

# Immunogenicity and reactogenicity of fractional vs. full booster doses of COVID-19 vaccines: a non-inferiority, randomised, double-blind, phase IV clinical trial in Brazil



Marco Antonio Moreira Puga,<sup>a,j</sup> Roberto Dias de Oliveira,<sup>b,c,j</sup> Patricia Vieira da Silva,<sup>a,j</sup> Vivek Charu,<sup>d</sup> Haley Hedlin,<sup>d</sup> Di Lu,<sup>d</sup> Amy Zhang,<sup>d</sup> Blake Shaw,<sup>d</sup> Joelle Ivy Rosser,<sup>e</sup> Jessica Couvillion Seidman,<sup>f</sup> Alice Scott Carter,<sup>f</sup> Farah Naz Qamar,<sup>g</sup> Stephen P. Luby,<sup>e</sup> Denise O. Garrett,<sup>f</sup> and Julio Croda<sup>a,h,i,\*</sup>



<sup>a</sup>Fiocruz Mato Grosso do Sul, Fundação Oswaldo Cruz, Campo Grande, MS, Brazil

<sup>b</sup>Curso de Enfermagem, Universidade Estadual de Mato Grosso do Sul, Dourados, MS, Brazil

<sup>c</sup>Programa de Pós-graduação em Ciências da Saúde, Universidade Federal da Grande Dourados, Dourados, MS, Brazil

<sup>d</sup>Quantitative Sciences Unit, Biomedical Informatics Research Division, Stanford University School of Medicine, Stanford, CA, USA

<sup>e</sup>Infectious Diseases and Geographic Medicine, Stanford University, Stanford, CA, USA

<sup>f</sup>Albert B Sabin Vaccine Institute, Washington, DC, USA

<sup>g</sup>Department Paediatric Infectious Diseases, The Aga Khan University, Pakistan

<sup>h</sup>Faculdade de Medicina, Universidade Federal de Mato Grosso do Sul - UFMS, Campo Grande, MS, Brazil

<sup>i</sup>Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, CT, USA

## Summary

**Background** Fractional doses of vaccine to protect against COVID-19 offer the potential to expand vaccine availability, reduce side effects, and enhance vaccination campaign efficiency. This study aimed to assess the immune response and safety of fractional doses of SARS-CoV-2 booster vaccines compared to full doses in immunocompetent adults aged 18–60 who had previously received a full series of Sinovac, AZD1222 (AstraZeneca), or BNT162b2 (Pfizer/BioNTech).

**Methods** This trial was structured as a parallel-group, double-blind, randomised Phase IV non-inferiority study, carried out in Campo Grande, Midwest, Brazil. After obtaining consent, eligible participants were randomised to one of 5–6 study arms, depending on their priming vaccine. Participants were followed for 21–60 days after vaccination through in-person visits and remote contact for blood collection and safety evaluation. Anti-spike binding IgG antibodies were measured by ELISA. The primary outcome was the difference in seroresponse rates between the full and fractional doses, with a non-inferiority threshold of 10%.

**Findings** A total of 1451 participants were randomised and administered booster vaccines between 5 July and 3 October, 2022. A half dose of BNT162b2 met the non-inferiority threshold, compared to a full dose in the Sinovac and AZD1222 primed groups. Sinovac induced an inferior response compared to AZD1222 and BNT162b2 full or fractional dose boosters in participants primed with Sinovac. Fractional booster doses of BNT162b2 consistently resulted in higher seroresponse rates (ranging from 35.4% to 78.3%) compared to fractional boosters of AZD1222 (ranging from 10.0% to 44.7%) or a full dose of Sinovac (4.2%). Both full and fractional dose vaccines were generally well tolerated. Local and systemic adverse events occurred across all treatment arms in line with expectations, with nine serious adverse events reported, none of which were determined to be related to study vaccination.

**Interpretation** Our data show that the immunogenicity of booster vaccines depends on the initial vaccine, baseline antibody levels, and the booster vaccine used. Fractional doses of BNT162b2 and AZD1222 were non-inferior to a full Sinovac booster in individuals primed with Sinovac. However, fractional doses of BNT162b2 were not non-inferior in BNT162b2-primed individuals, and AZD1222 fractional doses were only non-inferior in the AZD1222 priming arm. We advise against Sinovac as a booster. Fractional doses of BNT162b2 or AZD1222 remain practical alternatives for Sinovac-primed populations in resource-limited settings.

**Funding** Coalition for Epidemic Preparedness Innovations (CEPI)/Sabin Vaccine Institute.

The Lancet Regional Health - Americas  
2025;44: 101031

Published Online 22  
February 2025  
<https://doi.org/10.1016/j.lana.2025.101031>

\*Corresponding author. Fundação Oswaldo Cruz, Mato Grosso do Sul, Campo Grande, MS, 79074-460, Brazil.

E-mail address: [julio.croda@fiocruz.br](mailto:julio.croda@fiocruz.br) (J. Croda).

<sup>j</sup>These authors contributed equally.

Trial registration number: NCT05343871.

Copyright © 2025 The Author(s). 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/>).

**Keywords:** COVID-19 vaccines; Fractional doses; Immunogenicity; Non-inferiority study

### Research in context

#### Evidence before this study

We searched PubMed, Embase, and Cochrane Library, databases for studies published from December 1, 2019, to June 30, 2022, using the terms “COVID-19” or “SARS-CoV-2” and “vaccine” or “booster” or “fractional dose” or “dose sparing”. We included randomized controlled trials, observational studies, and preclinical studies that evaluated the immunogenicity, safety, and efficacy of fractional doses of COVID-19 vaccines compared to full doses. We excluded studies that were not peer-reviewed, had incomplete data, or used different vaccines for the primary and booster doses. We performed a review of the studies that reported seroresponse rates. We identified 12 studies that met our inclusion criteria, of which nine were randomized trials and three were observational studies. The studies involved different COVID-19 vaccines, such as Sinovac, AZD1222 (AstraZeneca), BNT162b2 (Pfizer/BioNTech), Ad26.COV2.S (Janssen), and NVX-CoV2373 (Novavax), and different fractional doses, ranging from 1/10 to 1/2 of the full dose. Overall, the studies showed that fractional doses of COVID-19 vaccines were non-inferior to full doses in terms of seroresponse rates.

#### Added value of this study

This is the largest study to compare the immunogenicity and safety of fractional doses of SARS-CoV-2 booster vaccines to full doses in immunocompetent adults aged 18–60 who had previously received a full series of Sinovac, AZD1222, or BNT162b2 vaccines. Our study involved a large and diverse sample of participants, randomized to one of 6 treatment arms assigning type and dose of the booster vaccine within

the priming vaccine group. We followed the participants for the primary outcome for 28 days after the intervention and collected blood samples and safety data through day 180. Our results showed that a half dose of BNT162b2 met the non-inferiority threshold, compared to a full dose in the Sinovac and AZD1222 primed groups. Sinovac showed inferiority compared to AZD1222 and BNT162b2 full or fractional dose boosters in participants primed with Sinovac. Both full and fractional dose vaccines were generally well tolerated, with no serious adverse events related to vaccination.

#### Implications of all the available evidence

Our study provides valuable and timely evidence to inform the design and implementation of booster vaccination strategies against COVID-19. Our findings suggest that fractional booster doses generate similar anti-spike antibody levels as full BNT162b2 and AZD1222 doses 28 days post-vaccination, irrespective of the initial vaccine. We advise against Sinovac as a booster, as it showed inferior immunogenicity and reactogenicity compared to AZD1222 and BNT162b2 full or fractional dose boosters. In financially constrained populations primed with Sinovac or AZD1222, opting for fractional BNT162b2 or AZD1222 doses is a practical alternative that could expand vaccine availability, reduce side effects, and enhance vaccination campaign efficiency. Our study also has implications for future research, as it highlights the need for more studies to evaluate the long-term durability and efficacy of fractional doses of COVID-19 vaccines, as well as their impact on the transmission and evolution of SARS-CoV-2 variants.

### Introduction

Since the emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), millions of individuals across the world have faced illness and mortality caused by coronavirus disease 2019 (COVID-19). By the end of 2023, more than 770 million cases and 7 million deaths due to COVID-19 have been reported worldwide.<sup>1</sup> The administration of COVID-19 vaccines has become crucial in managing the spread and impact of this disease.<sup>2,3</sup> However, due to the waning of immunity over time and the cost of vaccine doses, administering fractional doses of vaccine as a booster offers a potentially attractive strategy to increase vaccine coverage.<sup>4</sup> Studies have shown that reduced doses of some vaccines can generate high levels of protection, especially against severe forms and deaths from COVID-19, while potentially expanding the

vaccine supply by 450 million to 1.55 billion doses per month, based on the supply projections for 2023.<sup>5</sup>

At the outset of the COVID-19 pandemic, public health officials expressed concerns regarding the inequitable global distribution of vaccines. Current data indicates that these concerns were justified, as high-income countries have been able to vaccinate their populations much more rapidly compared to lower-income countries.<sup>1</sup> To date, more than 13 billion doses of COVID-19 vaccines have been administered worldwide, with 70.5% of the global population having received at least one dose of the vaccine.<sup>6</sup> Nonetheless, in the African continent, 39 out of every 100 individuals have received at least one vaccine dose, and 32.4% of the population is fully vaccinated,<sup>7</sup> and only around 29.0% of individuals in low- and middle-income countries have completed the primary two-dose vaccination regimen.<sup>8–11</sup>

In light of these disparities, policymakers and scientists are exploring the possibility of dose fractionation to conserve vaccine supplies and reduce the cost per dose. Currently, limited evidence exists regarding the optimal dosing for COVID-19 vaccines, and Experts on Immunization of the World Health Organization Strategic Advisory Group (SAGE/WHO) advocates further research, including prospective randomised trials to evaluate the safety and immunologic non-inferiority of fractional doses compared to full doses, particularly in the context of booster vaccinations.<sup>4</sup>

The present study aimed to assess and compare the humoral and cellular immune responses elicited by fractional and full booster doses of BNT162b2 (Pfizer/BioNTech) or AZD1222 (AstraZeneca) in immunocompetent adults who completed their initial vaccination series with BNT162b2, AZD1222, or Sinovac vaccines. Additionally, the safety and reactogenicity profiles of both fractional and full booster doses of the study vaccines in the second visit are described.

## Methods

### Trial design, population and oversight

A double-blind, parallel-arm, phase IV randomised non-inferiority trial was conducted in Campo Grande, Midwest, Brazil, as part of a platform trial designed and registered for implementation in both Brazil and Pakistan. The results presented here are from the Brazilian cohort only. A prespecified primary analysis was performed when all participants had completed a follow-up second visit.

The study recruited healthy adult participants aged 18–60 years residing in Campo Grande who provided written informed consent. Participants were excluded if they were medically ineligible to receive specific COVID-19 vaccines or had not completed their initial two-dose primary series of vaccinations. We also excluded individuals with a history of solid organ or bone marrow transplant, recent cancer diagnosis and treatment, current haemodialysis patients, those with confirmed or suspected immune-suppressing conditions, individuals on long-term use of immune-suppressing medications, and people with known HIV infection. During eligibility screening, pregnant individuals, anyone testing positive for SARS-CoV-2 on a rapid antigen test, those planning to leave the study area within six months, participants concurrently involved in other research trials related specifically to COVID-19 vaccines, illiterate people, and those suffering from severe or uncontrolled comorbidities were considered ineligible. The study protocol is available in the Stanford Digital Repository (<https://purl.stanford.edu/fr354zt8141>).

The study protocol, participant consent form and data collection forms were approved by the appropriate Institutional Review Boards (IRB) in each country. Ethical clearance in Brazil was granted by the local IRB

at the Federal University of Mato Grosso do Sul (CEP/UFMS) on 6 May 2022, with further endorsement from the national IRB (CONEP) on 1 June 2022. Additionally, Stanford University's IRB granted approval on 24 June 2022 ensuring robust ethical considerations were upheld during the study period. The trial was registered in [ClinicalTrials.gov](https://clinicaltrials.gov) (Identifier: NCT05343871).

Unblinded safety data were reviewed by an independent data and safety monitoring board. Only the pharmacists preparing the booster vaccines, the unblinded statisticians and the members of the independent data and safety monitoring board were aware of the trial-group assignments at the level of individual participants.

### Sample size calculation, randomisation and blinding

Sample size was calculated separately for the parallel trials in Brazil and Pakistan. The target enrolment was 90 per study arm (1440 participants total in Brazil), assuming a seroresponse rate of 95% with a non-inferiority margin of 10%, a statistical significance level of 5% (one-sided), to achieve 90% power with a potential loss to follow-up estimated at up to 10%. Three parallel groups were formed based on the primary vaccine series. Participants were randomised to five or six treatment arms to assign the booster vaccine, with the number of treatment arms depending on the primary vaccine series. The Sinovac primed group consisted of 540 participants randomised to receive a single booster dose of one of the following vaccines: AZD1222 (half dose), AZD1222 (full dose), BNT162b2 (one-third dose), BNT162b2 (half dose), or BNT162b2 (full dose), or Sinovac (full dose). The AZD1222 primed group consisted of 450 participants randomised to receive a single dose of one of the following vaccines: AZD1222 (half dose), AZD1222 (full dose), BNT162b2 (one-third dose), BNT162b2 (half dose), or BNT162b2 (full dose). The BNT162b2 prime group consisted of 450 participants randomised to receive a single dose of AZD1222 (half dose), AZD1222 (full dose), BNT162b2 (one-third dose), BNT162b2 (half dose), or BNT162b2 (full dose). A computer-generated randomisation list was prepared, and the participants were individually randomised using a block randomisation technique within each priming group, with randomly selected block sizes of 5 or 10 in the AZD1222 and BNT162b2 primed groups and 6 or 12 in the Sinovac primed group. The initial participants in each priming group were offered inclusion in the pseudovirus neutralisation and cell-mediated immunity sub-cohort until we enrolled approximately 20 participants per treatment arm. The study was double-blind, ensuring participants, data collectors (such as investigators and research staff), and some data evaluators (blinded trial statisticians) were unaware of the vaccine group allocation. Only the pharmacists involved in vaccine preparation and three unblinded statisticians had

knowledge of which vaccine each participant received. Vaccines were prepared with masking tape to maintain blinding on syringes. In addition to this measure, staff responsible for symptom monitoring, recording adverse events, laboratory personnel conducting analysis remained blinded to both the specific vaccine administered and dosage provided.

### Study procedures

The study vaccines were supplied by the Brazilian Ministry of Health (MoH). The manufacturer was responsible for guaranteeing the quality of the vaccine product, while the MoH supervised quality assurance during storage and transportation to the FIOCRUZ Clinical Research Site. The trial team identified the areas with the lowest booster vaccine coverage by analysing data from the National Immunisation Information System, which was obtained through collaboration with the State Health Office. In conjunction with local health teams, we conducted home visits to individuals in these neighbourhoods to ascertain their willingness to participate in the study, fulfil all necessary consent and eligibility requirements, provide blood and nasal swab samples for COVID-19 antigen-based tests, and for female participants of reproductive age, conduct a urine pregnancy test. After enrolment, random assignment was implemented through the REDCap platform. A team of pharmacists stationed on a support bus in the local neighbourhood prepared vaccine doses based on random assignments. These doses were then transported to each participant's residence using thermally insulated bags and thermometers to ensure accurate temperature control. Upon arrival at their residences, healthcare professionals promptly administered the vaccine to each participant. The team stayed at the participant's home for 30 min for evaluation and intervention in case of immediate adverse events after vaccination. Participants were provided with a dedicated emergency telephone number for contacting the on-call study physician if necessary and instructed to self-evaluate adverse events' severity levels if/when they occurred.

During the study, participants were regularly contacted by phone to monitor their symptoms and ensure their safety. They were asked to report any symptoms and confirm SARS-CoV-2 infection detected through PCR or rapid antigen testing. Daily contact was made between days 2 and 7, followed by weekly contact until the third visit ( $84 \pm 7$  days), and then every two weeks until the fourth visit ( $182 \pm 7$  days). The study consisted of four planned visits for  $1 \times 10$  mL venous blood collection to obtain serum after receiving the booster dose: enrolment (day 1), second visit (day 28), third visit (day 84), and last visit (day 182). The second visit was planned to occur between days 21 and 35, that is,  $28 \pm 7$  days. However, visits were conducted between 21 and 60 days after the administration of the booster dose. Participants enrolled in the cellular immunity and

pseudovirus neutralisation subcohort ( $n = 20$ /treatment arm) had additional blood collected (up to  $1 \times 10$  mL) during the first three visits. In this manuscript, we present the results obtained from baseline observations, as well as those collected during the second visit.

### Immunogenicity evaluation

Serum samples were analysed to assess humoral immunity, while in a subcohort, peripheral blood mononuclear cells (PBMC) were processed to measure cell-mediated immunity at baseline and 28 days after the booster. The Abbott Architect SARS-CoV-2 IgG Quant II (Abbott, Sligo, Ireland) assay measured anti-Spike IgG antibodies in all participants. Additionally, in the subcohort we conducted an anti-SARS-CoV-2 antibody neutralisation assay using a SARS-CoV-2 pseudotyped virus<sup>12</sup> against both Wuhan and Omicron strains. In the subcohort we also evaluated cell-mediated immunity by employing a standardised ELISPOT-based technique (T-SPOT®.Covid, Oxford Immunotec, UK) designed to detect T-cell immune responses to SARS-CoV-2 structural proteins, specifically spike (S) and nucleocapsid (N).

### Statistical analysis

#### Immunogenicity

The planned primary outcome was the difference in seroresponse rates in participants completing their second visit (occurring at day  $28 \pm 7$  days), comparing full and fractional doses of vaccines within each priming arm. Seroresponse was defined as either having detectable anti-spike IgG antibody titres at days 21–35 after booster vaccination for participants without detectable antibodies at baseline or an increase in anti-spike IgG antibody titre of four-fold or more among individuals with detectable pre-booster titres. Depending on the priming arm, various pairwise comparisons were made, including full dose BNT162b2 vs. fractional doses of BNT162b2, full dose AZD1222 vs. a fractional dose of AZD1222, and full dose Sinovac vs. fractional doses of BNT162b2 and AZD1222. Per-protocol analyses were conducted for the immunogenicity endpoints; participants who did not have a second sample available, experienced suspected COVID-19 infection, or became pregnant before the second study visit were excluded from all analyses.

During the trial, a large fraction of second visits occurred between 21 and 60 days after the administration of the booster dose. As such, we conducted a post-hoc analysis of the difference in seroresponse rates in participants completing their second visit during days 21–60, comparing full and fractional doses of vaccines within each priming arm. This post-hoc analysis, as well as the original planned primary outcome analysis are presented here.

This study was designed to evaluate whether the fractional dose booster vaccination is non-inferior compared to full dose booster vaccination. Fractional

doses were considered non-inferior if the following criteria were met: the upper limit of the 90% confidence interval of the two-proportion difference (computed as the difference between the proportion of seroresponders given the full dose minus the proportion of seroresponders given the fractional dose) was equal to or less than 10%. This definition for non-inferiority corresponds to a one-sided hypothesis test with a type I error rate ( $\alpha$ ) of 0.05, and a non-inferiority margin of 10%. Confidence intervals for the difference between two proportions were calculated using Newcombe's hybrid score interval.<sup>13,14</sup> Geometric mean titres (GMTs) were calculated according to the formula:  $\text{GMT} = \exp(\sum \log(\text{antibody titre})/n)$ .

In secondary analyses, we evaluated the effects of fractional vs. full booster dose vaccines on the quantitative anti-spike IgG titre (natural log transformed). Among participants in the subcohort, we evaluated the effects of fractional vs. full dose vaccines on neutralising antibody titres against Wuhan and Omiron strains and on T-cell activation against spike and nucleocapsid proteins. Within each priming group, and for each of the aforementioned outcomes, we modelled the average outcome at the second visit as a function of the booster vaccine arm, adjusting for the baseline value, using generalised linear models.

#### Safety and reactogenicity

An analysis was conducted to compare the safety and reactogenicity of fractional vs. full dose booster shots with AZD1222, BNT162b2, or a standard dose of Sinovac. The analysis evaluated the frequency and severity of adverse events (AEs) including local and systemic reactions during the seven days following vaccination, as well as unsolicited AEs, medically-attended AEs, Serious AEs, and AEs of special interest during the 28-day period after receiving the booster shot. Participants who received a booster were included in the safety analyses.

Analyses were performed in R v4.3.1 (R Project for Statistical Computing) and SAS version 9.4 (SAS Institute).<sup>13</sup>

#### Role of the funding source

The trial was funded by the Coalition for Epidemic Preparedness Innovations (CEPI) and sponsored by the Sabin Vaccine Institute. Authors who are employees of Sabin Vaccine Institute were involved in the conception and design of the trial and the collection, analysis, and interpretation of data, and some of them were part of the core writing team. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

### Cohort enrolment and baseline characteristics

Enrolment began on 5 July 2022 and continued until 3 October 2022. A total of 1452 participants were

randomised and 1451 were administered booster vaccines (one participant withdrew consent prior to vaccination; [Fig. 1](#)). After excluding participants who had a COVID-19 infection ( $n = 23$ , 1.6%) or became pregnant before visit 2 ( $n = 4$ , 0.3%), those who withdrew consent ( $n = 49$ , 3.3%) and those who were unavailable on the day of the visit ( $n = 164$ , 11.3%), blood samples were collected from 846 participants (58.3%) on days 21–35 after vaccination booster (pre-specified primary outcome), and from 1211 participants (84.0%) on days 21–60 after vaccination booster (post-hoc analysis).

Demographic characteristics, comorbidities, and baseline symptoms were relatively balanced within each priming group. At baseline, participants in the AZD1222 primed group tended to be older compared to those in the BNT162b2 and Sinovac primed groups (mean age 42 (SD 12) years vs. 31 (SD 9) and 34 (SD 11) years, respectively). A higher proportion of participants in the AZD1222 group had mild/moderate cardiovascular disease at baseline (15.3%,  $n = 69$ ) compared to the other groups, which ranged from 4.2% ( $n = 23$ ) in the Sinovac group to 6.0% ( $n = 27$ ) in the BNT162b2 group; [Table 1](#)). The average time elapsed since the completion of the primary vaccination series varied between priming arms (AZD1222: 12 (SD 2) months; Sinovac: 11 (SD 2) months; BNT162b2: 10 (SD 2) months), reflecting vaccine roll-out in Brazil. Sinovac and AZD1222 were among the first vaccines approved for emergency use. However, within each priming group, randomised arms demonstrated similar distributions of age, sex (determined through a structured questionnaire as biological sex), the highest level of education, comorbidities, and baseline symptoms ([Supplementary Tables S1–S3](#)). This was consistent when considering the analysis groups on day 21–60 and day 21–35 ([Supplementary Table S4](#)).

### Immunogenicity evaluation

While the pre-specified primary outcome was the difference in seroresponse rates in participants completing their second visit between days 21 and 35, a large fraction of participants' second visits occurred on days 36–60. The distribution of anti-spike IgG antibody titres is comparable between the groups of individuals sampled at 21–35 days and those sampled at 36–60 days ([Supplementary Figure S1](#)). As such, we performed a post-hoc analysis of the difference in seroresponse rates in participants who completed their second visit between days 21 and 60 after booster vaccination. Both the pre-specified primary outcome analysis and post-hoc analysis are presented in [Fig. 2](#).

The fractional dose of AZD1222 was non-inferior to a full dose of AZD1222 in the AZD1222 primed group (difference in seroresponse rates between full AZD1222 and half AZD1222:  $-3.9\%$ ; 90% CI:  $-12.8$  to  $5.2\%$ ); in contrast, non-inferiority of fractional doses of AZD1222 was not demonstrated in the BNT162b2 or Sinovac primed groups ([Fig. 2](#) and [Supplementary Table S5](#)).



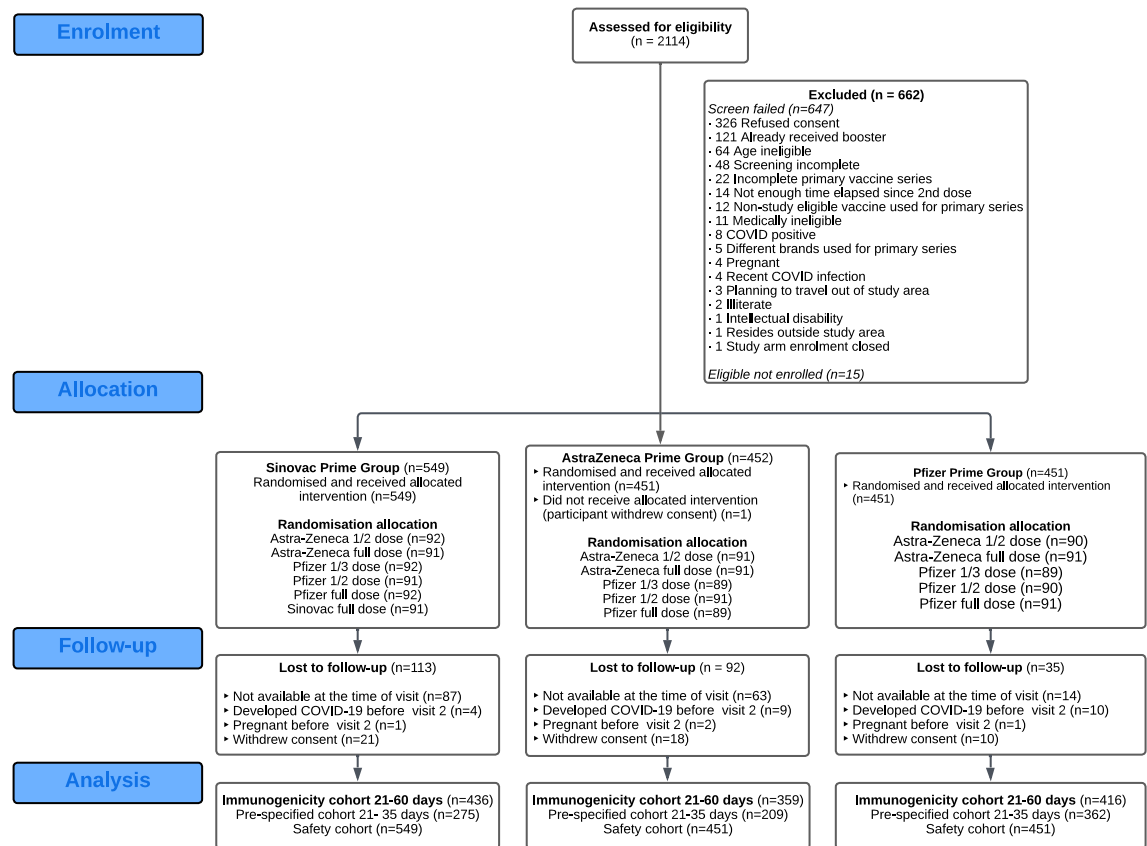


Fig. 1: Participant enrollment and follow-up in fractional vs. full COVID-19 booster dose trial.

The half-dose BNT162b2 booster was found to be non-inferior to the full dose of BNT162b2 in the AZD1222 primed group (−6.6%; 90% CI: −20.1 to 7.2%), and the Sinovac primed group (−4.2%; 90% CI: −15.6 to 7.5%). The one-third dose of BNT162b2 was non-inferior to the full dose of BNT162b2 only in the AZD1222 primed group (−5.6%; 90% CI: −19.0 to 8.0%). Among participants primed with BNT162b2, we did not find evidence that the fractional doses of BNT162b2 were non-inferior to the full doses of BNT162b2. In fact, among participants primed with BNT162b2, the one-third dose was inferior to the full BNT162b2 dose (32.1%; 90% CI: 19.5–43.2%), and inconclusive results were observed with the one-half dose of BNT162b2 (Fig. 2 and Supplementary Table S5).

The full dose of Sinovac was inferior compared to fractional doses of AZD1222 and BNT162b2: half AZD1222 (−21.2%; 90% CI: −30.8 to −11.7%), half BNT162b2 (−74.1%; 90% CI: −81.5 to −63.3%), and one-third BNT162b2 (−60.6%; 90% CI: −69.6 to −49.3%) in Sinovac primed group (Fig. 2 and Supplementary Table S5).

Point estimates of the treatment effects for all primed groups were broadly similar when comparing

vaccine intervals of 21–35 days and 21–60 days (Fig. 2). In some comparisons, particularly for the fractional vs. full doses of BNT162b2 in the AZD1222 and Sinovac primed arms, the findings in the 21–35 day cohort were inconclusive while the 21–60 day analysis found the fractional doses to be non-inferior to the full booster dose due to the smaller confidence intervals in the larger cohort.

The findings of the study revealed that the administration of the full dose of BNT162b2 resulted in a more considerable production of anti-spike antibodies than its fractionated doses across all primed arms (Supplementary Table S6, Fig. 3,  $p < 0.05$ ). Conversely, AZD1222 did not exhibit a substantial discrepancy between the full dose and its fractional dose in all primed arms (BNT162b2, AZD1222, and Sinovac;  $p = 0.71; 0.063; 0.24$ , respectively). It is important to mention that Sinovac demonstrated lower production of anti-spike antibodies than the fractional doses of BNT162b2 and AZD1222.

Our findings demonstrate that the fractional booster doses of BNT162b2 consistently resulted in substantially higher levels of anti-spike binding IgG antibodies (seroresponse rates ranged from 35.4% to 78.3%) compared to fractional boosters of AZD1222 (which

ranged from 10.0% to 44.7%) or full dose Sinovac (4.2%) (Supplementary Table S6).

Our subcohort study evaluated the levels of neutralising antibodies against both Wuhan and Omicron strains induced by full and fractional booster doses of AZD1222, BNT162b2 and Sinovac. The Log RLU (relative light unit) of concentrations of neutralising antibodies against both Wuhan and Omicron strains were comparable between the fractional and full dose arms for BNT162b2 and AZD1222 in all primed groups. There were no discernible differences observed (Supplementary Figures S2 and S3). The concentration of neutralising antibodies against Omicron at baseline was generally higher than those against the Wuhan strain, likely reflecting natural exposure to the dominant Omicron strain circulating at the time of our study (Supplementary Figures S2 and S3).

Participants in the subcohort were assessed for T cell activation and interferon gamma production at baseline and visit 2. There was no significant difference in T cell activation when stimulated with nucleocapsid proteins in all primary arms. In the Sinovac primary group, a statistically significant difference was observed in cell activation among participants who received a half dose of AZD1222, as well as among those who received one-third and half doses of BNT162b2, when compared to participants who received a full dose of Sinovac ( $p = 0.051$ ;  $p = 0.0011$ ,  $0.0031$ , respectively) (Supplementary Figure S4).

### Safety evaluation

All treatment groups experienced adverse events (AE), including both local and systemic. The vast majority of these AEs occurred within the initial 28 days following the booster vaccination, with 46.0% of events within 28 days being local and 54.0% being systemic (Table 2 and Fig. 4). Throughout the 180-day study period, there were a total of 74 medically attended AEs reported, out of which nine were categorized as serious AEs. It was concluded that none of these serious AEs were likely related to the vaccine. Importantly, no deaths were recorded during the duration of this research investigation.

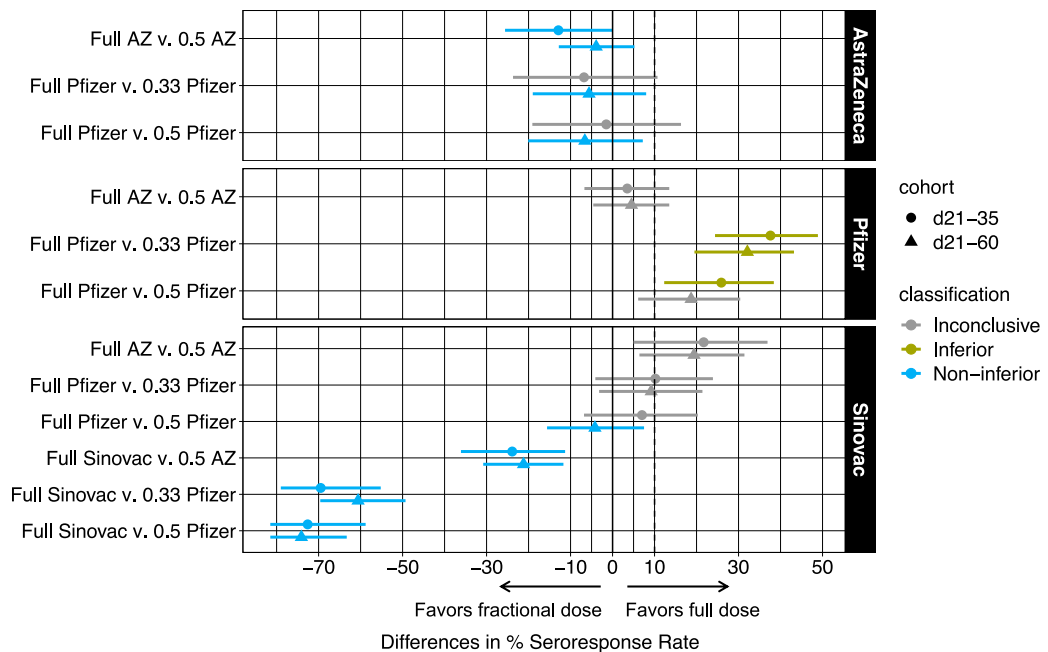
Out of 1451 participants, AEs were reported with the following frequencies observed in the initial 7 days post-vaccination: pain at the injection site (617, 42.3%), headache (329, 22.5%), muscle aches (227, 15.5%) and fatigue (166, 11.4%). Symptoms classified as 'other' were reported by 1.9% of participants during the same period; the most commonly described 'other' symptoms included: hypertension, renal colic, and insomnia. The Sinovac treatment arm had the fewest reports of adverse events during the first 7 days (1.2 events per person) followed by the one-third dose of BNT162b2 within the AZD1222 primed group (1.9 events per person) (Supplementary Table S7).

When compared across fractional dose type, the full dose of BNT162b2 resulted in a higher incidence of

Variable	Total	Sinovac	AZD1222	BNT162b2
<b>N</b>	1451	549	451	451
<b>Age</b> Mean (SD)	35 (11)	31 (9)	42 (12)	34 (11)
<b>Sex</b>				
Female	693 (47.8)	262 (47.7)	173 (38.4)	258 (57.2)
Male	758 (52.2)	287 (52.3)	278 (61.6)	193 (42.8)
<b>Highest education level</b>				
Primary/Middle school	411 (28.3)	140 (25.5)	156 (34.6)	115 (25.5)
10th Grade/Intermediate	753 (51.9)	331 (60.3)	189 (41.9)	233 (51.7)
Graduate	248 (17.1)	70 (12.8)	85 (18.8)	93 (20.6)
Master's or above	35 (2.4)	8 (1.5)	18 (4.0)	9 (2.0)
None	4 (0.3)	0 (0.0)	3 (0.7)	1 (0.2)
<b>Comorbidities (mild/moderate)</b>				
Cardiovascular disease	119 (8.2)	23 (4.2)	69 (15.3)	27 (6.0)
Respiratory disease	18 (1.2)	5 (0.9)	6 (1.3)	7 (1.6)
Gastrointestinal disease	9 (0.6)	2 (0.4)	5 (1.1)	2 (0.4)
Liver disease	3 (0.2)	0 (0.0)	2 (0.4)	1 (0.2)
Kidney disease	9 (0.6)	3 (0.5)	3 (0.7)	3 (0.7)
Endocrinological disease	42 (2.9)	6 (1.1)	25 (5.5)	11 (2.4)
Neurological disease	29 (2.0)	12 (2.2)	9 (2.0)	8 (1.8)
Rheumatologic disease	10 (0.7)	0 (0.0)	9 (2.0)	1 (0.2)
<b>Baseline symptoms reported within 5 days prior to screening</b>				
Fever	10 (0.7)	3 (0.5)	3 (0.7)	4 (0.9)
Cough	18 (1.2)	9 (1.6)	7 (1.6)	2 (0.4)
Headache	23 (1.6)	6 (1.1)	9 (2.0)	8 (1.8)
Sore throat	11 (0.8)	4 (0.7)	4 (0.9)	3 (0.7)
Upper respiratory congestion	27 (1.9)	10 (1.8)	9 (2.0)	8 (1.8)
Loss/change of smell or taste	3 (0.2)	0 (0.0)	3 (0.7)	0 (0.0)
Fatigue or tiredness	6 (0.4)	3 (0.5)	3 (0.7)	0 (0.0)
Body or muscle aches	15 (1.0)	5 (0.9)	7 (1.6)	3 (0.7)
Chills	5 (0.3)	2 (0.4)	2 (0.4)	1 (0.2)
Diarrhea	5 (0.3)	1 (0.2)	2 (0.4)	2 (0.4)
Nausea/vomiting	3 (0.2)	1 (0.2)	2 (0.4)	0 (0.0)
Chest pain	3 (0.2)	1 (0.2)	2 (0.4)	0 (0.0)
Shortness/difficulty breathing	4 (0.3)	1 (0.2)	2 (0.4)	1 (0.2)
Other	6 (0.4)	3 (0.5)	3 (0.7)	0 (0.0)
<b>Time elapsed (months) since finishing primary vaccine series</b> Mean (SD)	11 (2)	11 (2)	12 (2)	10 (2)

**Table 1: Demographics and baseline clinical characteristics of randomised participants by priming arm (N = 1451).**

systemic adverse events (AEs) within 28 days in the Sinovac and BNT162b2 primed groups (2.37 events per person in those receiving BNT162b2 vs. 0.98–1.38 receiving other doses and 1.90 vs. 1.09–1.61, respectively) (Supplementary Figure S5). In the AZD1222 primed group, the highest incidence of systemic AEs were in those receiving a one-half dose of AZD1222 (1.38 AEs per person) and Sinovac (1.45 AEs per person vs. 0.78–1.09 in participants receiving other boosters). When considering local AEs within 28 days of receiving the booster, the event rate among individuals receiving full BNT162b2 was 1.36 in the AZD1222 and 1.53 in the BNT162b2 primed groups. In contrast, those receiving a one half dose of BNT162b2 experienced local AEs at a



**Fig. 2:** Comparative analysis of seroresponse rates in participants receiving fractional vs. full booster dose by priming arm, day 21–35 cohorts and day 21–60.

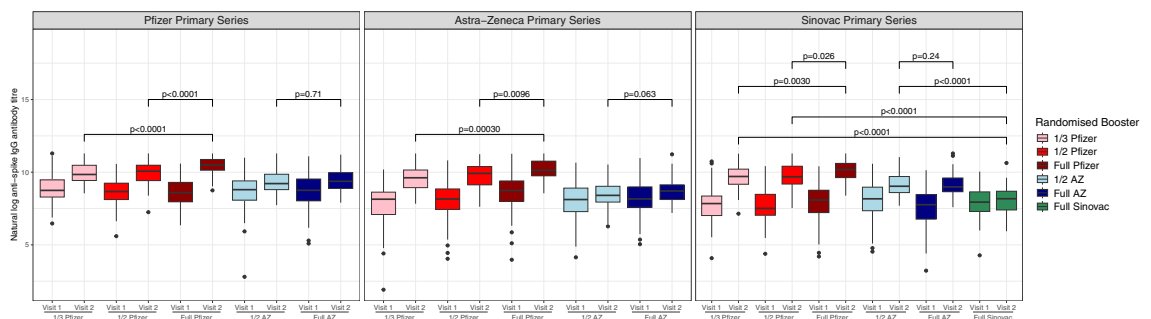
rate of 0.73 and 1.19 in the AZD1222 and BNT162b2 primed groups. Similar numbers of local adverse events were observed in the other booster dose groups (range to 0.74–0.84%) in the AZD1222 primed group and in the BNT162b2 primed group (range to 0.92–1.16) (Supplementary Table S8).

## Discussion

We observed that the full dose Sinovac booster exhibited inferior immunogenicity compared to fractional dose boosters of AZD1222 or BNT162b2. Notably, when individuals were initially primed with the BNT162b2 vaccine, administering a full dose for the booster resulted in a higher proportion of vaccinees meeting the

primary serological endpoint in contrast to half or one-third dose recipients. Intriguingly, the fractional doses of BNT162b2 demonstrated non-inferiority to the full dose when administered to subjects initially primed with Sinovac or AZD1222.

In cases where participants were initially primed with Sinovac, the Sinovac full dose booster was inferior to AZD1222 and BNT162b2 fractional dose boosters. These findings underscore the potential viability of fractional boosters in future vaccine schedules. It is crucial to note that, consistent with other studies, our research reaffirms the lower immunogenicity of the Sinovac vaccine.<sup>14–17</sup> These findings carry significant implications for public health decisions regarding booster shots and vaccination strategies, particularly in



**Fig. 3:** Distributions of anti-spike IgG antibody titres (natural log scale) by primary series and booster arm. Visit 1 represents baseline titres, and visit 2 displays the titres among participants whose second visit occurred within 21–60 days after randomization.



Booster assignment	Anosmia N (%)	Chills N (%)	Fatigue N (%)	Fever N (%)	Headache N (%)	Joint N (%)	Muscle N (%)	Nausea N (%)	Pain N (%)	Swelling N (%)	Tenderness N (%)
AZD1222-primed arm											
Astra-Zeneca 1/2 dose	0 (0)	4 (4.4)	15 (16.7)	5 (5.6)	26 (28.9)	1 (1.1)	10 (11.1)	3 (3.3)	34 (37.8)	2 (2.2)	12 (13.3)
Astra-Zeneca full dose	0 (0)	11 (12.2)	14 (15.6)	11 (12.2)	22 (24.4)	5 (5.6)	17 (18.9)	3 (3.3)	38 (42.2)	5 (5.6)	11 (12.2)
Pfizer 1/2 dose	0 (0)	1 (1.1)	10 (11.0)	3 (3.3)	19 (20.9)	0 (0)	8 (8.8)	2 (2.2)	43 (47.2)	3 (3.3)	8 (8.8)
Pfizer 1/3 dose	0 (0)	3 (3.3)	8 (8.9)	3 (3.3)	18 (20.0)	0 (0)	8 (8.9)	4 (4.4)	37 (41.1)	1 (1.1)	7 (7.8)
Pfizer full dose	1 (1.1)	3 (3.3)	6 (6.6)	3 (3.3)	28 (30.8)	0 (0)	10 (11.0)	1 (1.1)	51 (56.0)	5 (5.5)	11 (12.1)
BNT162b2-primed arm											
Astra-Zeneca 1/2 dose	0 (0)	2 (2.2)	6 (6.7)	3 (3.3)	16 (17.8)	1 (1.1)	11 (12.2)	5 (5.6)	27 (30.0)	2 (2.2)	4 (4.4)
Astra-Zeneca full dose	0 (0)	2 (2.2)	9 (9.9)	5 (5.5)	24 (26.4)	2 (2.2)	9 (9.9)	3 (3.3)	31 (34.1)	0 (0)	5 (5.5)
Pfizer 1/2 dose	1 (1.1)	0 (0)	9 (10.0)	4 (4.4)	17 (18.9)	1 (1.1)	10 (11.1)	3 (3.3)	30 (33.3)	0 (0)	3 (3.3)
Pfizer 1/3 dose	1 (1.1)	1 (1.1)	7 (7.9)	1 (1.1)	10 (11.2)	1 (1.1)	11 (12.4)	3 (3.4)	28 (31.5)	0 (0)	5 (5.6)
Pfizer full dose	1 (1.1)	3 (3.4)	11 (12.4)	4 (4.5)	15 (16.8)	2 (2.2)	11 (12.4)	4 (4.5)	45 (50.6)	3 (3.4)	9 (10.1)
Sinovac-primed arm											
Astra-Zeneca 1/2 dose	0 (0)	1 (1.1)	16 (17.8)	6 (6.7)	22 (24.4)	2 (2.2)	15 (16.7)	3 (3.3)	46 (51.1)	8 (8.9)	7 (7.8)
Astra-Zeneca full dose	1 (1.1)	7 (7.7)	23 (25.3)	19 (20.9)	36 (39.6)	2 (2.2)	21 (23.1)	4 (4.4)	46 (50.5)	4 (4.4)	5 (5.5)
Pfizer 1/2 dose	0 (0)	0 (0)	9 (9.9)	1 (1.1)	18 (19.8)	1 (1.1)	9 (9.9)	1 (1.1)	45 (49.4)	1 (1.1)	8 (8.8)
Pfizer 1/3 dose	1 (1.1)	0 (0)	7 (7.7)	4 (4.4)	21 (23.1)	2 (2.2)	10 (11.0)	5 (5.5)	41 (45.0)	1 (1.1)	5 (5.5)
Pfizer full dose	1 (1.1)	4 (4.3)	13 (14.1)	8 (8.7)	23 (25.0)	2 (2.2)	9 (9.8)	3 (3.3)	49 (53.3)	2 (2.2)	6 (6.5)
Sinovac full dose	0 (0)	1 (1.1)	3 (3.3)	0 (0)	9 (10.0)	0 (0)	4 (4.4)	1 (1.1)	24 (26.7)	0 (0)	4 (4.4)

Table 2: Incidence of adverse events in the initial 28 days post-vaccination by vaccine dose and priming group.

regions where the Sinovac vaccine has been extensively deployed.

Our analysis indicates that the use of fractional booster doses of BNT162b2 induced a marked increase in anti-spike binding IgG antibody levels. In contrast, the administration of fractional boosters of AZD1222 and full-dose Sinovac resulted in comparatively lower levels of these antibodies. This highlights the strong immunogenicity of BNT162b2 as a booster vaccine, regardless of the initial vaccination received. Selecting an appropriate booster vaccine can have a significant impact on immune response and antibody production levels.<sup>16–18</sup>

Our findings are consistent with previous studies on fractional booster doses of vaccines against SARS-CoV-2 in individuals previously vaccinated with Sinovac. A study from Thailand demonstrated that using fractional booster doses of AZD1222 resulted in antibody titres against the spike protein that were comparable to full doses at day 14 and day 90.<sup>19</sup> Similarly, a study conducted in Indonesia showed that fractional booster doses of BNT162b2 and AZD1222 elicited immune responses that were non-inferior to full doses while causing less reactogenicity.<sup>20</sup> The boosters of AZD1222 and BNT162b2 showed an increase in immune response, as measured by anti-spike IgG antibody levels, around day 28. Overall, the full dose arms of BNT162b2 had the highest levels of antibodies after vaccination, regardless of the initial priming vaccine.

We observed that all fractional doses performed better than a Sinovac full dose in stimulating T cells

against the spike protein. However, in this small sub-cohort, statistical significance was not consistently observed. All booster doses resulted in increased generation of neutralising antibodies against the Wuhan strain (the strain targeted by the booster doses). Neutralising antibody titres for the Omicron strain did not increase over time across all priming groups, suggesting a lack of immune response induced by study vaccination. There were also no differences between fractional and full dose arms. These findings align with expectations, since the vaccines targeted the original SARS-CoV-2 strain rather than specifically addressing the Omicron variant.

As shown in previous studies,<sup>21–25</sup> all vaccine boosters were found to be safe, with only nine serious AEs reported, all of which were determined to be unlikely or not related to the vaccine. Full and fractional dose vaccines were generally well tolerated. Local and systemic AEs occurred across all the treatment arms in line with expectations. All the local AEs and the vast majority of systemic AEs occurred within the first 28 days after boosting. Pain at the injection site was the most commonly reported adverse event in all treatment arms. Participants who were randomised to the Sinovac doses had the fewest reports of adverse events, followed by the one-third dose of BNT162b2. Despite these differences, all full and fractional doses were observed to be well tolerated and safe.

In this study, high baseline antibody titres were observed in a population with extensive exposure to both vaccination and infection. Brazil experienced

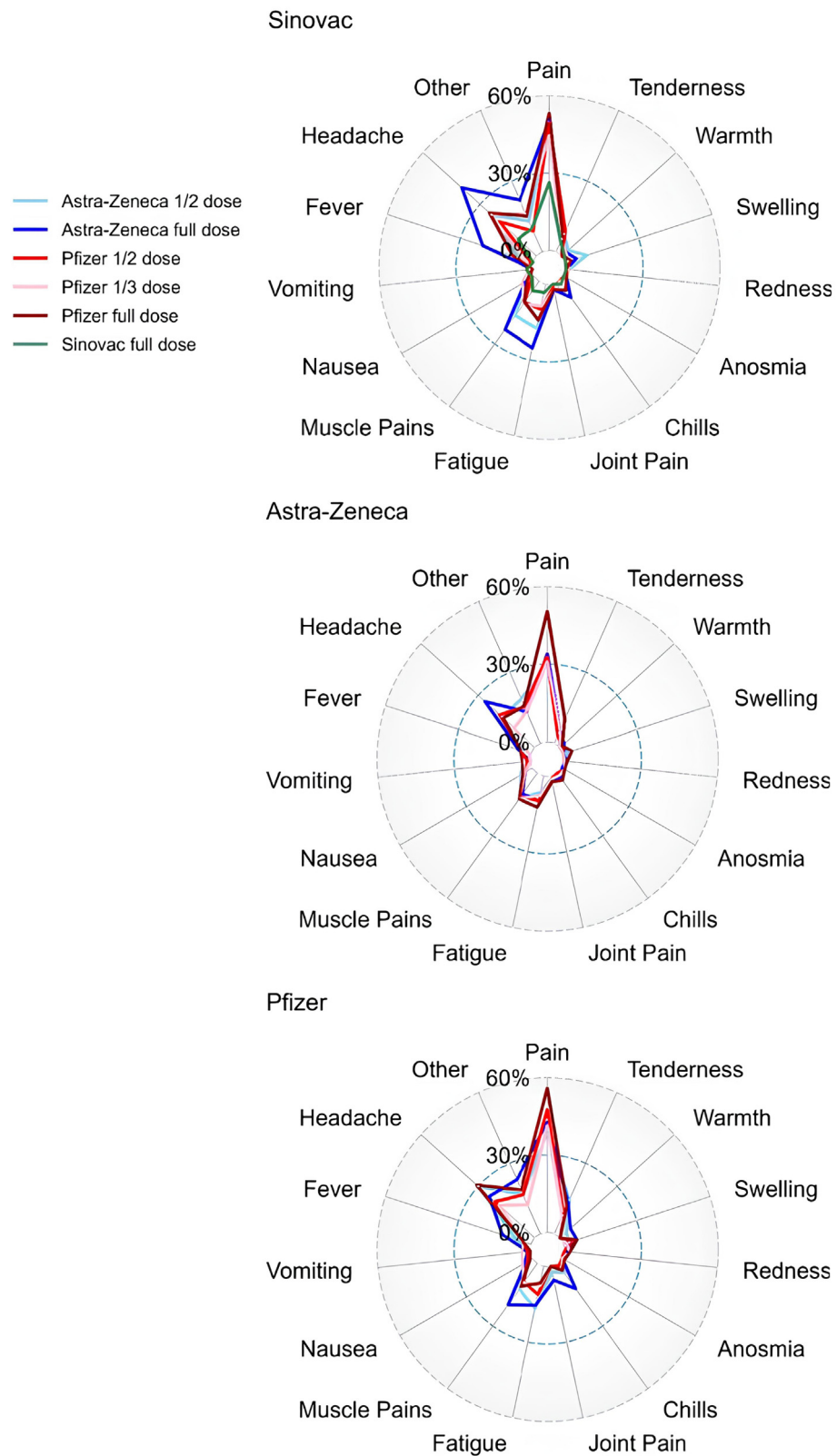


Fig. 4: Incidence of adverse events in the initial 28 days post-vaccination by vaccine dose and priming group.

widespread COVID-19 vaccination coverage along with a significant burden of the disease. Notably, Brazil ranks second in terms of total number of reported deaths attributed to COVID-19.<sup>11</sup> The overall seroresponse rates we observed were lower than expected, at 4.2–78% compared to the anticipated 95%. However, it is important to note that this pattern is consistent with what would be expected from the combined impact of broad vaccination efforts and natural infections on seroresponse rate. The information from this study provides valuable insights for informing future strategies related to booster vaccinations.

This study has some limitations. No data on participant ethnicity were collected, and as such we were unable to assess whether there were any differences in vaccine responses by ethnicity. The study population may have been biased toward healthier individuals, and the limited number of participants who tested positive for SARS-CoV-2 post-vaccination restricts conclusions about differential efficacy between treatment arms.

A high proportion of participants completed the follow-up visit outside the protocol-specified window. In August 2021, prior to study initiation, the government of Brazil began distributing booster doses of COVID-19 vaccines. Consequently, many people residing in the study area had already received additional doses of COVID-19 vaccines on their own. It is important to note that those who remained unboosted (and thus eligible for our study) may have been less inclined to seek healthcare services or to return to the second visit due to being in good health overall. Additionally, there was a decline in locally reported COVID-19 cases after enrolment began, which could have impacted participants' involvement during the follow-up period.

As per the original study design, the primary analysis focused on data from participants completing their second visit within a prespecified time frame of 21–35 days and a post-hoc analysis was conducted to include samples collected during the extended window from 36 to 60 days. This decision was biologically justified, as rapid changes in IgG titre dynamics were not anticipated between days 21 and 35 and 36–60 given that the study population was healthy adults with a history of prior vaccination. The inclusion of this extended window provided a more comprehensive assessment of the immunogenicity of fractional and full booster doses, reflecting the real-world challenges of adhering to strict follow-up schedules, whilst maintaining the integrity of the study findings.

Our data demonstrate that the immunogenicity of fractional booster doses depends on the priming vaccine. Fractional doses of BNT162b2 and AZD1222 produced similar levels of anti-spike antibodies compared to full doses in individuals primed with Sinovac, and AZD1222 fractional doses were non-inferior in the AZD1222 priming arm. However, fractional doses of BNT162b2 were not non-inferior in individuals primed with BNT162b2. We recommend against using Sinovac as a

booster vaccine. For populations primed with Sinovac or AZD1222, fractional doses of BNT162b2 or AZD1222 offer a practical alternative in resource-constrained settings. Conversely, for individuals primed with BNT162b2, a full booster dose of BNT162b2 is recommended for optimal effectiveness and protection.

#### Contributors

MAMP, RDO, and PVS were involved in data collection, data analysis, and manuscript drafting. VC, HH, DL, AZ, and BS were involved in the statistical analysis, and manuscript review. VC, HH, JIR, JCS, ASC, SPL, DG, and JC were involved in the study conception, design and manuscript review. RDO was involved in obtaining ethical and legal authorisations, and manuscript review. FNQ was involved in manuscript review. DG and JC had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. They were involved in the conception of the study and design, data analysis, and manuscript review. All authors confirm that they have had full access to all study data, accepted responsibility for submitting for publication, and read and approved the final manuscript.

#### Data sharing statement

After all data from this platform trial is collected and finalised, de-identified individual patient data used in this analysis and a corresponding data dictionary will be permanently available in the Stanford Digital Repository (<https://purl.stanford.edu/fr354zt8141>). Access to the data will adhere to the regulations and procedures established by the repository system.

#### Declaration of interests

All authors declare no competing interests, except for Blake Shaw, who received travel support from the Sabin Vaccine Institute, Haley Hedlin, whose institution received funding from CEPI/PATH to support her work, and Julio Croda, who received grants or contracts from Valneva/Butantan, CEPI/Sabin Institute, MSD, Takeda, Sanofi Pasteur, and NIH, as well as honoraria for presentations and advisory roles with Pfizer, Takeda, and Moderna/Zodiac.

#### Acknowledgements

We thank the trial participants, the site personnel who recruited participants and assisted with the trial, and the data and safety monitoring board members.

**Funding:** The trial is supported by the Coalition for Epidemic Preparedness Innovations (CEPI)/Sabin Vaccine Institute. Authors who are employees of Sabin Vaccine Institute were involved in the conception and design of the trial and the collection, analysis, and interpretation of data, and some of them were part of the core writing team. The Quantitative Sciences Unit is partially supported by the National Institutes of Health grant UL1 TR003142. The Stanford REDCap platform (<http://redcap.stanford.edu>) is developed and operated by the Stanford Medicine Research IT team. The REDCap platform services at Stanford are subsidised by (a) Stanford School of Medicine Research Office, and (b) the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through grant UL1 TR001085.

#### Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.lana.2025.101031>.

#### References

- 1 WHO. WHO coronavirus (COVID-19) dashboard [cited 2023 Oct 4]. Available from: <https://covid19.who.int>.
- 2 Barouch DH. Covid-19 vaccines - immunity, variants, boosters. *N Engl J Med*. 2022;387(11):1011–1020.
- 3 Watson OJ, Barnsley G, Toor J, Hogan AB, Winskill P, Ghani AC. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. *Lancet Infect Dis*. 2022;22(9):1293–1302.

- 4 WHO. Interim statement on dose-sparing strategies for COVID-19 vaccines (fractionated vaccine doses) [cited 2023 Mar 1]. Available from: [https://www.who.int/news/item/10-08-2021-interim-statement-on-dose-sparing-strategies-for-covid-19-vaccines-\(fractionated-vaccine-doses\)](https://www.who.int/news/item/10-08-2021-interim-statement-on-dose-sparing-strategies-for-covid-19-vaccines-(fractionated-vaccine-doses)).
- 5 Lu P, Zhou T, Santibanez TA, et al. COVID-19 bivalent booster vaccination coverage and intent to receive booster vaccination among adolescents and adults — United States, November–December 2022. *MMWR Morb Mortal Wkly Rep*. 2023;72:190–198. <https://doi.org/10.15585/mmwr.mm7207a5>.
- 6 Croda J, Ranzani OT. Booster doses for inactivated COVID-19 vaccines: if, when, and for whom. *Lancet Infect Dis*. 2022;22(4):430–432.
- 7 ONE Campaign. *ONE Africa COVID-19 Tracker. ONE data @ analysis*; 2023 [cited 2023 Nov 9]. Available from: <https://data.one.org/data-dives/covid-19-response/>.
- 8 Kreier F. Ten billion COVID vaccinations: world hits new milestone. *Nature*. 2022.
- 9 Rydland HT, Friedman J, Stringhini S, Link BG, Eikemo TA. The radically unequal distribution of Covid-19 vaccinations: a predictable yet avoidable symptom of the fundamental causes of inequality. *Humanit Soc Sci Commun*. 2022;9(1):1–6.
- 10 Hunter DJ, Abdool Karim SS, Baden LR, et al. Addressing vaccine inequity — Covid-19 vaccines as a global public good. *N Engl J Med*. 2022;386(12):1176–1179.
- 11 Mathieu E, Ritchie H, Rod  s-Guirao L, et al. *Our world in data*. Coronavirus Pandemic (COVID-19); 2020 [cited 2023 Oct 26]. Available from: <https://ourworldindata.org/covid-deaths>.
- 12 Mambelli F, Marinho FV, Andrade JM, et al. Recombinant Bacillus Calmette–Gu  rin expressing SARS-CoV-2 chimeric protein protects K18-hACE2 mice against viral challenge. *J Immunol*. 2023;210(12):1925–1937.
- 13 R Core Team. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2024. <https://www.R-project.org/>.
- 14 Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med*. 1998;17(8):873–890.
- 15 Agresti A, Caffo B. Simple and effective confidence intervals for proportions and differences of proportions result from adding two successes and two failures. *Am Stat*. 2000;54(4):280–288.
- 16 Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*. 2021;397(10269):99–111.
- 17 Valim V, Martins-Filho OA, Gouvea MDPG, et al. Effectiveness, safety, and immunogenicity of half dose ChAdOx1 nCoV-19 COVID-19 Vaccine: Viana project. *Front Immunol*. 2022;13:966416.
- 18 Chu L, McPhee R, Huang W, et al. A preliminary report of a randomized controlled phase 2 trial of the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine. *Vaccine*. 2021;39(20):2791–2799.
- 19 Nanthapaisal S, Puthanakit T, Jaru-Ampornpan P, et al. A randomized clinical trial of a booster dose with low versus standard dose of AZD1222 in adult after 2 doses of inactivated vaccines. *Vaccine*. 2022;40(18):2551–2560.
- 20 Fadlyana E, Setiabudi D, Kartasasmita CB, et al. Immunogenicity and safety in healthy adults of full dose versus half doses of COVID-19 vaccine (ChAdOx1-S or BNT162b2) or full-dose CoronaVac administered as a booster dose after priming with CoronaVac: a randomised, observer-masked, controlled trial in Indonesia. *Lancet Infect Dis*. 2023;23(5):545–555.
- 21 Menni C, Klaser K, May A, et al. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID symptom study app in the UK: a prospective observational study. *Lancet Infect Dis*. 2021;21(7):939–949.
- 22 Zhang Y, Zeng G, Pan H, 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):181–192.
- 23 Folegatti PM, Ewer KJ, Aley PK, 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*. 2020;396(10249):467–478.
- 24 Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383(27):2603–2615.
- 25 Amaro C, Monteiro C, Duarte AP. COVID-19 vaccines adverse reactions reported to the pharmacovigilance unit of Beira interior in Portugal. *J Clin Med*. 2022;11(19):5591.