of SARS-CoV-2 and with one dose of IIV4 and of PPV23 28 days apart. We did not exclude participants with comorbidities, but did exclude those with contraindications for vaccination, which shows a good representativeness of the general population.

In a randomised clinical trial involving 40 382 participants, the treatment of adults with two doses of inactivated SARS-CoV-2 vaccine significantly reduced the risk of symptomatic COVID-19 with a vaccine efficacy of 78.1 % [2]. One preprint study from Sri Lanka showed that Sinopharm BBIBP-CorV was highly efficient against the delta SARS-CoV-2 variant, which is the dominant variant across

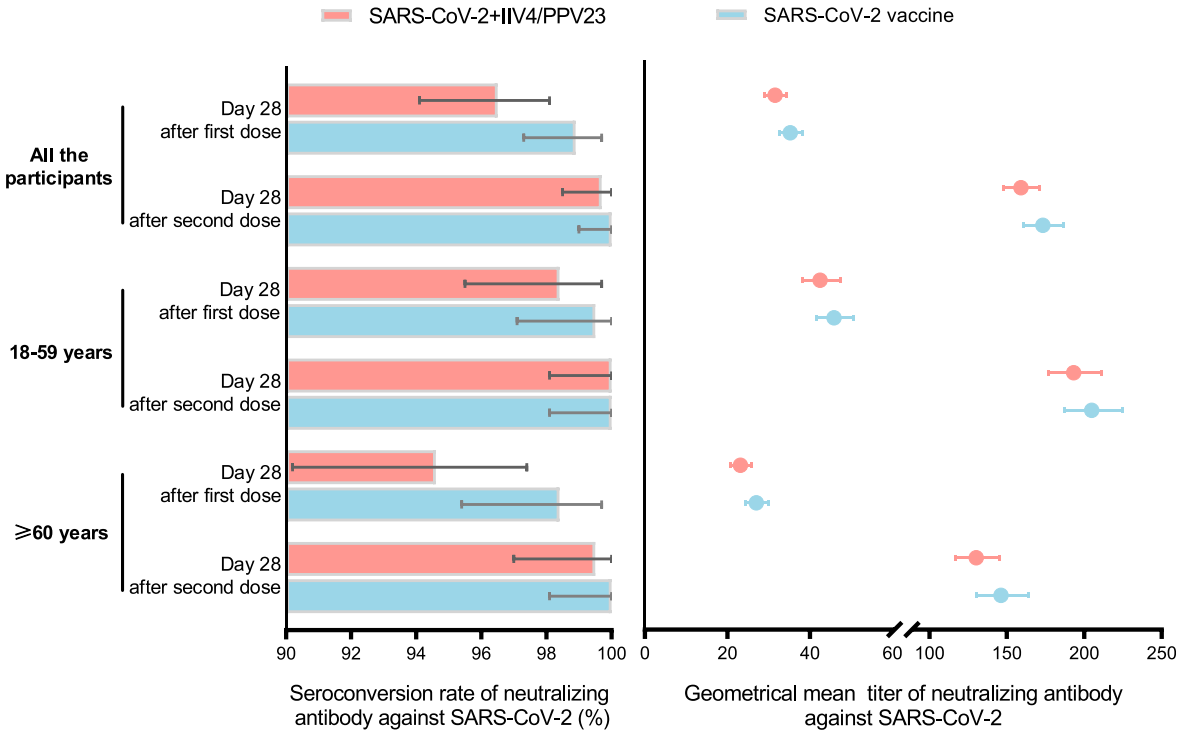

Fig. 2. Seroconversion rate and GMT of SARS-CoV-2 neutralising antibodies. The left bar chart shows the seroconversion rates (%) of neutralising antibodies with error bars showing 95 % CIs. The comparisons between the groups among all the participants found SARS-COV-2 + IIV4/PPV23 group to be non-inferior to SARS-CoV-2 vaccine ($p < 0{\cdot}025$). The right plot shows the post-vaccination GMT of SARS-CoV-2 neutralising antibodies and the error bars showing 95 % CIs. SARS-COV-2 + IIV4/PPV23 group was non-inferior to SARS-CoV-2 vaccine only ($p < 0{\cdot}025$). The pre-vaccination GMT of the SARS-CoV-2 neutralising antibodies was 2 (95 % CI 2–2). GMT = geometrical mean titre. IIV4 = quadrivalent split-virion inactivated influenza vaccine. PPV23 = 23-valent pneumococcal polysaccharide vaccine.

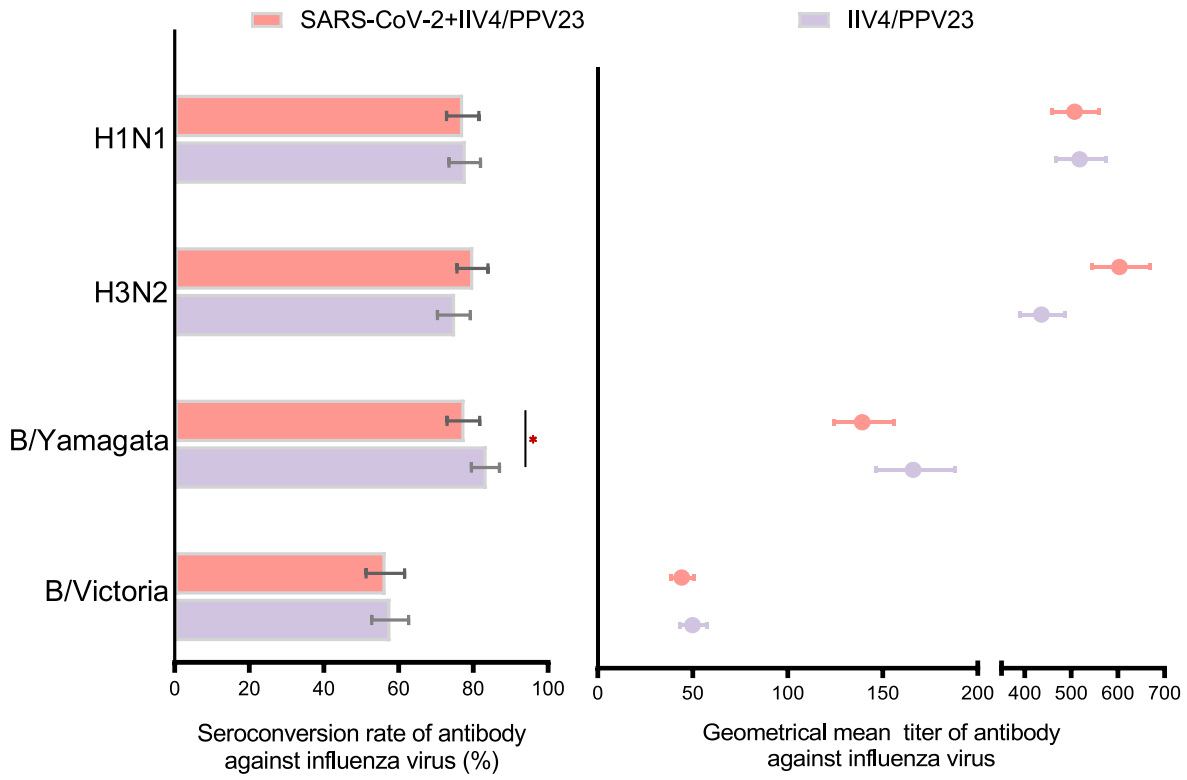

Fig. 3. Seroconversion rate and GMT of influenza virus antibodies on day 28. The left bar chart shows the seroconversion rates (%) of influenza virus antibodies and error bars show the 95 % CIs. For each strain, SARS-COV-2 + IIV4/PPV23 group was non-inferior to IIV4/PPV23 group (except for B/Yamagata on day 28: p = 0·080). The right plot shows the post-vaccination GMT of influenza virus antibodies and the error bars show the 95 % CIs. For all strains, SARS-COV-2 + IIV4/PPV23 group was non-inferior to IIV4/PPV23 group (both p < 0.025). GMT = geometrical mean titre. IIV4 = quadrivalent split-virion inactivated influenza vaccine. PPV23 = 23-valent pneumococcal polysaccharide vaccine.

the world [6]. Another study reported that a two-dose schedule with inactivated SARS-CoV-2 vaccines (BBIBP-CorV and Sinovac CoronaVac) was effective against infection with the Delta variant in real-world settings, with overall vaccine efficacy of 59.0 % [5]. A real-world study in Hong Kong showed that two-dose schedule with inactivated SARS-CoV-2 vaccines were still more than 70 % effective in preventing severe illness and death caused by the Omicron variant [9]. In a phase 1/2 trial, the inactivated SARS-CoV-2 vaccine (BBIBP-CorV) has been confirmed to be safe and immunogenic in individuals aged 18–59 years (GMT for 4 μg [6.5 U] group 211.2 [95 % CI 158.9– 280.6]) and 60 years and older (GMT for 4 μg [6.5 U] group 131.5 [95 % CI 108.2–159.7])[27]. In our trial, we found similar results for both the group given only the SARS-CoV-2 vaccine and the group coadministered with the SARS-CoV-2 vaccine and IIV4 and PPV23. Non-inferiority of the seroconversion rate and GMT of SARS-CoV-2 neutralising antibodies was observed in the combination group compared with the group given only SARS-CoV-2 vaccine. Coadministration with IIV4 and PPV23 might not affect SARS-CoV-2 vaccine immunogenicity, which need to be confirmed in larger international studies with diverse ethnic populations.

Influenza and pneumococcal pneumonia are both vaccine-preventable diseases. A 2013 *meta*-analysis of 25 studies found strong evidence of pneumococcal polysaccharide vaccine efficacy against invasive pneumococcal disease in adults, supporting a recommendation for use of pneumococcal polysaccharide vaccines [31]. Because PPV23 and IIV4 vaccination coverage remains low globally [17,26,32], specific strategies are required to increase PPV23 immunisation rates. Moreover, willingness to receive IIV4 and PPV23 since the beginning of the COVID-19 pandemic has increased among adults in China [25,26]. Based on the associated safety and immunogenicity, the coadministration of IIV4 and PPV23 with SARS-CoV-2 vaccination could become a novel strategy for improving the coverage of IIV4 and PPV23 vaccination in China and globally.

Overall, the immunogenicity of IIV4 and PPV23, including the seropositive and seroconversion rates and GMTs or GMCs, was acceptable for the differences between the IIV4 and PPV23 groups with or without the SARS-CoV-2 vaccine. For the seroconversion rates of the influenza virus strains A/H1N1, A/H3N2, and B/Victoria, SARS-CoV-2 vaccine coadministration with IIV4 plus PPV23 was not inferior to IIV4/PPV23 group and the differences in seroconversion rate between the two groups were minimal (−1% to 5 %). The immunogenicity of A/H3N2 was higher in the SARS-CoV-2 vaccine coadministered group, and for B/Yamagata the GMT in the SARS-CoV-2 vaccine coadministered group was not inferior to IIV4/PPV23 group, and the slight difference of seroconversion rate between the groups was acceptable. Further studies are needed to verify whether there is immune interference with B/Yamagata. Several studies have reported the added benefits of the coadministration of influenza vaccine and PPV23 vaccinations and reduced costs [23,33], which should be present for the three combined vaccines. The coadministration of SARS-CoV-2 vaccine with influenza vaccine is particularly important because this is the vaccine that will be most commonly used over the forthcoming influenza seasons.

The case-fatality rate of COVID-19 increases with age, with a higher case-fatality rate observed among patients aged 60 years and older [34,35]. Thus, older populations should be prioritised for SARS-CoV-2 vaccination. We found that, among those aged 60 years and older, the seroconversion rate of SARS-CoV-2 neutralising antibodies was greater than 99 % after two doses of SARS-

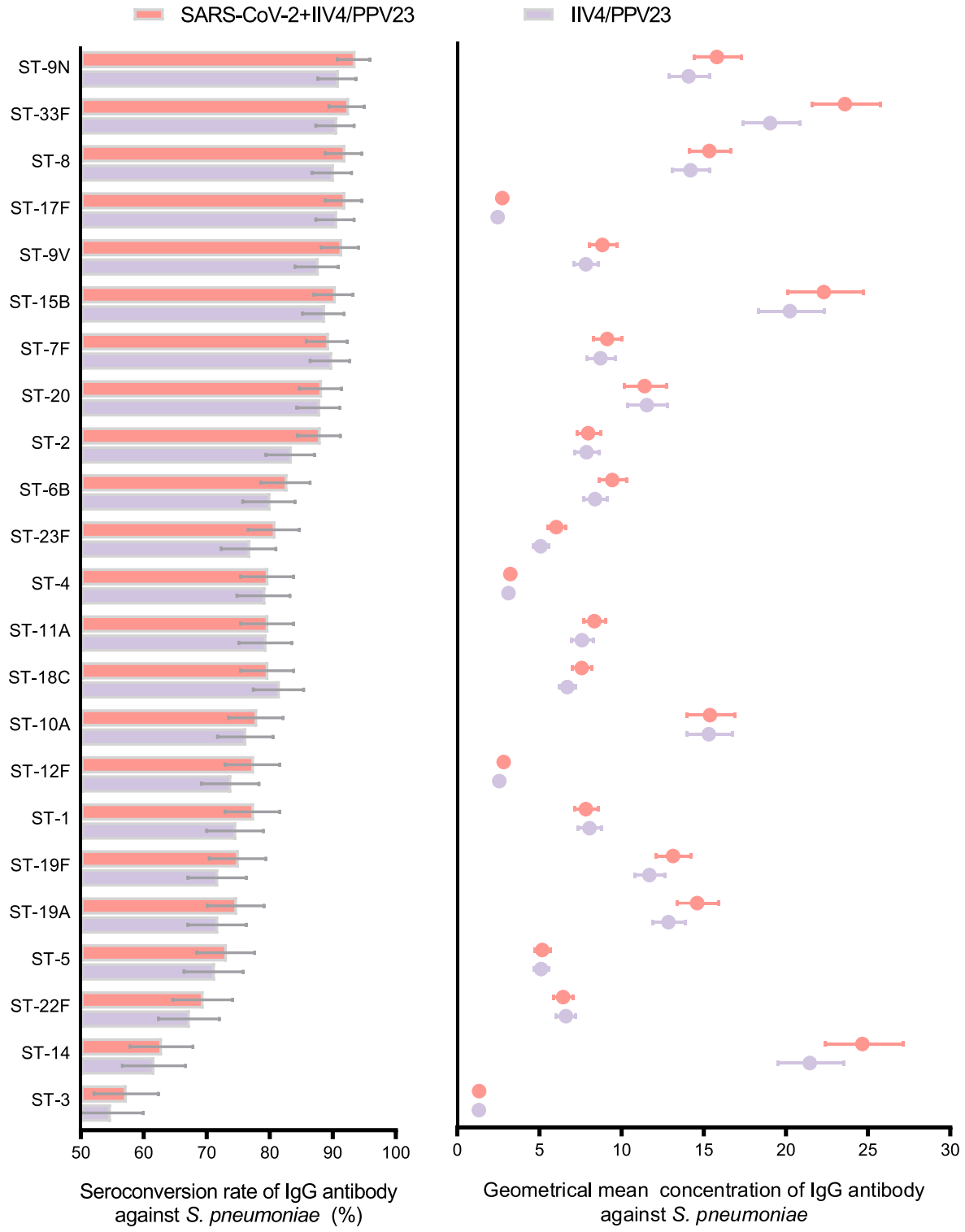

Fig. 4. Seroconversion rate and GMC of *S pneumoniae* IgG antibodies on day 56. The left bar chart shows the seroconversion rates (%) of the *S pneumoniae* IgG antibodies and the error bars show the 95 % CIs. For all serotypes, SARS-COV-2 + IIV4/PPV23 group was non-inferior to IIV4/PPV23 group (all $p < 0.025$). GMC = geometric mean concentration. IIV4 = quadrivalent split-virion inactivated influenza vaccine. PPV23 = 23-valent pneumococcal polysaccharide vaccine. S pneumoniae = *Streptococcus pneumoniae.*

CoV-2 vaccine in both of the SARS-CoV-2 vaccination groups. Moreover, the GMT of SARS-CoV-2 neutralising antibodies in this older group was lower than in the group aged 18–59 years, which was similar to that reported in a previous study with a small sample size [27]. Considering the lower level of GMTs after two-dose vaccination among those aged 60 years and older than among those aged 18–59 years, a booster dose might be required to strengthen the immune response in this population.

Table 2
Reported vaccine-related adverse events by the groups among participants.

Adverse events	SARS-CoV-2 + IIV4/PPV23 (Group A, n = 384)	SARS-CoV-2 vaccine (Group B, n = 384)	IIV4/PPV23 (Group C, n = 384)	P A vs B	A vs C
Local	101 (26)	34 (9)	85 (22)	<0.001	0.178
Pain	84 (22)	27 (7)	70 (18)	<0.001	0.207
Redness	16 (4)	1 (0)	13 (3)	<0.001	0.570
Swelling	20 (5)	4 (1)	14 (4)	<0.001	0.293
Induration	11 (3)	2 (1)	7 (2)	0.012	0.340
Rash	0 (0)	0 (0)	0 (0)	1.000	1.000
Pruritus	9 (2)	6 (2)	16 (4)	0.434	0.155
Systemic	37 (10)	43 (11)	28 (7)	0.478	0.243
Fever	3 (1)	5 (1)	1 (0)	0.477	0.316
Dizziness	10 (3)	9 (2)	7 (2)	0.816	0.462
Headache	5 (1)	6 (2)	3 (1)	0.761	0.477
Cough	3 (1)	4 (1)	1 (0)	0.704	0.316
Feeble	7 (2)	11 (3)	12 (3)	0.340	0.245
Nausea	4 (1)	4 (1)	1 (0)	1.000	0.178
Vomiting	1 (0)	0 (0)	2 (1)	1.000	0.563
Chest tightness	4 (1)	2 (1)	1 (0)	0.412	0.178
Diarrhea	3 (1)	3 (1)	1 (0)	1.000	0.316
Somnolence	8 (2)	10 (3)	3 (1)	0.633	0.129
Allergy	0 (0)	0 (0)	0 (0)	1.000	1.000
Myalgia	6 (2)	7 (2)	6 (2)	0.780	1.000
Facial neuritis	0 (0)	0 (0)	0 (0)	1.000	1.000
Arthralgia	1 (0)	5 (1)	2 (1)	0.101	0.563
Others	3 (1)	9 (2)	4 (1)	0.081	0.704
Any	117 (31)	60 (16)	97 (25)	<0.001	0.107

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IIV4, quadrivalent split-virion inactivated influenza vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine.

The safety of the combination of these three vaccines of interest is reassuring because no unexpected or severe adverse effects occurred. The most common adverse reaction consisted of injection-site pain. The frequency of adverse effects in the SARS-COV-2 + IIV4/PPV23 group was lower than the additive frequency of the other two groups. The pain in this coadministered vaccination group was mainly caused by the addition of IIV4 and PPV23, which could lead to uncomfortable vaccination experiences and subsequently increased the risk of vaccine hesitancy [36].

Our trial has some limitations. Individuals younger than 18 years were not recruited because the inactivated SARS-CoV-2 vaccine was not yet approved for use in this age group in China at the time of the study. Therefore, the safety and immunogenicity for the coadministration of these three vaccines remain unknown in this younger population and should be confirmed with future studies. Moreover, the long-term safety and immunogenic responses remain unclear and extended follow-up is required. Our findings are derived from an inactivated SARS-CoV-2 vaccine and so are not generalisable to mRNA-based, adenovirus vector-based, and other non-inactivated SARS-CoV-2 vaccines; therefore, further validation studies for these vaccines are needed. Our findings are derived from data from China and mainly from one ethnic group, and so need to be confirmed in other ethnicities and countries. Our exploratory subgroup analyses by age, and by influenza strain and *S pneumoniae* serotype should be interpreted with caution.

In this study, the coadministration of an inactivated SARS-CoV-2 vaccine with IIV4 plus PPV23 was safe with satisfactory immunogenicity against SARS-CoV-2, influenza virus, and *S pneumoniae*. Thus, the coadministration of IIV4 and PPV23 during vaccination with the inactivated SARS-CoV-2 vaccine could improve overall vaccine uptake and contribute to disease control. Larger and international studies are needed to confirm our findings. Further studies on persistence of the immune responses in our trial population and the safety and immunogenicity of the coadministration of these three vaccines in young children and other select populations are also needed.

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Data availability

Data supporting the findings in this manuscript are available from the corresponding author upon request.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Xiaoming Yang is the employee of the China National Biotec Group, receives the grant from National Program on Key

Research Project of China (2020YFC0842100) during the conduct of the study, and has four authorized patents of ZL202010559132.3, ZL202010645875.2, ZL202010537733.4 and ZL202010537730.0. Yuntao Zhang is the employee of the China National Biotec Group, receives the grant from The National Key Research and Development Project of China (2020YFC0842100) during the conduct of the study. Hui Wang is the employee of the Beijing Institute of Biological Products, receives the grants from The National Key Research and Development Project of China (2020YFC0842100) and the Beijing Municipal Science & Technology Commission (Z201100005420014) during the conduct of the study and has three authorized patents of ZL202010645875.2, ZL202010537733.4 and ZL202010537730.0, two pending patents of 202110052921.2 and 202110052933.5. Rui Ma is the employee of the Beijing Institute of Biological Products, receives the grant from The National Key Research and Development Project of China (2020YFC0842100) during the conduct of the study. Haiping Chen, Yanhui Xiao, Shasha Han, Min Zhang, Shengyi Wang and Linyun Luo are the employees of the China National Biotec Group. Yonghong Ge and Lei Zhang are the employees of the Chengdu Institute of Biological Products. Yong Zou and Xue Guo are the employees of the Changchun Institute of Biological Products. All other authors report no potential conflicts.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.07.033.

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