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Assessment of neutralizing antibody response as a correlate of protection against symptomatic SARS-CoV-2 infections after administration of two doses of the CoronaVac inactivated COVID-19 vaccine: A phase III randomized controlled trial

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SUMMARY

Background: The emergence of variants of concerns of SARS-CoV-2 highlights the need for comprehensively elucidating the correlates of protection for different COVID-19 vaccine types. Inactivated COVID-19 vaccines are currently amongst the most widely administered vaccines globally. However, investigations into the correlates of protection for inactivated COVID-19 vaccines are relatively rare.

Methods: Data from a phase III double-blind, randomized, placebo-controlled clinical trial (NCT0445659) that evaluated the efficacy and safety of the CoronaVac vaccine in healthcare professionals were utilized in this secondary analysis. Additionally, the correlation between neutralizing antibody levels measured by micro-cytopathic effect (CPE) neutralization assay and the occurrence of laboratory-confirmed infections was assessed using neutralizing antibodies measured in blood samples collected on day 28 after receiving two doses of the vaccine. Finally, the protective threshold required to provide 50% protection against symptomatic illness and virus infections was estimated.

Results: The risk of infection was negatively correlated with the levels of post-vaccination neutralizing antibodies measured on day 28 after the second dose. A neutralization titer of 30 (95% CI: 2–56) was predicted to provide 50% efficacy against symptomatic infection, whilst a titer of 42 (95% CI: 24–62) was predicted to provide 50% efficacy against total infection. Lastly, a neutralization titer of 247 (95% CI: 139–506) or higher was required to achieve 80% or higher protection against symptomatic infections.

Conclusions: The results highlight the value of neutralizing antibody response as a correlate of protection, which can be used to inform future vaccine development and implementation. Further studies of immune correlates of protection for other vaccines are warranted.

Introduction

COVID-19 vaccination is one of the most effective public health measures for containing the global pandemic elicited by SARS-CoV-2 and bringing the world back to pre-pandemic normalcy. However, with the emergence of novel variants of concern (VOCs) with a strong capacity for immune escape, protection against symptomatic infection conferred by prototype-strain-based COVID-19 vaccines was reduced. Consequently, alternative strategies to substitute

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antigens used in vaccine development with a more immunodominant antigen have been proposed. However, developing a new vaccine can be both time-consuming and labor-intensive, given that several stages of pre-clinical and clinical evaluations are required to be submitted to regulators. Under these circumstances, immune correlates of protection (CoPs) for specific vaccines hold considerable importance for accelerating vaccine approval in the presence of variants.

CoPs are defined as immune markers that can provide an indication of vaccinated individuals being protected from infections or the development of disease following subsequent exposure to the targeted virus.[1,2] They can be defined by measuring the levels of immunological markers and predicting the vaccine efficacy against a clinically relevant endpoint. In the absence of phase III efficacy data, new vaccines can be authorized for use in a relatively short time period using CoPs and immunogenicity data, as well as reliable safety data. CoPs have already been employed for influenza vaccines, which indicated that a post-vaccination hemagglutination inhibition titer (HAI) of 40 corresponded to approximately 50% protection against symptomatic infection.[3,4] Notably, established CoPs also have numerous other applications, such as defining population-level immunity and durability of protection. They have been reported for Moderna and ChAdOx1 COVID-19 vaccines, but no study on this topic has been reported for inactivated Covid-19 vaccines.[5,6]

In the present study, a similar methodology from previously published studies on CoPs in COVID-19 vaccines was adopted to analyze data from the PROFISCOV phase III clinical trial.[5–7] The neutralizing antibody level required to achieve 50% protection induced by two doses of CoronaVac against symptomatic and all infections caused by SARS-CoV-2 was estimated.

Methods

Study population

Study participants included in this study were from the PROFISCOV trial (NCT04456595), a phase III, randomized, multicenter, double-blind, placebo-controlled vaccine trial that aimed to evaluate the efficacy and safety of the adsorbed vaccine Covid-19 (inactivated) manufactured by Sinovac.[7,8] This study was carried out in 16 clinical sites in Brazil, with the majority of participants recruited between July 21, 2020, and October 2020. Healthy adult healthcare professionals working in COVID-19–specialized units with a clinically controlled disease were eligible for inclusion. Each participant in the trial was followed up for one year with active surveillance for COVID-19 after their inclusion in the study. A total of seven visits for the purpose of safety and immunogenicity were performed, including two vaccination visits (V1 and V2), two safety and immune response visits (SI1 and SI2), and four immune response visits (I1, I2, I3, and I4). Specifically, V1 and V2 were time points at which participants received the first and second doses. SI1 and SI2 were time points at weeks two and four after the second vaccination, respectively. Visit I1 was scheduled at 13 weeks after V1, I2 at 26 weeks after V1, I3 at 39 weeks after V1, and I4 at 52 weeks after V1. SARS-CoV-2 P.1 and P.2 variants were circulating during the trial period (Fig. S1).

Based on the sample collection time, a PB28 correlate cohort eligible for inclusion in the correlation of protection analysis was established according to the following criteria: 1) Participants finishing the two primary doses of CoronaVac vaccination; 2) SARS-CoV-2-naive participants, defined as either previous negative RT-PCR results or with undetectable neutralization titers (< 4) against SARS-CoV-2 prior to enrollment; 3) Participants receiving the second dose of CoronaVac at least 14 days after the first dose (but not later than 28 days); 4) Participants with available neutralization titer results on Day 28 after two vaccination doses (short for "PB28"); 5) PB28 samples were collected no later than a 14-day delay after the prespecified date (i.e., a two-week window). Participants who met all the above criteria were included in the correlation of protection analysis (Table S1).

Laboratory methods

At each visit, the blood samples of study participants were collected, and a micro-cytopathic effect (CPE) neutralization assay was used to determine neutralizing antibody levels. Compared to the plaque reduction neutralization test (PRNT), the gold standard for neutralizing antibody detection, this assay was more suitable for large-scale serum testing and vaccine evaluation with a higher throughput. The experimental protocol was consistent with that of previous trials.[9,10] Briefly, all serum samples were inactivated at 56 °C in a water bath for 30 min. Next, the serum was diluted fourfold (60 μL sample + 180 μL maintenance medium) using a cell maintenance medium (2% newborn calf serum-199 (2% sodium hydrogen carbonate) cell maintenance medium). The diluted serum was added to the cell plate at 100 μL/well, with each sample being diluted into 2 wells in parallel. The dilution range started from 1:4 to 1:8192 (serum titer was calculated before adding the virus). The SARS-CoV-2 used for neutralization was titrated to 100 CCID50/0.05 mL. Serum of different dilutions was mixed with 100CCID50/0.05 mL virus liquid in equal volume (50 μL + 50 μL) and then incubated in an incubator at a temperature of 36.5 °C and an atmosphere containing 5% CO_2 for 2 h. Negative serum control, positive serum control, serum sample, and cell control were set simultaneously. After incubation, 100 μL of Vero cell suspension (cell concentration: 1.0–2.0 × 10^5 cells/mL) was added to each well, and the resulting mixture was incubated in an incubator at 36.5 °C, 5% CO_2 for 5 days. CPE was examined after 3–5 days of incubation, and the neutralizing antibody titer of the to-be-tested serum sample was determined according to the observation results of CPE. The detailed experimental procedure is illustrated in the Supplementary Material.

Immune markers and study endpoints

Participants were sampled at 28 days post-second vaccination (PB28) to assess vaccine-elicited immune response. Neutralization antibody levels tested at this time point served as potential immune markers that may correlate with the protection. Three outcomes in this analysis were defined as follows: 1) symptomatic infections, defined as individuals with symptomatic COVID-19 infection, including but not limited to fever, cough, anosmia,[11] starting 7 days post PB28, and with a positive RT-PCR test. A 7-day window was set to exclude participants with infections around D28 to avoid confounding by infection. 2) asymptomatic infections, defined as individuals without any Covid-19 related symptoms (as defined in symptomatic infections), but with a positive RT-PCR test. Besides, to capture more asymptomatic individuals and enlarge the sample size, individuals with a 4-fold increase/seroconversion of neutralizing antibodies between serial serum samples were defined as having an asymptomatic infection. 3) All infections, defined as a combination of symptomatic and asymptomatic infections, with a positive RT-PCR test or predefined serology results (Table S2). For each endpoint, we only included participants with specific endpoints and noncases. For example, when estimating correlates of protection against symptomatic endpoints, we only included symptomatic and non-infected participants for our analysis, indicating asymptomatic participants were not included. However, we also conducted a sensitivity analysis by including asymptomatic infections as "not symptomatic infection" group to re-analysis the results. Previous immunogenicity studies established that the neutralizing antibodies elicited by CoronaVac persisted for approximately 6–8 months after both primary

and booster doses.[9,10] In the current study, an eight-month timeframe was set since PB28, indicating that only infections and/or illnesses that occurred during the eight-month period were included in the analysis.

Statistical analysis

The methodology framework used in our analysis was similar to that of previous studies on correlates of protection.[5,6] The distribution of neutralizing antibodies was initially compared by vaccination status (i.e., vaccine and placebo group) and infection status (i.e., noncases, symptomatic infections, and asymptomatic infections). Then, the geometric mean titer (GMT) of the PB28 neutralizing antibody was calculated. The neutralizing antibody titer below the detection limit (1:4) was set as 1:2, while titers reaching the upper limit (1:8192) were set as 1:8192. To describe the occurrence of symptomatic infection in the PB28 cohort (only including symptomatic infections and noncases), a survival analysis was performed using the Kaplan-Meier method to compare the cumulative incidence between the placebo and vaccine groups among participants included in the correlated analysis. The risk of survival was converted into the cumulative incidence by using one minus the survival risk.

Furthermore, a logistic regression analysis was conducted to establish the relationship between the occurrence of predefined outcomes and baseline factors, including age, gender, race (white and nonwhite), BMI (< 30 kg/m^2, ≥30 kg/m^2), and comorbidities among the placebo group. The estimated linear predictors (i.e., coefficient) derived from the logistic regression model among the placebo group were used to predict the baseline risk of exposure (occurrence of predefined outcomes at baseline) in the CoronaVac vaccine group. A generalized additive model (GAM) with a cubic spline smooth was applied to a log-transformed neutralization titer to calculate the absolute risk of a predefined outcome for each participant. The predicted baseline exposure risk was included as a linear covariate in the GAM model. The absolute risk for the full range of neutralization titers (2 to 8192) was subsequently predicted using the GAM model. To determine relative risks, the predicted absolute risk was compared to the overall risk among correlated participants in the placebo group. Afterward, vaccine efficacy was estimated using one minus the relative risk to establish the relationship between neutralizing antibody levels and vaccine efficacy. 95% CI was calculated from 10,000 bootstrap samples.

Results

A total of 13,166 participants were enrolled in the PROFISCOV study, of which 12,688 participants underwent randomization. 12,680 participants received at least one dose of the vaccine, comprising 6340 vaccine recipients and 6340 placebo recipients (Table S3). After excluding those who received incorrect vaccines, were vaccinated with only one dose, or withdrew during the follow-up period, 11,091 participants received two doses of vaccine/placebo, including 6063 (50.9%, 6063/11901) in the vaccine group and 5838 (49.1%, 5838/11901) in the placebo group, were eligible for subsequent analysis. In the vaccine group, only 1888 (31.1%, 1888/6063) participants underwent neutralization tests at baseline. According to predefined criteria for participant inclusion in the CoP analysis, 799 participants were selected for the PB28 cohort, including 583 (73.0%, 583/799) noncases, 172 (21.5%, 172/799) cases of symptomatic infection, and 44 (5.5%, 44/799) cases of asymptomatic infection (Fig. 1, Table 1).

In addition, the Kaplan-Meier method was applied to calculate both survival probability (i.e., the probability of not being symptomatic) and cumulative incidence. Notably, the survival probability in the placebo group rapidly decreased from 1 to approximately 0.25 during the first one hundred days following PB28 sampling, compared to that of approximately 0.75 in the vaccine group. The estimated cumulative incidence of symptomatic COVID-19 infection among correlated participants was 0.703/person-year (95% CI: 0.642–0.754) and 0.256/person-year (95% CI: 0.223–0.289) in the placebo and vaccine group, respectively, corresponding to an unadjusted vaccine efficacy of 63.6% (Fig. 2).

The distribution of PB28-neutralizing antibodies substantially varied between the vaccine and placebo groups, with most placebo participants having seronegative result, while that of the vaccinated participants ranged between 1:32 to 1:64 (Fig. 3A). In the vaccine group, the difference in the distribution was compared by predefined endpoints, revealing that the proportion of participants with titers higher than 1:64 was higher among noncases compared to those with symptomatic and asymptomatic infections. Of note, there was only one participant whose neutralizing titer was higher than 1:256 among infections (Fig. 3B). In addition, the GMT of the neutralization titer on Day 28 after the second dose was significantly higher among the noncases group than that of symptomatic and asymptomatic infections, with GMTs of 44.1 (95% CI: 39.9–48.6), 29.8 (95% CI: 25.7–34.6), and 22.9 (95% CI: 15.6–33.7), respectively (Fig. 3C).

The absolute risk of symptomatic infections and all infections decreased with higher levels of neutralizing antibodies collected on Day 28 after the second dose (PB28) (Fig. 4A). Likewise, the absolute risk was generally lower than that in the placebo group (Fig. 4A). The relative risk against the predefined outcomes exhibited a similar pattern to the predicted absolute risk. In this study, a neutralization titer of 30 (95% CI: 2–56) was predicted to provide 50% vaccine efficacy against symptomatic infection, whilst a titer of 42 (95% CI: 24–62) was anticipated to provide 50% vaccine efficacy against total infection (Fig. 4C). In order to achieve 80% or higher protection against symptomatic infections, a neutralization titer of 247 (95% CI: 139–506) was required. At the same time, the sensitivity analysis showed that neutralizing titers of 28 (95% CI: 12–62) for serum samples collected on Day 14 after the second dose could provide 50% efficacy against symptomatic infections (Fig. S2). For asymptomatic endpoints, infection risk decreased with increasing levels of PB28 neutralizing antibody. However, no significant correlation was identified between PB14 neutralizing antibody levels and vaccine efficacy protection against asymptomatic infection (Fig. S3). Meanwhile, including or removing asympotomatic pariticipants when estimating correlates of protection against symptomatic infection had small effect on our estimates (Fig. S4, Table S7).

Discussion

The purpose of this study was to examine the neutralizing antibody level of participants from the PROFISCOV study and estimate the CoPs provided by two doses of CoronaVac against symptomatic and total infections. Our results indicated that neutralizing titers of 30 (95% CI: 2–56) and 42 (95% CI: 24–62) in serum samples collected on Day 28 after two doses of CoronaVac could provide 50% vaccine efficacy against symptomatic and total infections, respectively. Meanwhile, a neutralization of 247 (95% CI: 139–506) could provide 80% vaccine efficacy against symptomatic infections. These findings collectively signaled the potential protective threshold for the inactivated COVID-19 vaccine.

It is critical to assess CoPs for various reasons, including accelerating vaccine approval when phase III efficacy data are lacking, validating novel vaccines following alterations in antigens, regimens, or populations, estimating population immunity, and predicting the durability of vaccine-elicited protection. Neutralizing antibodies have been established as an indicative immune marker well-correlated with protection from humoral immune response.[12] The mechanism of action of neutralizing antibodies encompasses

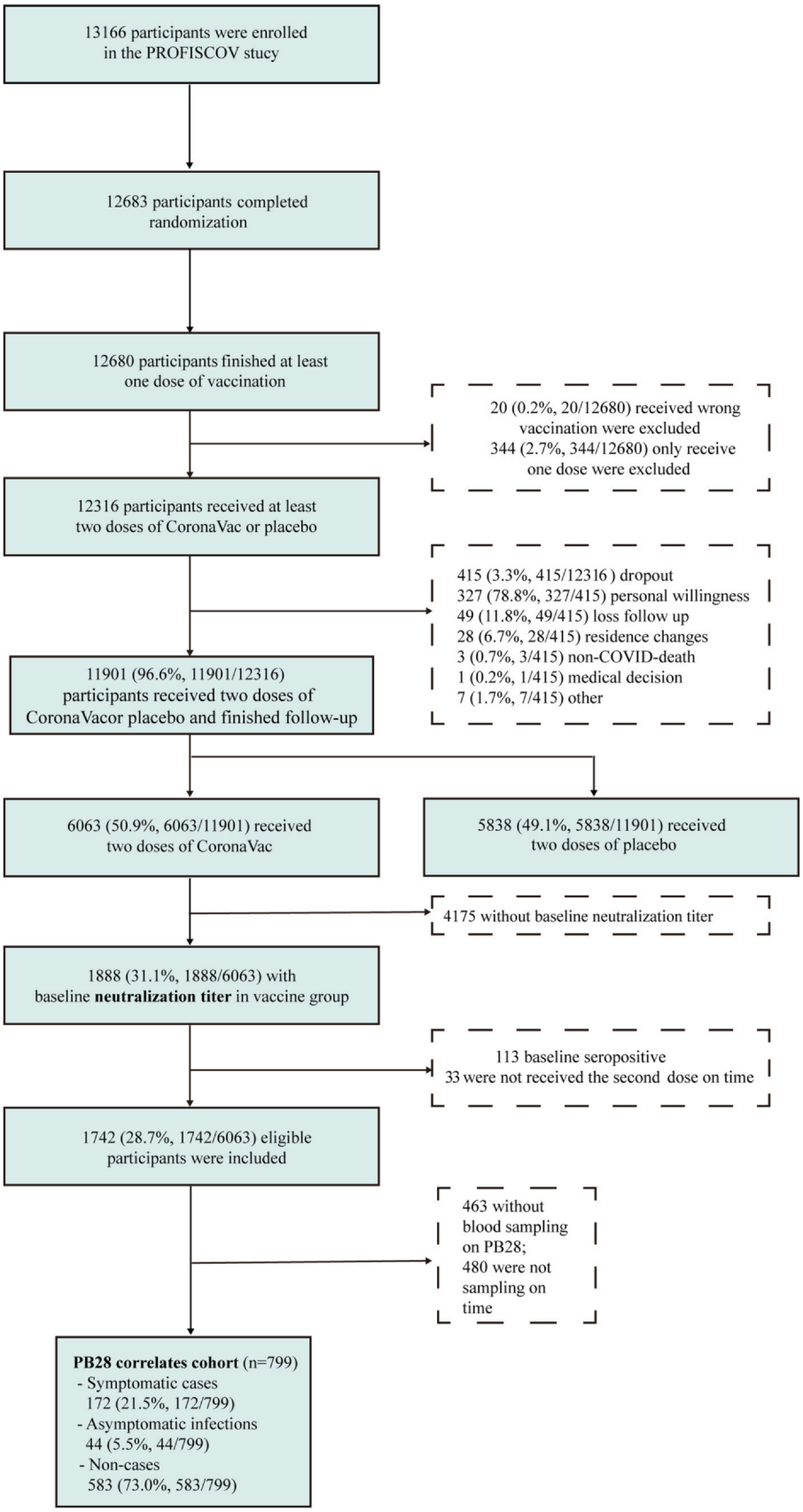

Fig. 1. Flowchart of selection of correlated participants.

Table 1
Characteristics of the PB28 correlate cohort.

	PB28 correlates cohort (n = 799)		
	Noncases (n = 583)	Symptomatic infection (n = 172)	Asymptomatic infection (n = 44)
Age group			
18–59 yrs	481 (82.5)	161 (93.6)	26 (59.1)
60+ yrs	102 (17.5)	11 (6.4)	18 (40.9)
Sex			
Female	332 (56.9)	116 (67.4)	24 (54.5)
Male	251 (43.1)	56 (32.6)	20 (45.5)
Race			
White	452 (77.5)	122 (70.9)	37 (84.1)
Black/African American	34 (5.8)	12 (7.0)	2 (4.5)
Indian/Native Alaska	0 (0.0)	0 (0.0)	0 (0.0)
Asian	18 (3.1)	1 (0.6)	1 (2.3)
Multiracial	79 (13.6)	37 (21.5)	4 (9.1)
BMI			
< 30	461 (79.1)	133 (77.3)	38 (86.4)
≥30	120 (20.6)	38 (22.1)	6 (13.6)
Unknown	2 (0.3)	1 (0.6)	0 (0.0)
Comorbidity			
No	193 (33.1)	64 (37.2)	11 (25.0)
At least one	390 (66.9)	108 (62.8)	33 (75.0)
Obesity	89 (15.3)	31 (18.0)	3 (6.8)
Malignant disease	3 (0.5)	2 (1.2)	0 (0.0)
Cardiovascular disease	79 (13.6)	12 (7.0)	8 (18.2)
Chronic lung disease	0 (0.0)	0 (0.0)	2 (4.5)
Diabetes	16 (2.7)	4 (2.3)	3 (6.8)
Other	203 (34.8)	59 (34.3)	17 (38.6)
Prior infection			
Yes	14 (2.4)	5 (2.9)	1 (2.3)
No	568 (97.4)	167 (97.1)	43 (97.7)
Unknown	1 (0.2)	0 (0.0)	0 (0.0)

preventing the interaction of infectious particles with host cells by blocking virions binding to receptors and virus uptake into host cells. A previous modeling study reported that a neutralizing antibody titer of 33 measured by live virus neutralization assay 14 days after the second dose of CoronaVac was necessary to achieve 50% efficacy against symptomatic Covid-19.[13] This result is consistent with our prediction that a neutralizing titer of 30 (95% CI: 2–56) could provide 50% protection against symptomatic infections. Our predictions of CoPs against symptomatic infections were further corroborated by the immunogenicity and vaccine efficacy/effectiveness data.[8,14] However, it is worthwhile acknowledging that a single protective threshold may not exist for all vaccines and clinical endpoints due to substantial variation between individuals, such as exposure risk, immune response level, and baseline disease. It is also important to recognize that correlation is not equivalent to causation, and the mechanistic involvement of neutralizing antibodies in the protection conferred by CoronaVac cannot be established without measurement of other potential correlates of protection.[15]

Previous studies documented the correlates of protection for an mRNA vaccine (Moderna) and an adenoviral vector vaccine (ChAdOx1 nCoV-19).[5,6] For the comparison of neutralizing antibodies within the same type of live virus neutralization assay, antibody levels induced by ChAdOx1 nCoV-19 for primary symptomatic and asymptomatic infections were 166 (95% CI:112–231) and 261 (95% CI:129–359), respectively, which were higher than the neutralization titer on the same sample-collection time induced by CoronaVac herein, in line with previous results from several immunogenicity evaluations.[16,17] However, the correlates of protection measured for ChAdOx1 nCoV-19 were comparable to that of our predictions for CoronaVac at the medium level of protection, with confidence intervals overlapping with each other. Specifically, the neutralization of 30 (95% CI: 2–56) and 64 (95% CI: 41–98) was estimated to provide 50% and 60% protection against symptomatic infections using CoronaVac, which was similarly close to the estimates of 41 (95% CI: 9–69) and 52 (95% CI: 20–90) for ChAdOx1 nCoV-19. To achieve a higher level of vaccine efficacy, the needed neutralization titer was higher for CoronaVac than ChAdOx1 nCoV-19, with 126 (95% CI: 76–185) and 71 (95% CI: 35–132) to achieve 70% protection and 252 (95% CI: 143–526) and 120 (95% CI: 56–298) to achieve 80% protection for these two vaccines, respectively. Nonetheless, it was not possible to estimate correlates of protection against asymptomatic infection, which was reported in the ChAdOx1 nCoV-19 study.

Our study was limited to a group of participants who received two doses of the CoronaVac vaccine in a setting where the P.1 and P.2 sublineages predominated, which may have restricted extrapolation to other subvariants, including Omicron. However, our results still provide preliminary evidence of a potential protective threshold for the inactivated vaccine. The study exposed that the average fold-reduction in antibody titer for Omicron XBB and EG.5 sublineages exceeded 8–50 fold compared to the antibody titer elicited by CoronaVac vaccination.[18,19] It is not practical to reach such a high antibody level through booster of inactivated vaccinations to

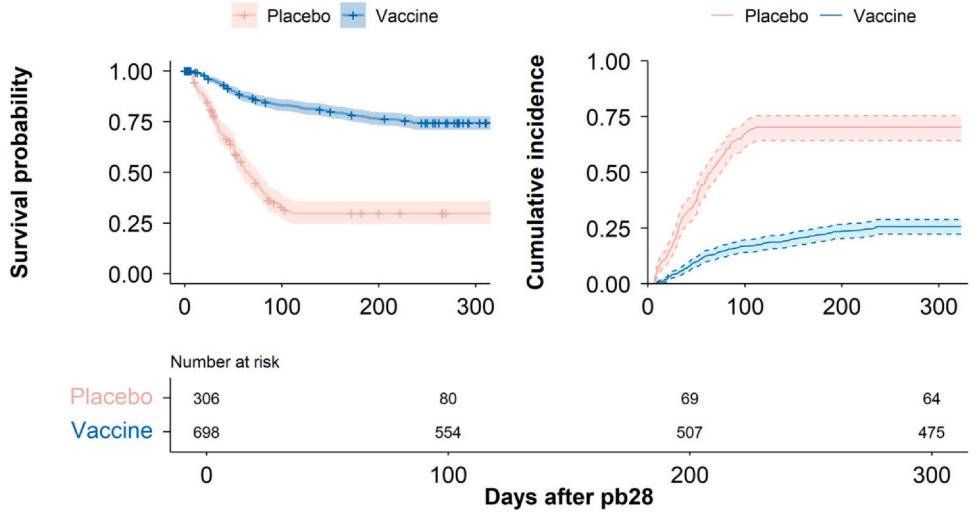

Fig. 2. Survival probability and estimated cumulative incidence.

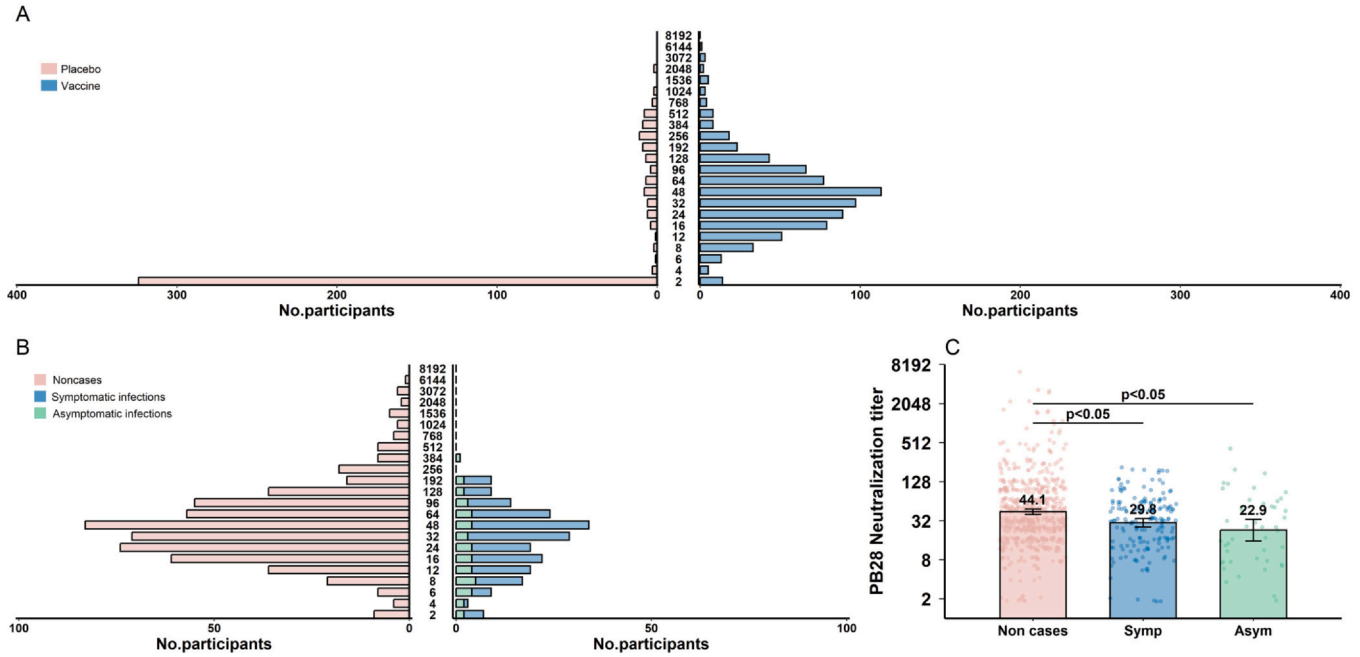

Fig. 3. Distribution and response level of neutralization antibody titers. (A) The distribution of neutralizing antibodies between the placebo and vaccine groups; (B) The distribution of neutralizing antibodies by predefined outcomes in the PB28 correlated cohort; (C) The GMTs of neutralizing antibodies by predefined outcomes in the PB28 correlated cohort.

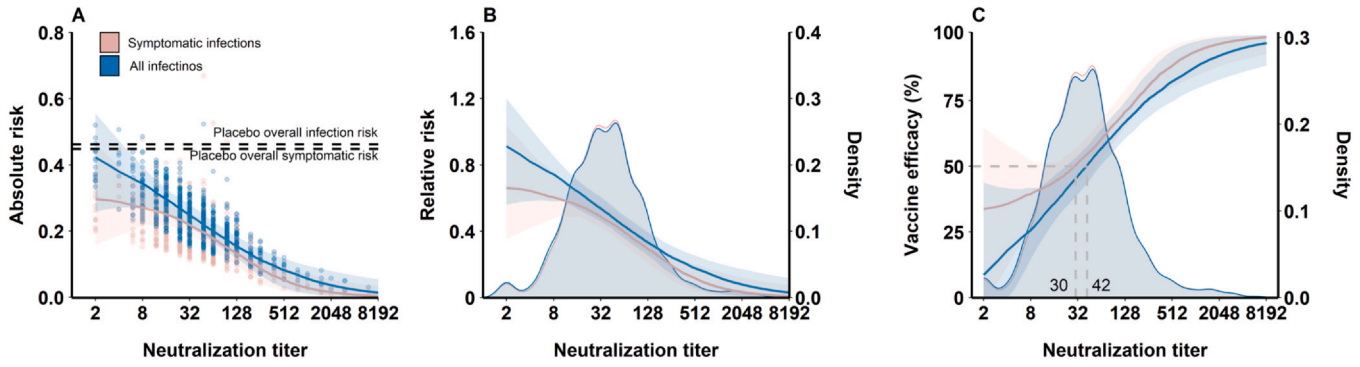

Fig. 4. Predicted absolute risk, relative risk, and efficacy against symptomatic and total infection in the PB28 correlated cohort. (A) The horizontal dashed line represents the average risk in the placebo group. The red and blue shape indicated symptomatic infections and all infection respectively; (B) The area under the curve represents the distribution of neutralizing antibodies; (C) The red and blue shape indicated symptomatic infections and all infection respectively.

compensate for the decline in antibodies caused by immune escape, which further implies that replacing antigens with new strains to develop a new generation of COVID-19 vaccine may be more effective. Future studies will be more informative if they estimate protective efficacy against the currently circulating variants based on our estimation framework.

Our study has several limitations that cannot be overlooked. To begin, the estimation of CoPs for the clinical endpoint of severe COVID-19 was not possible due to the limited sample size of participants that achieved this endpoint in our analysis. Secondly, indicators of cellular immunity and binding antibodies were not determined. The study solely focused on neutralizing antibodies as a potential immune marker, primarily ascribed to its well-established mechanism of preventing virus particles from infiltrating host cells through the formation of virus-antibody complexes and its strong correlation with protection induced by humoral immunity. Thirdly, potential variations in CoPs across different age groups, races, and ethnicities were not evaluated in the analysis due to the small sample size in these subgroups. Fourthly, due to the difficulty of capturing asymptomatic infections over the trial, the CoPs estimation for this endpoint had large uncertainty and unclear pattern. Fifthly, antibody waning was not considered in our study. Instead, only cross-sectional titer, 2–4 weeks after primary vaccinations, was used to establish correlation between titer and endpoints, which limited the consideration of antibody decay after vaccination. Finally, we were unable to convert predictions to the WHO unit, thereby limiting quantitative comparisons with other CoPs from various COVID-19 vaccines.

In summary, our results highlight the utility of neutralizing antibody response as a correlate of protection, which can be used to inform future vaccine development and implementation. Further evaluation of CoPs for different COVID-19 vaccine platforms is crucial in order to provide evidence for vaccine regulation and accelerate the approval process.

Disclaimer

The views expressed are those of the authors and do not necessarily represent the institutions with which the authors are affiliated.

Patient consent statement

Patient consents were not involved in our study.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Author contributions

H.Y. and D.C. conceived, designed, and supervised the study. X.C., X.M., Q.W., and Q.X. collected and checked the data. X.C., X.M., and Q.W. analyzed the data. X.C. wrote the first draft of the manuscript. X.C., W.L., C.B., W.M., H.Y., D.C. interpreted the results and revised the content. All authors approved the final version for submission and agreed to be accountable for all aspects of the work.

Data availability

De-identified data could be requested from the corresponding author. The code was available in online repository (https://github.com/cxhhhh24/coronavac_sop.git).

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Declaration of interests

H.Y. has received research funding from Sanofi Pasteur, GlaxoSmithKline, Yichang HEC Changjiang Pharmaceutical Company, Shanghai Roche Pharmaceutical Company, and SINOVAC Biotech Ltd. BJC has received consulting fees from AstraZeneca, Fosun Pharma, GSK, Haleon, Moderna, Novavax, Pfizer, Roche, and Sanofi Pasteur. All other authors report no competing interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106315.

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