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The Platform Trial In COVID-19 priming and BOOsting (PICOBOO): The immunogenicity, reactogenicity, and safety of licensed COVID-19 vaccinations administered as a second booster in BNT162b2 primed individuals aged 18- < 50 and 50- < 70 years old

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SUMMARY

Objectives: PICOBOO is a randomised, adaptive trial evaluating the immunogenicity, reactogenicity, and safety of COVID-19 booster strategies. Here, we present data for second boosters among individuals aged 18- < 50 and 50- < 70 years old primed with BNT162b2 until Day (D) 84.

Methods: Immunocompetent adults who had received two doses of BNT162b2 and any licensed COVID-19 booster at least three months prior were eligible. Participants were randomly allocated to BNT162b2, mRNA-1273 or NVX-CoV2373 1:1:1. The $\log_{10}$ concentration of anti-spike Ig Total was summarised as the geometric mean concentration (GMC). Reactogenicity and safety outcomes were captured.

Results: Between Mar 2022 and Aug 2023, 743 participants were recruited to the trial and had D28 samples available. Of these, 120 and 103 belonged to the 18- < 50 y and 50- < 70 y strata, respectively. The mean adjusted GMCs (95% credible intervals) peaked at D28; these were 41 262 (31 611, 51 105), 45 585 (34 194, 57 441) and 25 281 (20 021, 31 234) U/mL in the 18- < 50 y stratum and 30 753 (25 071, 36 704), 35 132 (27 523, 42 239) and 17 322 (13 983, 20 641) U/mL in the 50- < 70 y stratum following BNT162b2, mRNA-1273 and NVX-CoV2373, respectively. Limited neutralisation against Omicron subvariants was found following

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boosting with all vaccines. There were 4 possibly or probably-related adverse events in the 18- < 50 y stratum and 5 events in the 50- < 70 y stratum, and severe reactogenicity events were < 10% and < 11% in these strata, respectively.

Conclusions: Vaccines targeting Ancestral virus elicited boosted antibody responses to Ancestral virus but minimal neutralising antibody against Omicron variants.

Panel: Research in context

Evidence before this study

We searched PubMed from inception until 29 May 2024, using the search terms "COVID*" AND "VACCIN*" AND "booster OR fourth dose" and restricted this search to randomised controlled trials (RCTs). An open-label phase two RCT conducted at 22 sites in the United States evaluated immune responses to monovalent or bivalent variant mRNA and protein-based vaccines targeting wild-type, Beta (B.1.351), Delta (B.1.617.2), and Omicron BA.1 strains in 18–85 year olds who had received three doses of an mRNA vaccine (94–100%) or two doses of an mRNA vaccine and one dose of Ad26. COV2. S. This study found that vaccines targeting Beta or Omicron BA.1 elicited broadly cross-protective neutralizing antibody responses against SARS-CoV-2 variants (including B.1.351, BA.1 and BA.4–5) and Ancestral virus, regardless of prior SARS-CoV-2 infection history and age. Neutralisation responses were numerically lower following boosting with vaccines targeting Ancestral virus. A phase two RCT (COV-BOOST) evaluated the immune responses to second boosters with mRNA vaccines (BNT162b2 or mRNA-1273) following a first booster (third dose) of BNT162b2, after priming with two doses of AZD1222 or BNT162b2 in individuals aged > 30 years old. This trial found mRNA vaccines were well tolerated and boosted humoral responses to Ancestral SARS-CoV-2 and cellular responses to wild-type, Beta and Delta variants.

Added value of this study

These are the first RCT data reporting the immunogenicity, reactogenicity and safety of second booster (fourth doses) of mRNA and protein subunit COVID-19 vaccines in individuals aged 18- < 70 y primed with two doses of BNT162b2 until D84. Booster doses of BNT162b2, mRNA-1273 and NVX-CoV2373 were well tolerated and boosted humoral immune responses. Higher binding and neutralising antibodies against Ancestral SARS-CoV-2 were observed following boosting with mRNA vaccines compared to NVX-CoV2373 at all time points. Lower neutralising antibody responses were observed against BA.5 and XBB.1.5 Omicron strains compared to Ancestral virus following all vaccines until D84. Humoral immune responses were numerically higher in the 18- < 50 y stratum compared to the 50- < 70 y stratum.

Implication of all the available evidence

BNT162b2, mRNA-1273 and NVX-CoV2373 boosted humoral immune responses among adults primed with two doses of BNT162b2. The clinical relevance of the higher antibody responses following mRNA vaccines is uncertain in the absence of an established correlate of protection for Omicron variants. Limited neutralisation against Omicron variants following vaccination with vaccines targeting Ancestral virus support the need for boosting with vaccines with greater specificity for circulating subvariants.

Introduction

The past four years have seen the rapid development and deployment of Coronavirus 2019 (COVID-19) vaccines, changing epidemiology of COVID-19 disease, viral evolution and the widespread development of infection-induced, vaccine and hybrid immunity. Most countries, including Australia, have now lifted non-pharmacological prevention measures including restrictions on travel.[1] Robust evidence exists that vaccination provides strong protection against severe disease, hospitalisations, and death.[2–4] However, further evidence of the comparative effectiveness and cost-effectiveness are still required to inform whether periodic boosting should be recommended, and if so, in whom and with which vaccines and schedules.

The Platform trial In COVID-19 priming and BOOsting (PICOBOO) was established on 29 Mar 2022 to generate evidence of the immunogenicity, reactogenicity and safety of first and subsequent COVID-19 booster dose strategies against Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and its variants to inform practice and policy. Recruitment commenced in Australia shortly after the national recommendation for second booster doses in select populations and when Omicron BA.2 was the predominant circulating variant; by late 2022, Omicron subvariants BA.4 and BA.5 were dominant.[1] Here we report data on second booster (fourth) doses among the pre-defined strata of individuals aged 18- < 50 and 50- < 70 years old who had been primed with two doses of BNT162b2 vaccine (18- < 50y-BNT162b2 and 50- < 70y-BNT162b2, respectively) until Day 84 (D84).

Methods

Study design

PICOBOO is a parallel group, randomised, Bayesian adaptive platform trial. PICOBOO is currently randomising eligible participants to alternative first or subsequent COVID-19 booster dose strategies; participants are stratified by age group and their primary COVID-19 vaccination schedule. Recruitment is occurring in Perth, Adelaide, and Launceston (Australia).

The PICOBOO protocol is modular and hierarchical, including the Core Protocol,[5] the Booster Vaccination Substudy Protocol, and the Statistical Appendix.[6] The master protocol structure aims to ensure efficiency and standardised study procedures, data collection and endpoints for all substudies nested within the trial platform.

PICOBOO is registered with Australia's Therapeutic Goods Administration (CTN-00603–1) and the Australian and New Zealand Clinical Trials Registry (ACTRN12622000238774). This trial is approved by the Child and Adolescent Health Service Human Research Ethics Committee (RGS5222). Approval for use of the vaccines evaluated in this trial was provided by the vaccine manufacturers and the Commonwealth Government of Australia.

Participants

The PICOBOO platform includes Australians who have previously received primary vaccination against COVID-19. Participants are grouped into pre-defined strata according to the primary COVID-19 vaccine schedule received and age group. The full eligibility and stratification criteria for the platform are reported elsewhere.[5] The pre-specified 18- < 50y-BNT162b2 and 50- < 70y-BNT162b2 stratum includes individuals within the specified age bracket who had received two primary doses of BNT162b2 followed by a single dose of

any licensed first booster vaccine dose at least three months prior to randomisation. Immunocompromised individuals and those with an established contraindication to any study vaccine (e.g., history of anaphylaxis or myocarditis attributable to prior receipt of COVID-19 vaccine) were excluded.

Recruitment strategies are detailed in the PICOBOO core protocol.[5] Screening for eligibility was performed via an online questionnaire or telephone interview. At the baseline visit (D0), after discussing the study and confirming eligibility, online or written informed consent was obtained from all participants.

Recruitment to PICOBOO commenced on the 29 Mar 2022 and is ongoing. 18- < 50y-BNT162b2 and 50- < 70y-BNT162b2 strata participants were recruited between the 12 May 2022 and 13 Dec 2022. The data cut-off date for D28 sample results was 2 Aug 2023. The safety data cut-off date was 23 January 2024.

Randomisation and masking

Allocation to a single COVID-19 booster vaccine dose was centrally determined, irrespective of study site, using computer-generated random sequences prepared by an unblinded trial statistician. Equal assignment probabilities were used for all study vaccines and randomisation was stratified by stratum and booster dose number. Randomisation was performed by an unblinded research nurse using REDcap Version 14.3.11.[7] Further detail regarding randomisation, blinding and concealment is supplied in the PICOBOO core protocol.[5] Participants were blinded to their assignment until at least six weeks after randomisation, at which time the vaccination information was uploaded to the Australian Immunisation Register and accessible to participants. The trial statistician preparing interim analyses and members of the Data Safety Monitoring Committee were unblinded. All study staff became unblinded to the results of the first interim analysis following its release on 22 May 2023.

Procedures

PICOBOO is designed to evaluate up to three COVID-19 booster vaccines at any given time, including a maximum of one vaccine subtype from each vaccine manufacturer. During the reported study period, seven vaccines were evaluated in the platform. These included BNT162b2, mRNA-1273, NVX-CoV2373 initially and subsequently tozinameran/riltozinameran (Comirnaty Original/Omicron BA.1), elasomeran/imelasomeran (SPIKEVAX Bivalent Original/Omicron BA.1), tozinameran/famtozinameran (Comirnaty Original/Omicron BA.4–5) and elasomeran/davesomeran (SPIKEVAX Bivalent Original/Omicron BA.4–5). Three vaccines were evaluated as second boosters in the 18- < 50y-BNT162b2 and 50- < 70y-BNT162b2 primed strata, all derived from the Ancestral strain: (i) BNT162b2, a messenger ribonucleic acid (mRNA) vaccine, encoding the full-length SARS-CoV-2 spike protein administered as 30 μg (0·3 mL) intramuscularly; (ii) mRNA-1273, another mRNA vaccine, also encoding the full length SARS-CoV-2 spike protein, administered as 50 μg (0·25 mL) intramuscularly and (iii) NVX-CoV2373, a nanoparticle vaccine constructed from the full-length Ancestral strain pre-fusion trimers of the SARS-CoV2 spike glycoprotein, administered as 5 μg (0·5 mL) intramuscularly.

On the day of enrolment, participants were randomised to receive a single dose of one of the three study vaccines administered by a trained, unblinded study nurse per Australian guidelines; participants were observed for at least 15 min afterwards. Participants were also given an oral thermometer, tape measure, and a diary card to be used as a memory aid to record solicited and unsolicited adverse events (AEs). Participants were encouraged to present for polymerase chain reaction (PCR) testing in the context of symptoms concerning for active SARS-CoV-2 infection during follow-up. Rapid antigen test (RAT) kits were supplied to participants to expedite self-testing; those with a positive RAT were requested to confirm with a PCR test.

Study visits were scheduled on day 0 (D0), day 6–8 (D7), day 21–31 (D28) and day 70–98 (D84) post-randomisation. Bloods were collected prior to randomisation and at all subsequent study visits. Saliva samples were collected at all study visits except D7.

Electronic surveys were sent to participants on days 1 to 7 following randomisation, on D28 and three-monthly throughout study follow-up to capture patient-reported outcome (PRO) data.

Outcomes

All immunological analyses were performed on participants without evidence of intercurrent SARS-CoV-2 infection between D0 and D28 (or between D0 and D7 for D7 outcomes).[6] The $\log_{10}$ SARS-CoV-2 anti-spike immunoglobulin Total (Ig Total) was measured using the ROCHE platform. Ancestral SARS-CoV-2 anti-spike Ig Total was summarised for each study arm at each time point (D0, D7, D28, D84) as a geometric mean concentration (GMC; U/mL) with 95% credible intervals provided (95% CrI).

The concentration of anti-spike IgG (measured by Meso Scale Discovery [MSD] assay in AU/mL) against Ancestral SARS-CoV-2 and Omicron subvariants BA.5 and XBB.1.5 (D0, D28 and D84) was tested on all participant samples at D0, D28 and D84. Additional assays were performed on a dedicated immunological subset comprising the first 20 participants per vaccine intervention, for each booster dose number and stratum with D28 samples. The additional tests included the dilution of serum that neutralises 50% (normal neutralisation or NF_{50}) of Ancestral SARS-CoV-2 virus and Omicron XBB.1.5 at D0, D28 and D84 (measured by microneutralisation assay measured in IU/mL) and the percentage inhibition of virus measured by GenScript Surrogate Virus Neutralisation test (50- < 70y-BNT162b2 stratum only against Ancestral SARS-CoV-2 and Omicron BA.5).

Prior COVID-19 infections captured at baseline were based on self-reported infections and/or positive anti-nucleocapsid protein antibody status (anti-NCP).[6] Solicited reactogenicity events were captured on D1–7 following randomisation to the vaccine intervention. Adverse events (AEs) causally related to study vaccination were reported until D28. Sudden unexpected serious adverse events (SUSARs) and Adverse Events of Special Interest are detailed in the Core Protocol[5] and were collected throughout the duration of the study. Serious adverse reactions (SARs) were defined as causally related adverse events that resulted in death, were life-threatening, required unplanned hospitalisation or prolongation of existing hospitalisation or resulted in persistent or significant disability or incapacity and were reported throughout the duration of the study. Additional patient reported outcome (PRO) data capturing intercurrent SARS-CoV-2 infections and associated time off school, work or usual activities and unplanned hospitalisations were collected at D28 and 3-monthly throughout the study.[5]

Statistical analysis

Statistical analyses were pre-specified using the estimands framework[8] and are detailed in the Statistical Appendix[6] and supplementary materials. Unadjusted summary statistics are presented as median (interquartile range [IQR]) for continuous variables and frequency (percentage) for categorical variables.

A single Bayesian three-level hierarchical linear model was used to model all the available data (including data from participants belonging to strata not reported here) as it was anticipated that immune responses to each study vaccine were likely to be, in part, mutually informative across COVID-19 booster dose number, age groups, and across the mRNA vaccines.[6] The model estimated the posterior distribution of the mean outcome for each study vaccine in

each stratum and for each booster dose number, conditional on a set of predefined covariates including sex, outcome at baseline, previous COVID-19 infection, and time epoch. All posterior distributions presented have been marginalised (averaged) over time epoch and therefore can be interpreted as representing the mean during the respective period of recruitment.

A maximum sample size of 50 participants per study vaccine per stratum and booster dose number was targeted, allowing for up to 5% attrition from loss to follow-up or intercurrent COVID-19 infection before D28. This was based on simulations used to estimate the probability of achieving desirable precision on the D28 anti-spike Ig Total GMC estimates as described in the Statistical Appendix.[6] AEs were coded and reported according to the Medical Dictionary for Regulatory Activities (MEDRA). For further detail regarding the statistical methods, including the pre-trial simulations, please refer to the Statistical Appendix.[6] All statistical analyses were performed using STAN,[9] via the R package cmdstanr[10] in R,[11] version 4.2.2.

Role of the funding source

Funders who supported this trial had no role in the study design, data collection, analysis, interpretation or writing of this manuscript.

Results

There were 743 participants recruited to the PICOBOO platform during the reported study period (*S1*). Of these, 120 and 103 participants belonging to the 18- < 50y-BNT162b2 and 50- < 70y-BNT162b2 strata, respectively, were randomised to receive a second booster vaccine dose (Fig. 1). The median (IQR) age of participants in these strata was 31·1 (24·4, 41·5) years and 55·7 (53·0, 59·9) years, respectively. There were 91 females (76%) and 27 males (22%), and 85 females (83%) and 18 males (17%), in each stratum, respectively. Baseline characteristics for participants are presented in Table 1. Overall, 74 of the 120 participants in the 18- < 50-BNT162b2 stratum (62%) and 27 out of 103 participants in the 50- < 70-BNT162b2 stratum (26%) had a history of prior COVID-19 infection at baseline; these data are broken down by site in *S2*. The immunological subset comprised 60 participants per stratum; the baseline characteristics for these participants are presented in *S3*.

Raw anti-spike Ig Total concentrations against Ancestral SARS-CoV-2 at D0, D7, D28 and D84 are presented in *S4*. The posterior distributions of the GMCs of Ancestral anti-spike Ig Total at D7, D28 and D84 are presented in Fig. 2 and additional modelled data are provided in *S5*. At the time of the second scheduled analysis (Nov 8 2023), the D28 estimates each met the pre-specified precision criteria for the stopping criterion (0·16 for BNT162b2 and mRNA-1273 and 0·18 for NVX-CoV2373 for 18- < 50y-BNT162b2; 0·17 for BNT162b2 and 0·18 for mRNA-1273 and NVX-CoV2373 for 50- < 70y-BNT162b2).

Raw data regarding neutralisation are presented in *S6* and posterior distributions for neutralisation against Ancestral SARS-CoV-2 are presented in Table 2 and *S7*. The posterior mean of the adjusted geometric mean NF_{50} for Ancestral SARS-CoV-2 at D28 was 389, 482 and 259 IU/mL for the 18- < 50y-BNT162b2 stratum and 262, 288 and 130 IU/mL for the 50- < 70y-BNT162b2 stratum following receipt of BNT162b2, mRNA-1273 and NVX-CoV2373, respectively. At D84, these values were 325, 272 and 253 IU/mL for the 18- < 50y-BNT162b2 stratum, respectively, and 202, 241 and 102 IU/mL for the 50- < 70y-BNT162b2 stratum, respectively. The neutralisation activity detected against Omicron XBB.1.5 at D28 or D84 following any study vaccine dose was minimal. The proportion of participants with neutralisation activity below the lower limit of detection at D28 for Omicron XBB.1.5 was 42% (8/19), 25% (5/20) and 74% (14/19), respectively, for the 18- < 50y-BNT162b2 stratum and 76% (13/17), 72% (13/18) and 88% (15/17), respectively, for the 50- < 70y-BNT162b2 stratum. At D84, these values were 50% (10/20), 33% (6/18) and 67% (12/18), respectively, for the 18- < 50y-BNT162b2 stratum and 69% (11/16), 71% (12/17) and 88% (15/17), respectively, for the 50- < 70y-BNT162b2 stratum.

Surrogate neutralisation (percentage inhibition) testing against Ancestral SARS-CoV-2 was similar across all study arms at D28, with

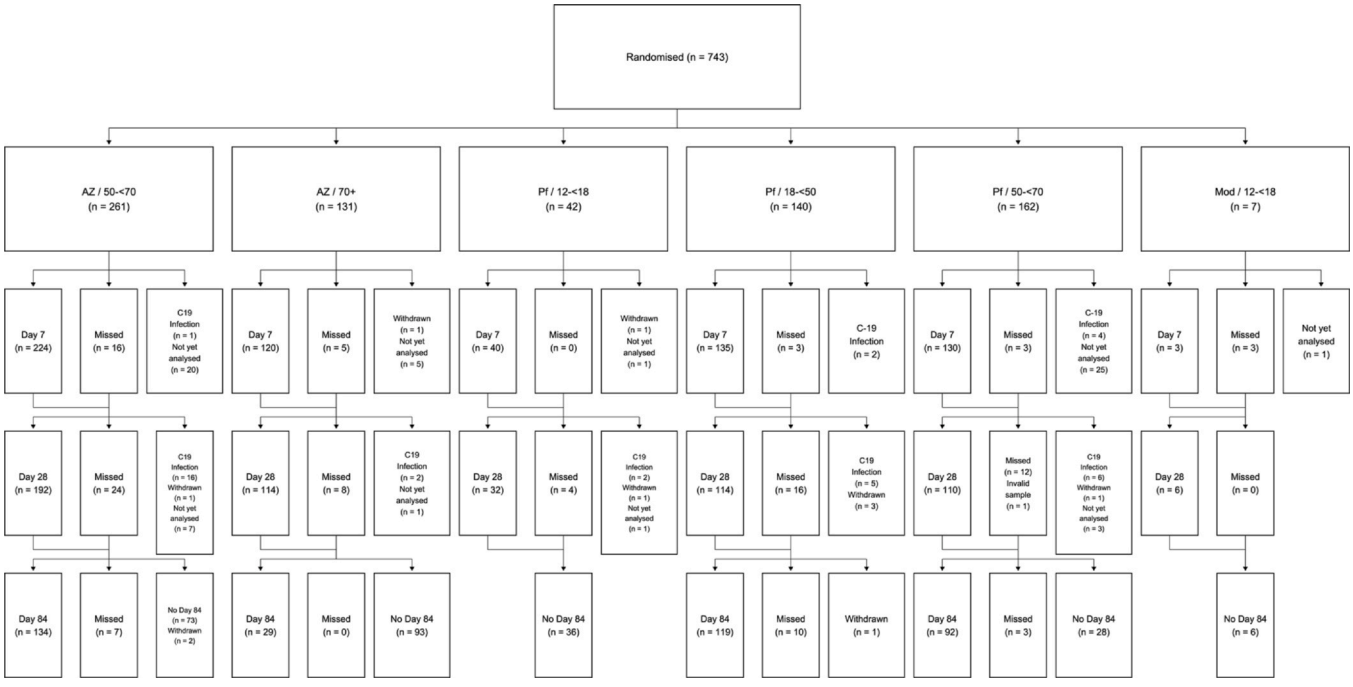

Fig. 1. CONSORT diagram for participants recruited to the 18- < 50y-BNT162b2 (A) and 50- < 70y-BNT162b2 (B) strata for second booster vaccines. Participants were excluded from subsequent analyses if they became infected with COVID-19 (C19 Infection) or had withdrawn. Participants that missed visits (Missed) were eligible to be included in subsequent analyses.

Table 1
Baseline characteristics for study participants recruited to the 18- < 50y-BNT162b2 and 50- < 70 y BNT162b2 strata for second booster vaccines summarised according to study arm.

	18- < 50y-BNT162b2			50- < 70y-BNT162b2		
	BNT162b2 (N = 39)	mRNA-1273 (N = 42)	NVX-CoV2373 (N = 39)	BNT162b2 (N = 35)	mRNA-1273 (N = 33)	NVX-CoV2373 (N = 35)
Age (years)[a]	27·5 (23·6, 40·0)	34·4 (25·5, 41·7)	33·9 (25·4, 41·4)	56·2 (53·5, 59·5)	54·4 (52·8, 58·8)	56·2 (52·8, 60·2)
Sex[b]						
Male	9 (23%)	5 (12%)	13 (33%)	5 (14%)	9 (27%)	4 (11%)
Female	30 (77%)	26 (86%)	25 (64%)	30 (85%)	24 (73%)	31 (89%)
Other	0 (0%)	1 (2%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Ethnicity[b]						
Indigenous Australian	2 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
European Caucasian	34 (87%)	39 (93%)	34 (87%)	34 (97%)	33 (100%)	33 (94%)
Asian	1 (3%)	1 (2%)	4 (10%)	1 (3%)	0 (0%)	1 (3%)
Indian Subcontinent	1 (3%)	2 (5%)	1 (3%)	0 (0%)	0 (0%)	1 (3%)
South American	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Comorbidity[b]						
Any	17 (44%)	17 (40%)	16 (41%)	18 (51%)	16 (48%)	19 (54%)
Allergy	7 (18%)	4 (10%)	2 (5%)	8 (23%)	2 (6%)	6 (17%)
Diabetes	0 (0%)	0 (0%)	0 (0%)	1 (3%)	3 (9%)	1 (3%)
Hypertension	0 (0%)	2 (5%)	1 (3%)	7 (20%)	7 (21%)	7 (20%)
Cardiovascular disorder	1 (3%)	0 (0%)	0 (0%)	5 (14%)	1 (3%)	2 (6%)
Respiratory disease	5 (13%)	6 (14%)	5 (13%)	6 (17%)	2 (6%)	3 (9%)
Blood disorder	1 (3%)	1 (3%)	2 (5%)	2 (6%)	4 (12%)	4 (11%)
Neurological condition	2 (5%)	3 (7%)	0 (0%)	1 (3%)	1 (3%)	0 (0%)
Liver disease	0 (0%)	0 (0%)	0 (0%)	2 (6%)	3 (9%)	0 (0%)
Previous COVID-19 vaccine received[b]						
BNT162b2	35 (90%)	30 (71%)	32 (82%)	26 (74%)	19 (58%)	24 (69%)
mRNA-1273	4 (10%)	12 (29%)	7 (18%)	9 (26%)	14 (42%)	11 (31%)
Days since previous COVID-19 vaccine[a]	277 (225, 309)	275 (224, 307)	268 (244, 301)	196 (174, 236)	196 (182, 233)	218 (196, 258)
Previous COVID-19 infection[b]						
Any	23 (59%)	27 (64%)	24 (62%)	6 (17%)	10 (30%)	11 (31%)
Anti-NCP	23 (59%)	27 (64%)	24 (62%)	5 (14%)	9 (27%)	11 (31%)
Self-reported	20 (51%)	27 (64%)	24 (62%)	4 (11%)	10 (30%)	9 (26%)
Days since previous COVID-19 infection[1,c]	109 (86, 160)	126 (107, 173)	185 (139, 229)	92 (54, 114)	126 (98, 150)	102 (89, 124)
Ancestral anti-spike Ig (U/mL)[a]	13 277 (6 750, 32 439)	13 261 (5 342, 28 666)	9 192 (5 958, 23 783)	8 282 (2 135, 14 109)	9 382 (3 427, 18 848)	4 831 (2 872, 12 333)
Ancestral anti-spike IgG MSD (AU/mL)[a]	252 078 (114 202, 540 776)	270 682 (85 117, 396 277)	232 031 (118 687, 436 871)	114 610 (58 900, 229 502)	161 057 (70 180, 282 583)	86 133 (57 479, 345 182)
Omicron BA.5 anti-spike IgG MSD (AU/mL)[a]	76 768 (33 979, 159 248)	67 569 (22 044, 153 202)	73 432 (25 794, 111 534)	36 469 (15 042, 64 200)	47 283 (19 640, 78 691)	24 163 (15 765, 72 215)
Omicron XBB.1.5 anti-spike IgG MSD (AU/mL)[a]	31 054 (19 875, 73 226)	33 081 (13 354, 64 574)	36 850 (15 648, 65 517)	19 456 (10 121, 36 879)	29 929 (14 067, 44 005)	13 945 (8 817, 33 210)

[a] Median (interquartile range).
[b] Frequency (percentage).
[c] Days since previous COVID-19 infection is summarised only for participants with a self-reported previous COVID-19 infection.

sustained responses observed until D84. At all timepoints, surrogate neutralisation against Omicron BA.5 was minimal compared to Ancestral SARS-CoV-2 (*S9*).

The posterior distributions of the adjusted GMC of anti-spike IgG (by MSD assay) against Ancestral SARS-CoV-2 and Omicron subvariants BA.5 and XBB.1.5 (D28 and D84) at D28 and D84 are presented in Fig. 3 and were lower at all timepoints for the Omicron subvariants BA.5 and XBB.1.5 after all vaccines. The raw MSD data is presented in *S10,* and unadjusted fold-changes are presented in *S11–12*.

Reactogenicity and safety data are detailed in Table 3 with injection site pain, fatigue and myalgias the most common symptoms reported following booster vaccination and were generally higher after mRNA vaccines that the NVX-CoV2373. Severe reactogenicity events were uncommon across all study participants (< 10% in the 18- < 50y-BNT162b2 stratum and < 11% in the 50- < 70y-BNT162b2 stratum, respectively). There was only one local severe reaction elicited in the 50- < 70y-BNT162b2 stratum (pain at the injection site, mRNA-1273). Fever was reported in < 5% across all study vaccines across both strata. Severe systemic reactions in the 50- < 70y-BNT162b2 stratum included fatigue (BNT162b2 n = 3, mRNA-1273 n = 1), headache (BNT162b2 n = 1, mRNA-1273 n = 1, NVX-CoV2373 n = 1), arthralgia (mRNA-1273 n = 1), myalgias (NVX-CoV2373 n = 1) and chills (NVX-CoV2373 n = 1). Severe systemic reactions in the 18- < 50y-BNT162b2 stratum included fatigue (mRNA-1273 n = 4), chills (BNT162b2 n = 2, mRNA-1273 n = 2), headache (BNT162b2 n = 1, mRNA-1273 n = 1, NVX-CoV2373 n = 1), arthralgia (BNT162b2 n = 1), myalgias (mRNA-1273 n = 1) and nausea/vomiting (mRNA-1273 n = 1).

There were four possibly related AEs in previously healthy individuals from the 50- < 70y-BNT162b2 stratum. These included alopecia (mRNA-1273), chilblains (BNT162b2), and two episodes of paraesthesia (mRNA-1273 and NVX-CoV2373) in separate participants. In the 18- < 50y-BNT162b2 stratum, there were five events thought to be probably related to mRNA-1273 vaccination; these included episodes of unilateral lymphadenopathy, migraine, and chest tightness in individuals (< 24 h after vaccination) in individuals with a history of asthma, and an episode of abdominal cramping and chest tightness (< 24 h after vaccination) in previously healthy individuals. Neither participant with chest pain sought medical review. PRO data including COVID-19 infections after randomisation are presented in Table 4. There were no hospitalisations due to COVID-19. There were two hospitalisations unrelated to study vaccine: an admission for presyncope and another for constipation.

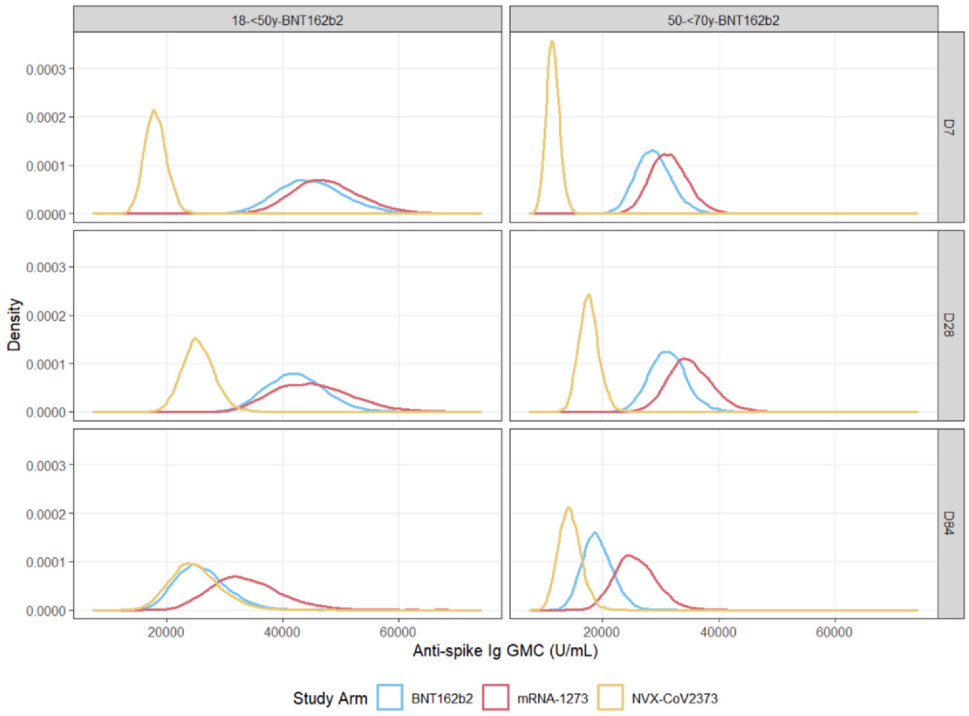

Fig. 2. Posterior distributions of the anti-spike Ig Total adjusted GMC against Ancestral SARS-CoV-2 at D7, D28 and D84 for each study arm in participants recruited to the 18- < 50y-BNT162b2 and 50- < 70y-BNT162b2 strata for second booster vaccines without COVID-19 infection after randomisation and before D28 (D7 for D7 distributions).

Table 2
Posterior distributions of the adjusted geometric mean NF_{50} of Ancestral SARS-CoV-2 at D28 and D84 for each study arm in participants recruited to the 18- < 50y-BNT162b2 and 50- < 70y-BNT162b2 strata for second booster vaccines without COVID-19 infection after randomisation and before D28 in the immunological subset.

	Timepoint	Study Arm	N	Mean (SD)	95% HDI	Mean GMC	GMC 95% HDI
18- < 50y-BNT162b2	D28	BNT162b2	19	2·58 (0·10)	(2·37, 2·78)	389	(217, 574)
		mRNA-1273	20	2·67 (0·10)	(2·47, 2·87)	482	(274, 718)
		NVX-CoV2373	19	2·40 (0·10)	(2·20, 2·59)	259	(156, 388)
	D84	BNT162b2	20	2·49 (0·13)	(2·23, 2·75)	325	(153, 535)
		mRNA-1273	18	2·41 (0·13)	(2·15, 2·67)	272	(124, 437)
		NVX-CoV2373	17	2·38 (0·13)	(2·11, 2·63)	253	(119, 414)
50- < 70y-BNT162b2	D28	BNT162b2	17	2·41 (0·08)	(2·26, 2·57)	262	(179, 361)
		mRNA-1273	18	2·45 (0·08)	(2·30, 2·60)	288	(197, 394)
		NVX-CoV2373	16	2·11 (0·08)	(1·95, 2·26)	130	(88, 181)
	D84	BNT162b2	16	2·30 (0·09)	(2·10, 2·47)	202	(125, 294)
		mRNA-1273	17	2·37 (0·09)	(2·20, 2·56)	241	(146, 345)
		NVX-CoV2373	17	2·00 (0·10)	(1·81, 2·18)	102	(62, 147)

SD: standard deviation HDI: highest density interval. GMC: geometric mean concentration.

Discussion

These data build on evidence previously reported from the open-label phase two COVAIL[12] and phase two RCT COV-BOOST trials.[13] Specifically, we present the first RCT data of the immunogenicity, reactogenicity, and safety of mRNA and protein subunit COVID-19 vaccines delivered as a second booster (fourth dose) in immunocompetent adults aged 18- < 50 and 50- < 70 years old primed with two doses of BNT162b2, until D84 post-booster.

A higher proportion of participants belonging to the 18- < 50 y age cohort had evidence of prior SARS-CoV-2 infection at baseline (59% for the BNT162b2 group, 64% for the mRNA-1273 group and 62% for the NVX-CoV2373 group) compared to the 50- < 70 y stratum (17%, 30% and 31%, respectively). Correspondingly, higher concentrations of baseline anti-spike Ig were found in the 18- < 50 y cohort compared to the 50- < 70 y group. The reasons for this are likely related to different public health prevention behaviours employed by these different age groups due to the higher risk of severe disease and death in older age cohorts.

There are several important findings from this study. Vaccines targeting Ancestral virus elicited boosted antibody responses to SARS-CoV-2, with higher numerical values observed in younger (18- < 50 y) compared to older (50- < 70 y) cohorts primed with two doses of BNT162b2. This is likely due to the increased prior SARS-CoV-2 infections in the younger age group due to less adherence to public health preventive measures resulting in better immune priming and may also be explained, at least in part, by immunosenescence, which is an established phenomenon resulting in lower vaccine antibody responses observed in older populations.[14] Higher antibody levels were found following receipt of mRNA vaccines (BNT162b2 and mRNA-1273) compared to the protein subunit vaccine (NVX-CoV2373) across both strata at all time points. Total Ig GMCs peaked at D7 following mRNA vaccines, whereas responses following receipt of NVX-CoV2373 peaked at day 28. Antibodies declined with more rapid decline after the BNT162b2 vaccine, falling by 36% and 38% from D28 to D84 in the younger and older adults respectively (Table S5, Fig. 2). The decline was less marked after mRNA-1273 (14% and 26% respectively) and NVX-CoV273 (3% decline

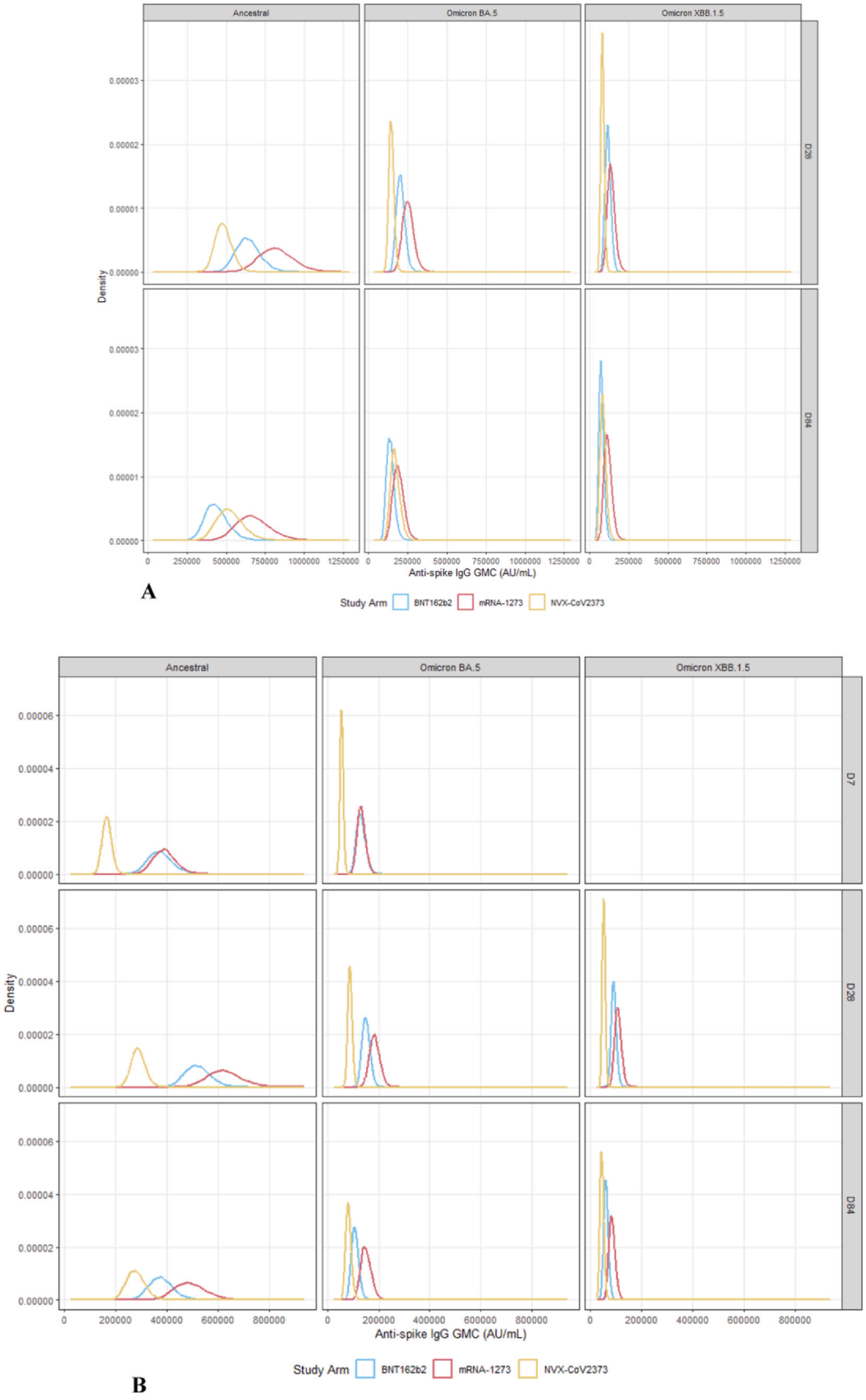

Fig. 3. Posterior distributions of the anti-spike IgG GMC (by MSD assay) against Ancestral SARS-CoV-2 and Omicron subvariants BA.5 and Omicron XBB.1.5 (D28 and D84) at D7, D28 and D84 for each study arm in participants recruited to the 18- < 50y-BNT162b2 (D28 and D84) (A) and 50- < 70y-BNT162b2 (B) strata for second booster vaccines without COVID-19 infection after randomisation and before D28 (or prior to D7 for D7 distributions).

Table 3
Reactogenicity events D1–7 by study arm for participants recruited to the 18- < 50y-BNT162b2 and 50- < 70y-BNT162b2 strata for second booster vaccines.

	18- < 50y-BNT162b2[1]	18- < 50y-BNT162b2[1]	18- < 50y-BNT162b2[1]	50- < 70y-BNT162b2[1]	50- < 70y-BNT162b2[1]	50- < 70y-BNT162b2[1]
	BNT162b2 (N = 39)	mRNA-1273 (N = 42)	NVX-CoV2373 (N = 39)	BNT162b2 (N = 35)	mRNA-1273 (N = 33)	NVX-CoV2373 (N = 35)
Pain at the injection site	39 (100%)	41 (98%)	21 (54%)	30 (86%)	31 (94%)	20 (57%)
Redness at the injection site exceeding 2.5 cm	3 (8%)	4 (10%)	0 (0%)	1 (3%)	4 (12%)	4 (11%)
Swelling or induration at the injection site exceeding 2.5 cm	3 (8%)	7 (17%)	1 (3%)	6 (17%)	8 (24%)	1 (3%)
Fever	2 (5%)	1 (2%)	0 (0%)	1 (3%)	2 (6%)	0 (0%)
Headaches	30 (77%)	30 (71%)	19 (49%)	26 (74%)	19 (58%)	16 (46%)
Fatigue (tiredness)	36 (92%)	33 (79%)	25 (64%)	28 (80%)	22 (67%)	17 (49%)
Chills (shivering)	10 (26%)	15 (36%)	0 (0%)	9 (26%)	11 (33%)	5 (14%)
Widespread muscle pain	28 (72%)	26 (62%)	7 (18%)	15 (43%)	18 (55%)	6 (17%)
Joint pain (not at the injection site)	17 (44%)	11 (26%)	0 (0%)	10 (29%)	12 (36%)	4 (11%)
Nausea/vomiting	10 (26%)	17 (40%)	2 (5%)	3 (9%)	6 (18%)	4 (11%)
Diarrhoea	5 (13%)	8 (19%)	2 (5%)	3 (9%)	3 (9%)	8 (23%)
Chest pain	3 (8%)	4 (10%)	0 (0%)	0 (0%)	1 (3%)	1 (3%)

Table 4
PRO data including cumulative intercurrent COVID-19 infections and time off usual activities owing to infection by study arm for participants recruited to the 18- < 50y-BNT162b2 and *50- < 70y-BNT162b2 strata for second booster vaccines*.

	18- < 50y-BNT162b2			50- < 70y-BNT162b2		
	BNT162b2 (N = 39)	mRNA-1273 (N = 42)	NVX-CoV2373 (N = 39)	BNT162b2 (N = 35)	mRNA-1273 (N = 33)	NVX-CoV2373 (N = 35)
Intercurrent COVID-19 infection within 7 days						
Any[a]	0 (0%)	1 (2%)	0 (0%)	1 (3%)	1 (3%)	1 (3%)
PCR[a]	..	0 (0%)	..	0 (0%)	1 (3%)	0 (0%)
RAT[a]	..	1 (2%)	..	1 (3%)	1 (3%)	1 (3%)
Anti-NCP[a]	..	1 (2%)	..	1 (3%)	0 (0%)	1 (3%)
Days off work[b,c]	..	1 (1, 1)	..	..	7 (7, 7)	3 (3, 3)
Intercurrent COVID-19 infection within 28 days						
Any[a]	0 (0%)	1 (2%)	2 (5%)	4 (11%)	3 (9%)	2 (6%)
PCR[a]	..	0 (0%)	1 (3%)	1 (3%)	1 (3%)	1 (3%)
RAT[a]	..	1 (2%)	2 (5%)	4 (11%)	3 (9%)	1 (3%)
Anti-NCP[a]	..	1 (2%)	2 (5%)	3 (9%)	2 (6%)	2 (6%)
Days off work[b,c]	..	1 (1, 1)	6 (5, 6)	6 (3, 7)	0 (0, 4)	5 (4, 6)
Intercurrent COVID-19 infection within 84 days						
Any	2 (5%)	6 (14%)	8 (21%)	6 (17%)	9 (27%)	5 (14%)
PCR[a]	0 (0%)	3 (7%)	3 (8%)	2 (6%)	2 (6%)	1 (3%)
RAT[a]	2 (5%)	5 (12%)	8 (21%)	6 (17%)	7 (21%)	4 (11%)
Anti-NCP[a]	0 (0%)	4 (10%)	6 (15%)	4 (11%)	6 (18%)	5 (14%)
Days off work[b,c]	5 (5, 5)	6 (3, 7)	7 (4, 8)	6 (3, 7)	3 (0, 7)	4 (4, 7)

[a] Frequency (percentage).
[b] Median (interquartile range).
[c] Days off work is summarised only for participants with a self-reported COVID-19 infection.

in younger adults and 17% in older adults). As a result, despite a much higher initial response to BNT162b2 booster in younger adults, the Total Ig levels were similar to NVX-CoV2373 by D84. The modelled data presented here adjust for baseline Total anti-spike Ig and history of prior SARS-CoV-2 infection, and both the raw and modelled data replicate similar patterns of treatment effect across the study interventions. In the absence of an established correlate of protection from disease against currently circulating SARS-CoV-2 variants, the clinical significance of these data are unclear. The antibody responses following a BNT162b2 booster reported in our study are not directly comparable to the COV-BOOST data. COV-BOOST data are reported across a broader age cohort with a higher median age (> 70 y), and the primary endpoint in the COV-BOOST trial captured IgG rather than Ig Total, measured at D14 rather than D28. The primary analysis for COV-BOOST was also restricted to SARS-CoV-2 seronegative patients (modified intention-to-treat population).[13]

While all vaccine interventions boosted neutralisation activity against Ancestral SARS-CoV-2, the observed neutralisation activity against Omicron subvariants BA.5 and XBB.1.5 was minimal prior to and after their second booster. Neutralisation activity against Ancestral virus was greatest at D28 compared to D84, and higher in the 18- < 50 y stratum compared to 50- < 70 y stratum. Neutralisation activity against Ancestral virus observed for participants in the 18- < 50y-BNT162b2 and 50- < 70y-BNT162b2 strata was greater than that observed in the 50- < 70 y age cohort primed with two doses of AZD1222 enrolled in the same study; these data are reported elsewhere.[15]

Further data are required to advance our understanding of the relationship between the immune responses after vaccination and protection against SARS-CoV-2 infection and disease. While data suggest SARS-CoV-2 binding and neutralising antibody concentrations correlate with protection against symptomatic infection for early derived SARS-CoV-2 variants, it is unclear how these correlates apply for newer, antigenically distinct variants such as Omicron XBB.1.5, JN.1 and KP2 and KP3. In our study, the level of neutralising antibodies against the Omicron XBB.1.5 variant were not boosted by a fourth dose of the ancestral derived monovalent vaccines. There

was a 3 to 6-fold reduction in binding IgG titres against Omicron subvariants BA.5 and XBB.1.5 spike protein at D28 compared to the ancestral spike in the MSD assay. We found that binding antibody levels vary with different variants and were associated with lower neutralising antibody levels against those strains. This might be explained by the presence of multiple mutations in the receptor binding domains, a finding substantiated by the existing medical literature.[16,17] These data suggest that adults who may have already received a fourth dose of COVID-19 vaccine, would still benefit from receiving the current XBB.1.5 booster vaccines which have been shown to elicit better neutralising antibody against circulating variants.[18]

Higher rates of severe reactogenicity events were observed in both strata reported here compared to other cohorts following second boosters, with 10% of cases from the 18- < 50y-BNT162b2 stratum experiencing severe fatigue following mRNA-1273 and 11% of cases belonging to 50- < 70y-BNT162b2 experiencing severe fatigue following BNT162b2 vaccination.[12,19] This is consistent with data reported globally which has found higher rates of reactogenicity and adverse events following mRNA compared to protein subunit vaccines.[19,20] Overall, reactogenicity events and SARs reported in this trial remain small and are within acceptable limits.

This study has two main limitations. First, PICOBOO was not designed to evaluate vaccine effectiveness against infection or disease. Differences in post-randomisation SARS-COV-2 infection between sites should be interpreted in the context of differences in local transmission, non-pharmacological prevention measures (such as mask wearing and border closures) and testing approaches in different jurisdictions at different stages of the pandemic.[21] SARS-CoV-2 infections ascertained after randomisation are likely to represent an underestimate of the true number of infections, with a declining propensity for people with symptoms to test for COVID-19 as the pandemic evolved.[22] Second, we only report on short-term humoral responses for immunocompetent older Australian adults who had received priming doses of BNT162b2; we will report on cellular and longer term humoral immune responses to these vaccines as data become available.

The strengths of PICOBOO include its adaptive design, which has provided agility to evaluate newly approved COVID-19 vaccines in the platform as soon as they have become available for use. These data support a shift in National policy to recommend boosting with monovalent XBB.1.5 vaccines. Additional data from this trial are expected to assist policymakers charged with deciding whether further COVID-19 boosters will be required in Australia and globally, and if so, in whom, and what vaccines and schedules should be recommended. The use of a Bayesian hierarchical model allowed sharing of information across different levels, enhancing the efficiency of antibody GMC estimates, enabling precise and robust inferences to be made.[23] This approach allowed all data to contribute meaningfully to the analyses, including data from a small number of participants who received first booster doses. Less variability was observed in the D28 anti-spike Ig Total concentrations than anticipated. Our assumptions about the variance in antibody responses which informed the Bayesian model were derived from COV-BOOST following first (rather than second) booster doses. The hierarchical model structure and the similarity in antibody responses across the mRNA vaccines may also have improved our precision more than expected. As a result, the desired precision for the D28 anti-spike Ig Total GMC estimates may have been reliably exceeded with fewer participants. Future trials may require fewer participants.

Author contributions

TS and PR conceived the trial. The primary design was elaborated by CM, ME, JR, JM, and MD with subsequent input from all PICOBOO investigators. JM, MD, TS conceived the statistical methods. MD was the unblinded statistician, while JM was blinded until the first interim analysis. CM and George Salama coordinated the implementation of this study together with site primary investigators UW, HM and KF. Laboratory assays were conducted by MCT, RT, SN and KS, FM, ZE, NC and RB. All authors had access to the data from this study and were responsible for the decision to publish. CM and MD drafted the primary version of this manuscript. All authors reviewed and approved the final version for publication and met criteria for authorship as per the ICMJE recommendations.

Data Availability

The PICOBOO Core Protocol, Booster Vaccination Substudy protocol and associated Laboratory and Statistical Appendices together with the interim analyses are available on the trial website (https://picoboo.com.au/). De-identified participant data that underlie the results reported in this article will be shared with investigators whose proposed use of the data has been approved by the Child and Adolescent Service Human Research Ethics Committee.

Declaration of Competing Interest

KF and TS are members of the Australian Technical Advisory Group on Immunisation (ATAGI) which advises the government on vaccine policy; their involvement as investigators on this trial has been declared to ATAGI. MP is involved in an ovarian cancer clinical trial that received funding from AstraZeneca. MP was involved in performing immunological assays on biological specimens obtained from participants in this trial, but was not involved in participant recruitment, data collection or the analysis of results. SNF leads the UK National Institute for Health and Care Research funded trial of third and fourth dose COVID-19 boosters. SNF acts on behalf of University Hospital Southampton NHS Foundation Trust, UK as an Investigator and/or providing consultative advice on clinical trials and studies of vaccines funded or sponsored by vaccine manufacturers including Moderna, Sanofi, Janssen, Pfizer, AstraZeneca, GlaxoSmithKline, Novavax, Seqirus, Medimmune, Merck and Valneva vaccines and antimicrobials. PR also reports acting on behalf of University of Western Australia, as an Investigator and/or providing consultative advice on clinical trials and studies of vaccines funded or sponsored by vaccine manufacturers including Moderna, Sanofi, Janssen, Pfizer, AstraZeneca, GlaxoSmithKline, Novavax, Seqirus, Merck and Clover Biopharmaceutical vaccines. HSM is an investigator on clinical vaccine trials funded by Industry. Her institution receives funding for investigator led research from Sanofi, Pfizer, Seqirus, and Moderna. UW is an Investigator for industry sponsored clinical vaccine trials. They receive no personal financial payment for this work. The other authors declare that they have no competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106346.

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