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Reactogenicity and immunogenicity following heterologous and homologous third dose COVID-19 vaccination in UK adolescents (Com-COV3): A randomised controlled non-inferiority trial

E. Kelly [a,1], M. Greenland [a,1], P. de Whalley [a], G.C. Macaulay [a], P.K. Aley [a], E. Plested [a], S. Koleva [a], J. Cotton [a], J. Kinch [a], T. Madupuri [a], R.C. Read [b,c], M. Ramsay [d], C. Cameron [e], D.P.J. Turner [f,g], P. Heath [h], P. Connor [i], K. Cathie [b], S.N. Faust [b,c], I. Banerjee [j], K. Man [k], F. Shackley [l], S. O' Riordan [m], S. Owens [n], T. Polychronakis [o], H. Trari Belhadef [a], Y. Mujadidi [a], A. Singha [a], L. Cantrell [a], E. Clutterbuck [a], R. Anslow [a], T. James [p], B. Hallis [q], M. Matheson [q], L. Chang [r], T. Lambe [a,s], J.S. Nguyen-Van-Tam [t], M.D. Snape [a,2], A.M. Minassian [a,2], X. Liu [a,*,2]

[a] Oxford Vaccine Group, NIHR Oxford Biomedical Research Centre, Department of Paediatrics, University of Oxford, Oxford, UK
[b] NIHR Southampton Clinical Research Facility and Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[c] Faculty of Medicine and Institute for Life Sciences, University of Southampton, Southampton, UK
[d] Immunisation and Countermeasures Division, National Infection Service, Public Health England, London, UK
[e] Health Protection Scotland, Glasgow, UK
[f] University of Nottingham, UK
[g] Nottingham University Hospitals NHS Trust, Nottingham, UK
[h] Vaccine Institute, St. George's, University of London and St. George's University Hospitals NHS Trust, London, UK
[i] Noah's Ark Children's Hospital for Wales, University Hospital of Wales, Cardiff, UK
[j] Royal Manchester Children's Hospital, Manchester University Hospitals Foundation Trust, UK
[k] Royal Free Hospital NHS Foundation Trust, London, UK
[l] Sheffield's Children NHS Foundation Trust, Sheffield, UK
[m] Leeds Teaching Hospital NHS Foundation Trust, Leeds, UK
[n] Newcastle Upon Tyne Hospitals NHS Foundation Trust, UK
[o] Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[p] Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[q] UK Health Security Agency, Porton Down, Salisbury, UK
[r] Nuffield Department of Medicine, University of Oxford, Oxford, UK
[s] Chinese Academy of Medical Science (CAMS) Oxford Institute, University of Oxford, Oxford, UK
[t] Population and Lifespan Health, University of Nottingham, Nottingham, UK

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SUMMARY

Background: The emergence of SARS-CoV2 variants combined with waning vaccine-induced immunity and breakthrough infections has highlighted the need for booster doses to maintain protection against SARS-CoV2 infection and disease.

Methods: Com-COV3 was a phase II, multicentre, randomised controlled trial, recruiting across 11 UK sites from June 2022 to June 2023, with follow-up visits to February 2024. Healthy 12–15-year-olds who had received a two-30 μg dose BNT162b2 primary regimen at least 90 days previously were randomised 1:1:1:1:1 to receive either BNT162b2 30 μg, BNT162b2 10 μg (adult vaccine formulation), BNT162b2 10 μg (paediatric formulation), NVXCoV2373, or Meningococcal B vaccine (control). The primary objective was to determine if SARS-CoV-2 anti-spike antibody following a 10 μg dose of the adult formulation of BNT162b2 was non-inferior to the paediatric formulation at 28 days post-third vaccination. The last five participants were randomised using a 1:3:3:1:1 ratio to prioritise recruitment to the study groups required for the co-primary endpoint. Although recruitment ceased early, the sample size required to fulfil the primary objective was met.

Findings: 281 participants were recruited (mean age 14 years old, 57% female). Adverse reactions were

* Corresponding author.
E-mail address: Xinxue.liu@paediatrics.ox.ac.uk (X. Liu).
[1] Joint first authors.
[2] Joint senior authors.

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mostly mild-to-moderate. Local reactogenicity was mildest following NVXCoV2373. Frequency of adverse events was similar for both full dose and fractional dose BNT162b2 groups. Four serious adverse events occurred: three in the paediatric and one in the adult 10 μg BNT162b2 group. Immunogenicity of 10 μg BNT162b2 (adult) was both non-inferior and superior to that of 10 μg BNT162b2 (paediatric); adjusted geometric mean ratio (aGMR) anti-spike IgG 1.50 (one-sided 95% CI 1.25 to ∞). Compared with 30 μg BNT162b2, anti-spike IgG at day 28 post-third dose were similar in the 10 μg BNT162b2 (adult) group [aGMR 0.93 (95% CI 0.75–1.14)] and significantly lower in the 10 μg BNT162b2 (paediatric) [aGMR 0.64 (95% CI 0.52–0.78)] and NVXCoV2373 [aGMR 0.77 (95% CI 0.63–0.95)] groups. Compared with 30 μg BNT162b2, levels of neutralising antibodies against Omicron BA.5 and XBB.15 were similar across vaccine groups.

Interpretation: All booster regimens evaluated elicited a robust immune response. 10 μg fractional adult BNT162b2 vaccine demonstrated similar immunogenicity compared with 30 μg BNT162b2 and superior immunogenicity compared with 10 μg paediatric BNT162b2 vaccine. Fractional doses of the adult BNT162b2 vaccine are an alternative to the paediatric formulation for booster campaigns in adolescents.

Introduction

COVID-19 immunisation is highly effective at reducing the risk of severe disease and hospitalisation from SARS-CoV-2 infection. However, waning of the immune response following two-dose COVID-19 primary immunisation has been shown to occur.[1,2] Although adolescents are at lower risk of severe disease and death from SARS-CoV-2 infection than older populations, the emergence of more recent variants in 2022 rendered the paediatric population more vulnerable to infection and severe illness with highest rates of paediatric hospitalisation and infection at the time induced by SARS-CoV-2 variants of concern Delta and Omicron.[3] Indeed, studies in both adults and children have demonstrated reduced vaccine effectiveness and a rapid decline in protection against SARS-CoV-2 variants, particularly Omicron, after the primary series.[4–8] Following two-dose BNT162b2 (Pfizer-BioNTech) vaccination during an Omicron predominant period, vaccine effectiveness declined to 16% among adolescents within 6 months after vaccination.[7] Booster vaccination, however, has been shown to restore protection against hospitalisation and Omicron-related infection to levels observed against Delta.[4,7,8] These findings prompted many high-income countries to recommend a third COVID-19 booster dose to combat waning vaccine effectiveness.[5] However, policy regarding adolescent immunisation varied, and continues to vary, globally.

A 10 μg dose of BNT162b2 has been recommended for children aged between 5 and 11 years, administered as 0.2 mL using a specially designed paediatric formulation of the vaccine. A two 10 μg-dose paediatric BNT162b2 regimen as the primary vaccine series has already been shown to be highly immunogenic when administered to children aged 5 to 11 years, and comparably immunogenic to a two 30 μg-dose BNT16b2 adult formulation schedule administered to 18–25-year-olds.[9] Furthermore, COVID-19 vaccines have been shown to elicit more robust immune responses in adolescents compared with adults.[10] A one-third dose might also potentially reduce the risk of myocarditis observed after mRNA COVID-19 vaccines.[11] However, it is not known whether the immune response to 10 μg administered using the adult formulation of BNT162b2 (hereafter referred to as 'adult BNT-10') is non-inferior to the same dose administered using the paediatric formulation of BNT162b2 (hereafter referred to as 'paediatric BNT-10'). The possibility of using a one-third dose of the adult formulation of BNT162b2 as a booster might also offer benefits in terms of cost-effectiveness, greater vaccine availability, and future pandemic preparedness, in addition to an improved reactogenicity profile.

Heterologous COVID-19 booster vaccine schedules in adults have been shown to elicit enhanced protection against Delta and Omicron SARS-CoV-2 variants and greater immunogenicity compared with primary and homologous boost schedules.[12,13] The COV-BOOST trial, which evaluated seven different third dose COVID-19 vaccine schedules, demonstrated robust immune responses and favourable reactogenicity following heterologous booster immunisation in adults.[14] The trial also investigated fractional dose COVID-19 booster options and showed that fractional dose BNT162b2 as a third dose induced an immune response comparable to full dose BNT162b2.[14,15] In Cohort A of the Com-COV3 trial, which examined the immunogenicity of heterologous and fractional second dose COVID-19 vaccine schedules in adolescents, NVXCoV2373 Nuvavoxid® (Novavax, hereafter referred to as 'NVX') given as the second dose following 30 μg BNT162b2 (Pfizer-BioNTech; henceforth referred to as 'BNT-30') as the first dose, demonstrated higher humoral and cellular immune responses and higher neutralising antibody titres against Omicron compared with a two-dose 30 μg BNT162b2 homologous regimen, suggesting a heterologous schedule could potentially afford greater protection against SARS-CoV-2 when compared with the licensed schedule.[16]

Here we report the results of Cohort B of the Com-COV3 trial, where we investigated whether adult BNT-10 is non-inferior to paediatric BNT-10 when given as a booster dose in adolescents, and examined the reactogenicity and immunogenicity of homologous, heterologous, and fractional third dose COVID-19 vaccine schedules in adolescents when administered at least three months after a two-30 μg dose BNT162b2 schedule given as the primary series.

Methods

Study design

Com-COV3 was a UK multicentre, single-blind, phase II, randomised controlled non-inferiority trial investigating the reactogenicity, immunogenicity and safety of homologous, heterologous, and fractional third dose (mixed) COVID-19 vaccine schedules. The trial contained two cohorts. Cohort A assessed mixed second dose COVID-19 vaccine schedules in adolescents and was reported previously.[16] This paper reports the results of Cohort B. This trial was approved by the South-Central Berkshire Research Ethics Committee (21/SC/0310), the University of Oxford, and the Medicines and Healthcare Products Regulatory Agency. Recruitment to Cohort B took place across eleven UK National Health Service and academic institutions between 01 June 2022 and 30 June 2023. The study protocol is accessible at https://comcovstudy.org.uk/study-protocol.

Participants

Participants were healthy adolescents (well-controlled mild-to-moderate comorbidities were permitted) aged between 12 and 15.5

years who had received two 30 μg doses of BNT162b2 at least 90 days prior to enrolment. Individuals belonging to a 'high risk' group susceptible to severe COVID-19 disease (e.g., those with an immunosuppressive condition) were not eligible to participate in the trial. A full list of inclusion and exclusion criteria can be found in the protocol (accessible at https://comcovstudy.org.uk/study-protocol).

Randomisation and masking

A computer-generated randomisation list was created by the study statistician. Participants were initially randomised (1:1:1:1:1) to receive BNT-30 (wild-type SARS-CoV-2), adult BNT-10 (administered giving one-third the volume of the adult vaccine formulation), paediatric BNT-10 (administered using the paediatric formulation), full dose NVX (heterologous schedule), or two doses of the 4CMenB vaccine given 3 months apart (control group). The control group received the Comirnaty Original/Omicron BA.1 (15/15 μg)/dose vaccine as their third COVID-19 vaccine 6 months after enrolment. Due to ongoing recruitment challenges and following discussion with the Trial Steering Committee (TSC), study randomisation was changed to 1:3:3:1:1 to prioritise recruitment to the fractional dose BNT162b2 groups to achieve the participant numbers required to meet the study's co-primary endpoint (i.e., non-inferiority between the two 10 μg BNT162b2 formulation groups). The change to randomisation was proposed on 5th December 2022 and approved as part of a substantial amendment to the trial on 9th June 2023. However, due to the ongoing recruitment challenges, the TSC recommended ceasing recruitment on 30th June 2023. There were 5 participants recruited using the new randomisation.

Participants were randomised using block randomisation. Initially, block sizes of 5 and 10 were used. Randomisation was performed at the time of the first study visit and stratified by study site and history of positive COVID-19 test. After the randomisation ratio was changed to 1:3:3:1:1, a random block size of 9 was used.

Participants and laboratory staff were blinded to the vaccine schedule received. The blind was maintained by applying masking tape to the vaccine syringe and vaccines were prepared out of sight of participants. Unblinding of participants took place 56 days after receipt of their study vaccine.

Procedures

Eligible participants were invited to attend a screening and enrolment visit (day 0). A detailed medical history was taken from participants at their enrolment visit and a physical examination performed if required. Parents and participants had the opportunity to read a pre-approved participant information sheet (separate information sheets tailored to parents and participants were provided to enhance comprehension) prior to enrolment. A video presentation of the participant information sheet was also made available to participants and their parents at the first study visit. Written informed consent was obtained from each participant's parent or guardian in addition to signed assent from all participants. Final eligibility was assessed by a study doctor. Study group randomisation and vaccination took place at the day 0 visit. Blood samples for COVID-19 immunogenicity assays (anti-spike IgG, anti-nucleocapsid IgG, cellular responses) were taken at the day 0 visit, prior to vaccination. Participants also took a COVID-19 lateral flow test (Flowflex) at this visit. If this was positive, the remainder of the visit was deferred for at least 4 weeks.

Six vaccines were used in the study and all vaccines were administered by intramuscular injection in the upper arm. BNT-30 was given as a 0.3 mL intramuscular injection, paediatric BNT-10 as 0.2 mL, adult BNT-10 as 0.1 mL, NVX as 0.5 mL, 4CMenB (Bexsero Meningococcal Group B vaccine) as 0.5 mL and Comirnaty Original/Omicron BA.1 (15/15 μg)/dose as 0.3 mL injection. All study vaccines were administered using a 23-gauge (25 mm) needle.

Participants were observed for at least 15 minutes after vaccination. Participants were supplied with an oral thermometer, tape measure, and a link to an electronic diary at the day 0 visit. They were requested to record solicited, unsolicited, and medically attended adverse events (AEs). Participants were also provided with COVID-19 lateral flow test kits (Flowflex) and asked to perform a COVID-19 lateral flow test every week for 4 weeks between the first and second visits, or if they developed symptoms suggestive of COVID-19. Diaries were reviewed daily by a study doctor for AEs, adverse events of special interest (AESIs), and serious adverse events (SAEs). The follow-up visit schedule is outlined in the protocol (accessible at https://comcovstudy.org.uk/study-protocol) and occurred up to 7 months after vaccination.

Participants randomised to the control arm of the study received their COVID-19 vaccine [Comirnaty Original/Omicron BA.1 (15/15 μg)/dose] at the day 182 visit. Control group participants were also required to record solicited, unsolicited, and medically attended AEs in an e-diary for 28 days after this visit. They were provided with COVID-19 lateral flow test kits (Flowflex) and asked to perform a COVID-19 lateral flow test every week between the day 182 visit and their final study visit (day 210), 28 days after vaccination.

Laboratory methods

Humoral immune responses were measured by testing serum samples at all study visit timepoints for anti-SARS-CoV-2 spike IgG antibodies using a validated Enzyme Linked Immunosorbent Assay (ELISA) at UK Health Security Agency (HSA), Porton Down (reported as ELISA laboratory units [ELU]/mL). This assay was validated at Nexelis (Laval, QC, Canada) and the technology transferred to UKHSA. The conversion factors to international standard units are included in the appendix (Supplementary Table 1). Sera were also analysed at days 0, 84, and 182 to assess anti-nucleocapsid IgG serostatus at Porton Down, UKHSA by ECLIA (Cobas platform, Roche Diagnostics). An assay cut-off index (COI) below 1.0 was reported as seronegative. Samples collected at days 28, 84, 182, and 210 (control group only) were tested using a microneutralization assay to assess 50% focus reduction neutralisation titres ($FRNT_{50}$) for live SARS-CoV-2 virus lineage Victoria and Omicron sublineages BA.5 and XBB.15 at the University of Oxford, Oxford, UK, as previously described.[17] Testing was performed in four study groups: BNT-30, adult BNT-10, paediatric BNT-10, and NVX.

A modified T-SPOT-Discovery test performed at Oxford Immunotec (Abingdon, UK) was used to detect IFN- γ secreting T cells specific to whole spike protein epitopes, designed based on the Wuhan-Hu-1 sequence (YP_009724390.1). Peripheral blood mononuclear cells (PBMCs) to which T-cell Xtend reagent had been added to extend PBMC survival, were tested within 32 hours of venepuncture using T-SPOT-*Discovery* ELISpot test panel 14 (full spike, Wuhan) and panel 22 (Omicron). T-cell frequencies were reported as spot-forming cells (SFC) per 250,000 PBMCs with a lower limit of detection of one in 250,000 PBMCs.

Outcomes

The primary outcome was reactogenicity measured through solicited systemic reactions for seven days after vaccination. The co-primary outcome was to determine whether the SARS-CoV-2 anti-spike antibody by ELISA following adult BNT-10 (0.1 mL) is non-inferior to paediatric BNT-10 (0.2 mL) at 28 days post-third vaccination. Secondary outcomes included immunogenicity (anti-spike immunoglobulin, cellular responses via ELISpot) and safety (assessed through SAEs, AESIs). The incidence of SARS-CoV-2 infection and virus neutralisation titres were exploratory outcomes. The full

Table 1
Demographics and baseline characteristics by study arm in enroled participants.[a]

Characteristic	Pfizer full dose adult formulation N = 56	Pfizer 1/3 dose adult formulation N = 58	Pfizer full dose paediatric formulation N = 55	NVX-CoV2373 full dose N = 56	4CMenB N = 56	Total N = 281
Age (years)						
Mean (SD)	14.2 (0.8)	14.2 (0.9)	14.1 (0.8)	14.1 (0.9)	14.0 (0.9)	14.1 (0.9)
Range	12.4, 15.4	12.6, 15.5	12.5, 15.5	12.6, 15.5	12.5, 15.3	12.4, 15.5
Sex						
Male	24 (43%)	24 (41%)	22 (40%)	28 (50%)	24 (43%)	122 (43%)
Female	32 (57%)	34 (59%)	33 (60%)	28 (50%)	32 (57%)	159 (57%)
Ethnicity						
White	46 (82%)	55 (95%)	48 (87%)	49 (88%)	53 (95%)	251 (89%)
Mixed	4 (7.1%)	1 (1.7%)	1 (1.8%)	4 (7.1%)	2 (3.6%)	12 (4.3%)
Asian	4 (7.1%)	2 (3.4%)	3 (5.5%)	2 (3.6%)	0 (0%)	11 (3.9%)
Other	2 (3.6%)	0 (0%)	3 (5.5%)	1 (1.8%)	1 (1.8%)	7 (2.5%)
Prefers not to give	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Days since previous COVID-19 vaccination						
Mean (SD)	235.7 (96.4)	240.1 (78.7)	248.5 (96.0)	255.1 (90.2)	244.6 (97.4)	244.8 (91.5)
Range	98.0, 487.0	93.0, 459.0	91.0, 496.0	108.0, 493.0	94.0, 501.0	91.0, 501.0
Previous positive COVID-19 test						
No	16 (29%)	18 (31%)	18 (33%)	16 (29%)	17 (30%)	85 (30%)
Yes	40 (71%)	40 (69%)	37 (67%)	40 (71%)	39 (70%)	196 (70%)
Baseline serostatus[b]						
Seropositive	48 (86%)	51 (88%)	48 (87%)	51 (91%)	45 (80%)	243 (86%)
Seronegative	8 (14%)	7 (12%)	7 (13%)	5 (8.9%)	11 (20%)	38 (14%)

SD, standard deviation.
[a] Data presented are frequency (percentage) for categorical variables and mean (standard deviation)/range for continuous variables.
[b] Anti-nucleocapsid IgG data were unavailable for 8 participants. Previous COVID-19 test results were used to impute the data for these participants.

list of outcome measures can be found in the protocol (https://comcovstudy.org.uk/study-protocol).

Statistical analysis

The trial was designed to detect non-inferiority between adult BNT-10 and paediatric BNT-10 at 28 days post-third dose. The sample size calculation assumed a standard deviation of 0.3 of anti-spike IgG on a log10 scale based on Cohort A data, a non-inferiority margin of 0.67, and the true mean difference between the two study groups to be zero (or a geometric mean ratio (GMR) of one). Originally, the study aimed to recruit 76 participants in the co-primary outcome study groups to achieve 90% power at a two-sided 5% type I error level assuming a 15% attrition rate for an effective sample size of 64 participants in each group. Following recruitment challenges, the sample size assumptions were revised to a one-sided 5% type I error level requiring 62 participants in the co-primary outcome study groups for an effective sample size of 52 participants in each group to achieve 90% power using the same non-inferiority margin of 0.67.

The primary outcome analysis population for reactogenicity included participants who received a third dose. The maximum severity for each solicited systemic AE across seven days after third vaccination was derived for each participant and summarised by group. Participants with no diary data across the seven days were excluded. Safety secondary outcomes included SAEs and AESIs throughout the study, solicited local AEs across seven days after third vaccination, and unsolicited AEs within 28 days after third vaccination. Local solicited AEs were analysed similarly to systemic AEs.

The immunogenicity co-primary outcome analysis was non-inferiority of anti-spike IgG for adult BNT-10 compared with paediatric BNT-10. The primary analysis was conducted on the per-protocol (PP) population at 28 days post-third dose. All participants who received a third vaccine as randomised, with endpoint data available, no self-reported COVID-19 infection within 28 days post-vaccination, and no protocol deviations of timing of blood samples were included. A sensitivity analysis in the modified intention-to-treat (mITT) population at 28 days post-third dose was conducted, including all participants who received a third vaccination, with endpoint data available, and no self-reported COVID-19 infection within 28 days post-vaccination. For the mITT analysis, participants were analysed according to their randomisation, irrespective of the vaccine they received. Immunogenicity secondary outcomes included anti-spike immunoglobulins and cellular immune responses by ELISpot at days 0, 28, 84 and 182 post study vaccination in the mITT populations. Exploratory live virus neutralising antibodies (VNA) at days 28, 84, and 182 post study vaccination in the mITT populations were reported. For the control group only, these data were also collected at day 210 post-control vaccination (28 days post-third COVID-19 vaccination).

Immunogenicity outcomes were summarised using geometric mean concentrations (GMCs) and two-sided 95% confidence intervals (CIs). The titres were transformed using log10 scale. Data below the lower limit of detection (LLOD) were imputed with a value equal to half the threshold before transformation. Data above the validated upper limit of detection were included in analyses. The raw values were used as they were deemed meaningful. Adjusted GMRs and CIs were calculated as the antilogarithm of the difference between the mean of the log10 transformed titre in study groups compared to a reference study group. The linear regression models were adjusting for study site, previous positive COVID-19 test, age, interval between second and third dose, and baseline immunogenicity value as fixed effects. Missing outcome data were not imputed. Complete case analysis was performed for the covariates in the models.

The adjusted GMR for the co-primary outcome was presented with a one-sided 95% CI. Non-inferiority was concluded if the lower limit of the CI lay above the 0.67 non-inferiority margin. Other outcomes were presented with two-sided 95% CIs. Adjusted GMRs for anti-spike immunoglobulins and cellular immune responses compared study arms to the control group as the reference. Adjusted GMRs for anti-spike immunoglobulins, cellular immune responses, and live VNA compared study arms to the BNT-30 study arm as the reference.

Exploratory anti-nucleocapsid immunoglobulins at day 0, 84, and 182 post-third vaccination in the mITT populations were analysed to

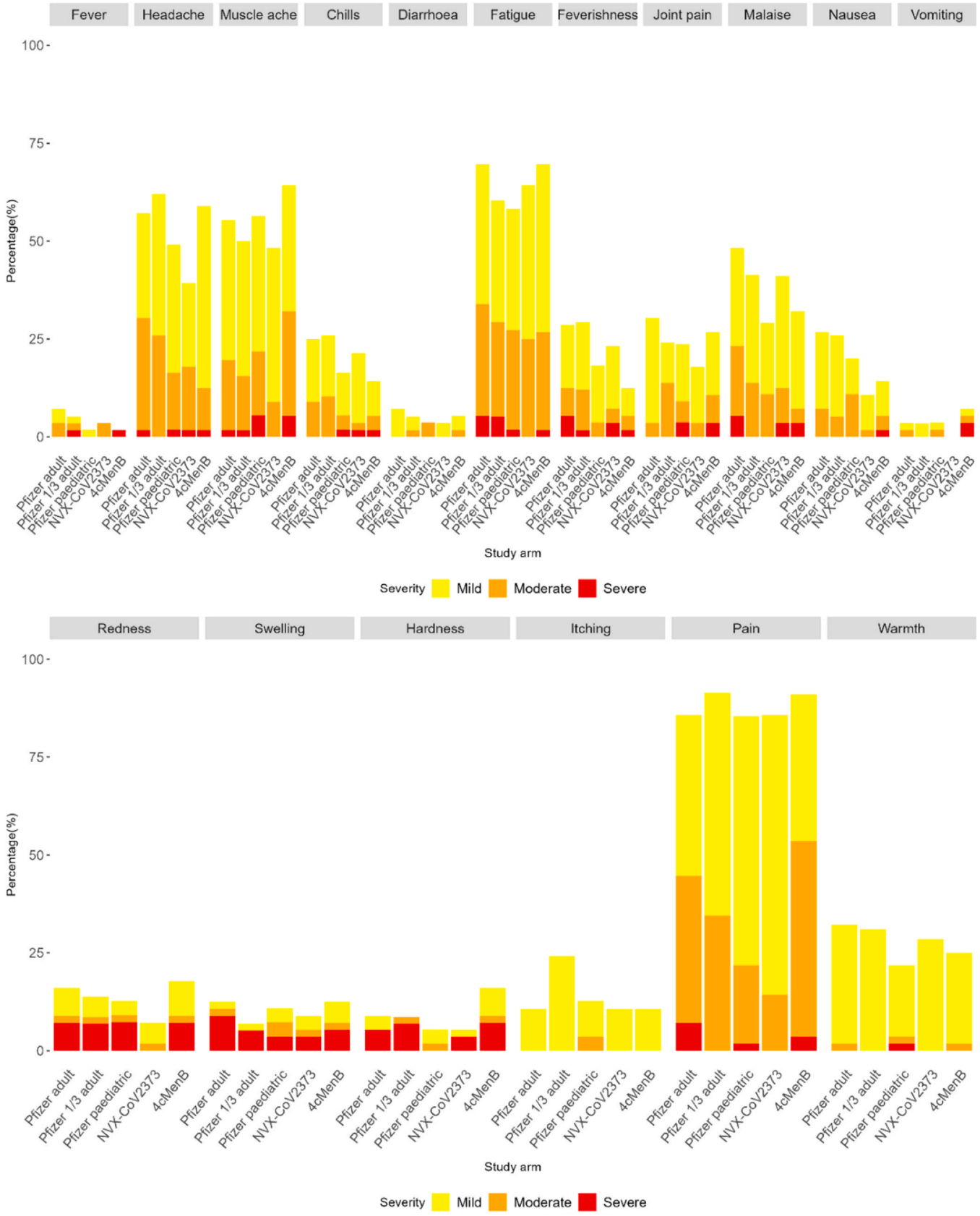


Fig. 1. Severity of solicited adverse reactions in days 0–7 after third vaccination by study arm as self-reported in participant electronic diaries in the safety analysis population. The severity presented is the participant's highest severity across 7 days following vaccination for each solicited adverse event. Fever: Mild: 38.0 °C to < 38.5 °C; Moderate: 38.5 °C to < 39 °C; Severe: ≥39.0 °C. Feverish: Self-reported feeling of feverishness. For systemic symptoms, grading was classified as Mild – easily tolerated with no limitation on normal activity; Moderate – some limitation of daily activity; Severe – unable to perform the normal daily activity. There were no self-reported SARS-CoV-2 infections in days 0–7 after vaccination. There was one participant who received the NVXCoV2373 vaccine at the day 0 visit who had a headache and general malaise on day 6 post-vaccination but did not record these in their diary and are not included in the analysis. There was one participant who received the Bivalent COVID-19 vaccination at day 182 visit for whom diary data are completely missing following COVID-19 vaccination.

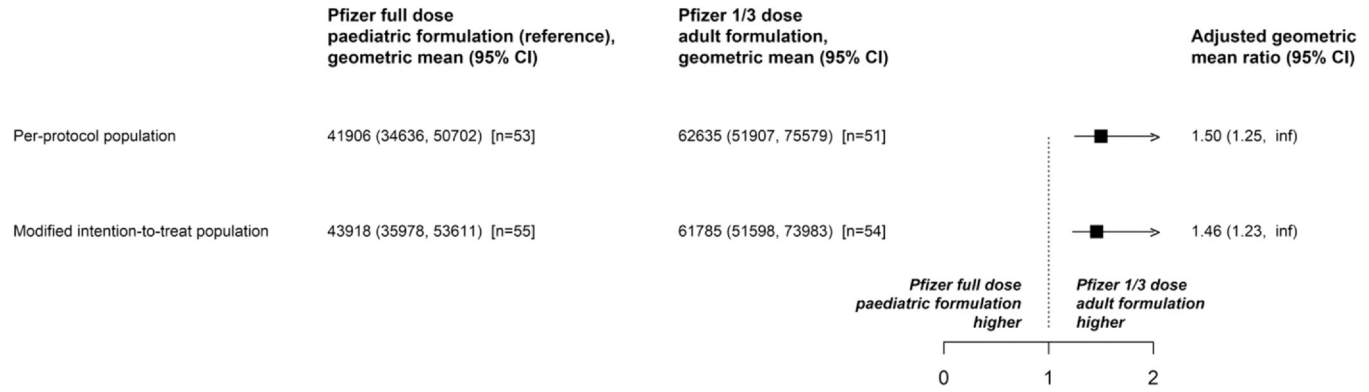


Fig. 2. Co-primary immunogenicity outcome – SARS-CoV-2 anti-spike antibody, ELU/mL at 28 days post-third vaccination. CI, confidence interval. Data presented are the geometric means and their corresponding 95% confidence intervals, and the adjusted geometric mean ratios and their corresponding one-sided 95% confidence intervals. The boxes indicate the adjusted geometric mean ratio, and the horizontal lines indicate the corresponding 95% confidence intervals. The geometric mean ratios are adjusted for study site, age, interval between second and third COVID-19 vaccinations, any previous positive COVID-19 test, and baseline immunogenicity value as fixed effects. The vertical dotted line refers to an adjusted geometric mean ratio of one and indicates the line of no difference. A confidence interval that lies completely to one side and not intersecting the line of no difference indicates a significant difference in the geometric mean concentrations between adult 10 µg BNT162b2 study arm and the reference paediatric 10 µg BNT162b2 study arm.

determine the frequency of seropositivity to anti-SARS-CoV-2 nucleocapsid IgG at enrolment and seroconversion throughout the study.

Immunogenicity sensitivity analyses were conducted excluding participants who were considered to have had a 'breakthrough infection' during follow-up. A 'breakthrough infection' was defined as either: a self-reported SARS-CoV-2 infection after 28 days following third dose, a two-fold rise in anti-nucleocapsid IgG between day 28 and day 84 and between day 84 and day 182, a two-fold rise in anti-spike antibodies between day 28 and day 84 and between day 84 and day 182, or a seroconversion of anti-nucleocapsid IgG serostatus. Distributions according to the different definitions of SARS-CoV-2 infections during follow-up were presented across study arms.

Statistical analyses were performed using R 4.3.1 and RStudio 2023.12.1+402.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between 1st June 2022 and 30th June 2023, 298 participants were screened, of whom 283 participants were eligible. At the day 0 visit, one participant was excluded, and 282 participants underwent randomisation (Supplementary Figure 1). Baseline characteristics were balanced across the study arms (Table 1). The mean age of participants was 14.1 (range 12.4–15.5) years. Most participants were white (89%) and 57% were female. The mean interval between second and third COVID-19 vaccination was 244.8 (range 91–501) days. More than half of participants (64%) reported at least one previous COVID-19 infection, and the proportion was balanced between arms.

There was no clear difference in the frequency of local and systemic solicited reactions between study arms and most systemic reactions were mild-to-moderate. Fatigue, muscle ache, and headache were among the most frequently reported systemic adverse reactions. Among local reactions, pain and warmth were most often reported (Fig. 1, Supplementary Table 3). Most reactions were short-lived (Supplementary Figure 3). Most systemic adverse reactions reported by control group participants following the Comirnaty Original/Omicron BA.1 vaccine at day 182 were mild-to-moderate (Supplementary Figures 4 and 5, Supplementary Table 3). Pain at the injection site was the most frequently reported local reaction.

In total, there were 182 AEs reported by 119 participants (Supplementary Table 4). Of these, 23 (13%) represented AESIs. Except for one event (a case of peripheral nerve facial palsy, also reported as an SAE), all AESIs were related to COVID-19 infections (Supplementary Tables 5 and 6). AEs were most frequently reported by participants in both 10 µg BNT162b2 arms [28/55 (51%) in paediatric BNT-10; 26/58 (45%) in adult BNT-10] and by participants in the control arm [28/56 (50%)]. Axillary lymphadenopathy and tenderness were reported most frequently as related AEs by participants who received BNT-30 or BNT-10 (adult and paediatric) (Supplementary Tables 7 and 8).

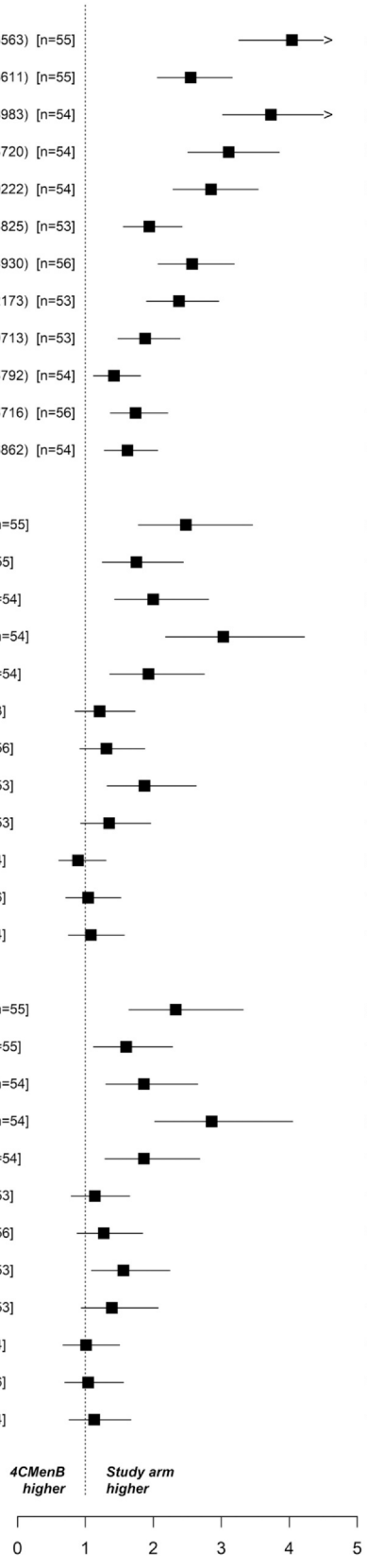
Of the four SAEs reported, three occurred in paediatric BNT-10 (Supplementary Table 5). Only one SAE (peripheral facial nerve palsy) was deemed possibly related to the study vaccine paediatric BNT-10. All but one SAE (a new diagnosis of idiopathic intracranial hypertension with a hereditary component, assessed as unrelated to the study vaccine received) had fully resolved by the end of the trial. All SAEs occurred more than three months after vaccination.

In the PP population, anti-spike IgG GMC at 28 days post-boost in paediatric BNT-10 was 41,906 (95% CI 34,636–50,702) and in adult BNT-10 was 62,635 (95%CI 51,907–75,579). Compared with paediatric BNT-10, adult BNT-10 was not only non-inferior with aGMR of 1.50 (one-sided 95% CI: 1.25–∞), but also superior (aGMR: 1.50, two-sided 95% CI: 1.21–1.85). The sensitivity analysis in the mITT population showed similar results (Fig. 2, Supplementary Figure 6).

Compared with the control arm, humoral and cellular responses were significantly boosted at 28 days post-boost in the four COVID-19 vaccine arms (Figs. 3 and 4A). In the four COVID-19 vaccine arms, the aGMRs of anti-spike IgG in all participants ranged from 2.55 (95% CI: 2.06–3.16) in paediatric BNT-10 to 4.04 (95% CI: 3.26–5.00) in BNT-30. By day 182, the anti-spike IgG response persisted and was significantly higher in the COVID-19 vaccine arms compared with the control arm, the aGMR ranging from 1.42 (95% CI: 1.12–1.81) in paediatric BNT-10 and 1.88 (95% CI: 1.48–2.39) in BNT-30. A similar pattern was also observed for cellular responses with significantly higher T-cell responses seen at 28 days in the COVID-19 vaccine arms compared with the control arm. This difference was no longer statistically significant by 182 days post-vaccination.

Across the four COVID-19 vaccine arms, anti-spike IgG concentrations post-vaccination were similar between BNT-30 and adult BNT-10 during the follow-up: GMC at 28 days post-boost was 68,374 ELU/mL (95% CI 55,946–83,563) and 61,785 (51,598–73,983) in BNT-

		4CMenB (reference), geometric mean (95% CI)	Study arm, geometric mean (95% CI)	Adjusted geometric mean ratio (95% CI)
SARS-CoV-2 anti-spike antibody, ELU/mL, against Wuhan strain				
28	30µg adult BNT162b2	16284 (12896, 20563) [n=52]	68374 (55946, 83563) [n=55]	4.04 (3.26, 5.00)
	10µg paediatric BNT162b2	16284 (12896, 20563) [n=52]	43918 (35978, 53611) [n=55]	2.55 (2.06, 3.16)
	10µg adult BNT162b2	16284 (12896, 20563) [n=52]	61785 (51598, 73983) [n=54]	3.73 (3.02, 4.62)
	NVX-CoV2373	16284 (12896, 20563) [n=52]	51837 (42170, 63720) [n=54]	3.11 (2.51, 3.85)
84	30µg adult BNT162b2	15201 (11705, 19740) [n=53]	41730 (34673, 50222) [n=54]	2.85 (2.29, 3.54)
	10µg paediatric BNT162b2	15201 (11705, 19740) [n=53]	28178 (22799, 34825) [n=53]	1.94 (1.56, 2.42)
	10µg adult BNT162b2	15201 (11705, 19740) [n=53]	36994 (30461, 44930) [n=56]	2.57 (2.07, 3.19)
	NVX-CoV2373	15201 (11705, 19740) [n=53]	34400 (28059, 42173) [n=53]	2.38 (1.90, 2.96)
182	30µg adult BNT162b2	12550 (9909, 15893) [n=54]	24337 (19934, 29713) [n=53]	1.88 (1.48, 2.39)
	10µg paediatric BNT162b2	12550 (9909, 15893) [n=54]	19059 (15267, 23792) [n=54]	1.42 (1.12, 1.81)
	10µg adult BNT162b2	12550 (9909, 15893) [n=54]	21637 (17524, 26716) [n=56]	1.74 (1.37, 2.21)
	NVX-CoV2373	12550 (9909, 15893) [n=54]	21478 (17174, 26862) [n=54]	1.62 (1.28, 2.06)
Cellular response, SFC per million PBMCs, against Victoria strain				
28	30µg adult BNT162b2	57 (41, 79) [n=52]	146 (117, 183) [n=55]	2.48 (1.78, 3.46)
	10µg paediatric BNT162b2	57 (41, 79) [n=52]	97 (73, 127) [n=55]	1.75 (1.25, 2.44)
	10µg adult BNT162b2	57 (41, 79) [n=52]	124 (99, 155) [n=54]	2.00 (1.43, 2.81)
	NVX-CoV2373	57 (41, 79) [n=52]	157 (123, 199) [n=54]	3.03 (2.18, 4.22)
84	30µg adult BNT162b2	50 (38, 65) [n=53]	105 (81, 135) [n=54]	1.93 (1.36, 2.75)
	10µg paediatric BNT162b2	50 (38, 65) [n=53]	71 (52, 98) [n=53]	1.21 (0.85, 1.73)
	10µg adult BNT162b2	50 (38, 65) [n=53]	81 (59, 110) [n=56]	1.31 (0.92, 1.87)
	NVX-CoV2373	50 (38, 65) [n=53]	95 (79, 112) [n=53]	1.87 (1.32, 2.63)
182	30µg adult BNT162b2	58 (44, 77) [n=54]	80 (60, 106) [n=53]	1.35 (0.93, 1.96)
	10µg paediatric BNT162b2	58 (44, 77) [n=54]	55 (41, 73) [n=54]	0.89 (0.61, 1.30)
	10µg adult BNT162b2	58 (44, 77) [n=54]	67 (50, 88) [n=56]	1.04 (0.71, 1.52)
	NVX-CoV2373	58 (44, 77) [n=54]	61 (46, 82) [n=54]	1.08 (0.75, 1.57)
Cellular response, SFC per million PBMCs, against Omicron strain				
28	30µg adult BNT162b2	67 (50, 91) [n=52]	158 (118, 210) [n=55]	2.33 (1.64, 3.32)
	10µg paediatric BNT162b2	67 (50, 91) [n=52]	104 (77, 141) [n=55]	1.60 (1.12, 2.28)
	10µg adult BNT162b2	67 (50, 91) [n=52]	136 (105, 178) [n=54]	1.86 (1.30, 2.65)
	NVX-CoV2373	67 (50, 91) [n=52]	183 (147, 228) [n=54]	2.86 (2.02, 4.05)
84	30µg adult BNT162b2	59 (45, 76) [n=53]	115 (90, 146) [n=54]	1.86 (1.29, 2.68)
	10µg paediatric BNT162b2	59 (45, 76) [n=53]	81 (58, 112) [n=53]	1.14 (0.79, 1.65)
	10µg adult BNT162b2	59 (45, 76) [n=53]	88 (65, 118) [n=56]	1.27 (0.88, 1.84)
	NVX-CoV2373	59 (45, 76) [n=53]	95 (74, 121) [n=53]	1.56 (1.09, 2.24)
182	30µg adult BNT162b2	59 (44, 78) [n=54]	82 (62, 109) [n=53]	1.39 (0.94, 2.07)
	10µg paediatric BNT162b2	59 (44, 78) [n=54]	57 (41, 78) [n=54]	1.01 (0.67, 1.50)
	10µg adult BNT162b2	59 (44, 78) [n=54]	68 (50, 91) [n=56]	1.04 (0.70, 1.56)
	NVX-CoV2373	59 (44, 78) [n=54]	65 (47, 88) [n=54]	1.13 (0.76, 1.67)



(caption on next page)

Fig. 3. Immune responses following third dose vaccination by study arm in the modified intention-to-treat population. CI, confidence interval. Data presented are the geometric means, adjusted geometric mean ratios and their corresponding 95% confidence intervals. The boxes indicate the adjusted geometric mean ratio, and the horizontal lines indicate the corresponding 95% confidence intervals. The geometric mean ratios are adjusted for study site, age, interval between second and third COVID-19 vaccination, any previous positive COVID-19 test, and baseline immunogenicity value as fixed effects. SARS-CoV2 anti-spike antibodies against Wuhan variant were used as a proxy for baseline immunogenicity values in the case of live virus neutralising antibody models where corresponding baseline immunogenicity values were not available. The vertical dotted line refers to an adjusted geometric mean ratio of one and indicates the line of no difference. A confidence interval that lies completely to one side and not intersecting the line of no difference indicates a significant difference in the geometric mean concentrations between the study arm and the reference study arm.

30 and adult BNT-10, respectively, with an aGMR of 0.93 (95% CI 0.75–1.14). On the other hand, the GMC in paediatric BNT-10 was significantly lower than the BNT-30 arm during the whole study period with aGMRs of 0.63 (0.52–0.78), 0.68 (0.55–0.85), and 0.76 (0.61–0.96) at 28-, 84-, and 182-days post-boost. For NVX, the anti-spike IgG GMC was significantly lower at 28 days (aGMR of 0.77, 95% CI: 0.63–0.95), but this difference was no longer significant at 182 days post-boost, with aGMR of 0.86, 95% CI: 0.68–1.09 (Supplementary Figure 6).

Live VNA titres against Victoria were significantly lower in BNT-10 and NVX groups compared with BNT-30 at 28 days post-boost (Supplementary Figure 7). However, across the four COVID-19 vaccine arms, VNA titres against Victoria were not significantly different by the end of the study. There was no statistically significant difference between BNT-10, NVX and BNT-30 groups across all time points for VNA titres against both Omicron BA.5 and XBB.15 except for the paediatric BNT-10 arm, which had significantly lower VNA titres at day 84 against Omicron BA.5 and XBB.15. Similar decay rates were seen across all vaccine groups after excluding breakthrough infections (Fig. 4D-F).

Overall, cellular responses to the Victoria strain were lower in adult and paediatric BNT-10 across all time points compared with BNT30, but only responses in paediatric BNT-10 reached statistical significance (Supplementary Figure 6). There was no statistically significant difference in cellular responses between NVX and BNT-30 arms. A similar cellular response pattern to Omicron was observed between vaccine groups (Supplementary Figure 6). After removing breakthrough infections, a similar pattern of decay was observed between the four COVID-19 vaccine arms (Fig. 4B-C).

Anti-spike IgG, VNA against Victoria strain, and cellular responses to Victoria and Omicron strains at day 210 (28 days following Comirnaty Original/Omicron BA.1 vaccination) in the control arm were similar to the immune responses at day 28 in the BNT-30 arm. However, significantly higher VNA titres against Omicron BA.5 and XBB.15 were observed following Comirnaty Original/Omicron BA.1 vaccination [aGMR of 2.00 (95% CI 1.47–2.71) and aGMR 3.30 (95% CI 2.20–4.95), respectively, (Supplementary Figure 8)].

Overall, 33% of participants experienced breakthrough infection by any definition after vaccination, and all had a two-fold increase in anti-nucleocapsid IgG (Supplementary Table 9, Supplementary Figure 9). The proportion of breakthrough infections by any definition was similar across all study groups, including the control arm [range 14 (26%) in BNT-30 to 20 (36%) in adult BNT-10]. Overall, 6.3% (17/271) of participants self-reported infection detected by COVID-19 lateral flow test (Flowflex) with the lowest proportion observed in the BNT-30 (1/53, 1.9%) and the highest in the control arm (7/54, 13%). A similar pattern was also observed for breakthrough infections defined by a two-fold rise in anti-spike IgG.

Discussion

This is the first reported study to investigate reactogenicity and immunogenicity of heterologous and fractional third dose COVID-19 vaccine schedules following priming with homologous BNT-30 in adolescents. It demonstrates that heterologous COVID-19 immunisation in adolescents is highly immunogenic and well tolerated across all regimens evaluated. This is also the first trial to demonstrate that a 10 µg dose administered using the adult BNT162b2 vaccine formulation is superior to a 10 µg dose administered using the paediatric BNT16b2 formulation (assessed through the day 28 anti-spike IgG response). Reactogenicity was similar across the study arms despite the use of lower vaccine doses, and all vaccine schedules were well tolerated. All study arms elicited robust immune responses though, when compared with BNT-30, paediatric BNT-10 was less immunogenic than the full or partial dose adult formulations.

Adult BNT-10 elicited a superior immune response to paediatric BNT-10 and a comparable immune response to BNT-30 in both the PP and mITT populations when given as a third dose. The significant difference in immunogenicity between the formulations may be accounted for by differences in vaccine constitution or preparation. However, the mechanism of action, active ingredients and list of excipients are identical for both vaccines.[18,19] Vaccine preparation was followed in accordance with the trial vaccine preparation and administration standard operating procedure. Both vaccines share similar preparation steps though differ in the concentration of solution used for dilution: 1.8 mL (adult BNT162b2) versus 1.3 mL (paediatric BNT162b2) of sodium chloride (0.9%). Following dilution, one adult BNT162b2 vial contains 2.25 mL from which six 30 µg doses (each of 0.3 mL) can be extracted, while one paediatric BNT162b2 vial contains 2.6 mL from which ten 10 µg doses (each of 0.2 mL) can be extracted. It is possible that the differences in diluent may have contributed to the significant difference in immunogenicity observed between the formulations with a more concentrated formulation inducing more potent responses.

In this trial, we showed that adult BNT-10 as a third dose generated a robust immune response similar to BNT-30 in 12- to 15-year-olds. Comparable immunogenicity has already been demonstrated between a two-10 µg BNT162b2 dose prime schedule in 5- to 11-year-olds and a two-30 µg BNT162b2 schedule in 18- to 25-year-olds. Correspondingly, when compared to results from the COV-BOOST trial in which adult participants (aged 30 years or older) received 30 µg BNT162b2 as a third dose, higher peak anti-spike IgG antibody concentrations were observed in our study in both the 10 µg adult [61,785 (95% CI 51,598–73,983) and 10 µg paediatric BNT162b2 [43,918 (95%CI 35,978–53,611) groups in adolescents compared with anti-spike IgG concentrations observed after 30 µg BNT162b2 in seropositive adults [37,916 (95% CI 26,907–53,429)] using the same immunoassay.[14] Greater immunogenicity after vaccination has already been documented in children and adolescents than in the adult population.[9,10] Taking into account increasing global SARS-CoV-2 seroprevalence, fractional dosing of adult formulation BNT162b2 may therefore suffice for subsequent ‘booster’ vaccine doses in adolescents to bolster the immune response against infection, should this be required by national agencies, while allowing for more cost-effective and efficient use of vaccine supplies as well as greater vaccine availability and schedule flexibility.

Heterologous COVID-19 booster schedules have been shown to confer enhanced protection against SARS-CoV-2 compared with both primary vaccine and homologous schedules.[13,15,20] However, data on heterologous third dose schedules in children and adolescents are scarce. In Cohort A of the Com-COV3 trial, heterologous second dose NVXCoV2373 following BNT162b2 prime demonstrated enhanced immunogenicity and greater protection against SARS-CoV-2 compared with the licensed two-dose homologous BNT162b2

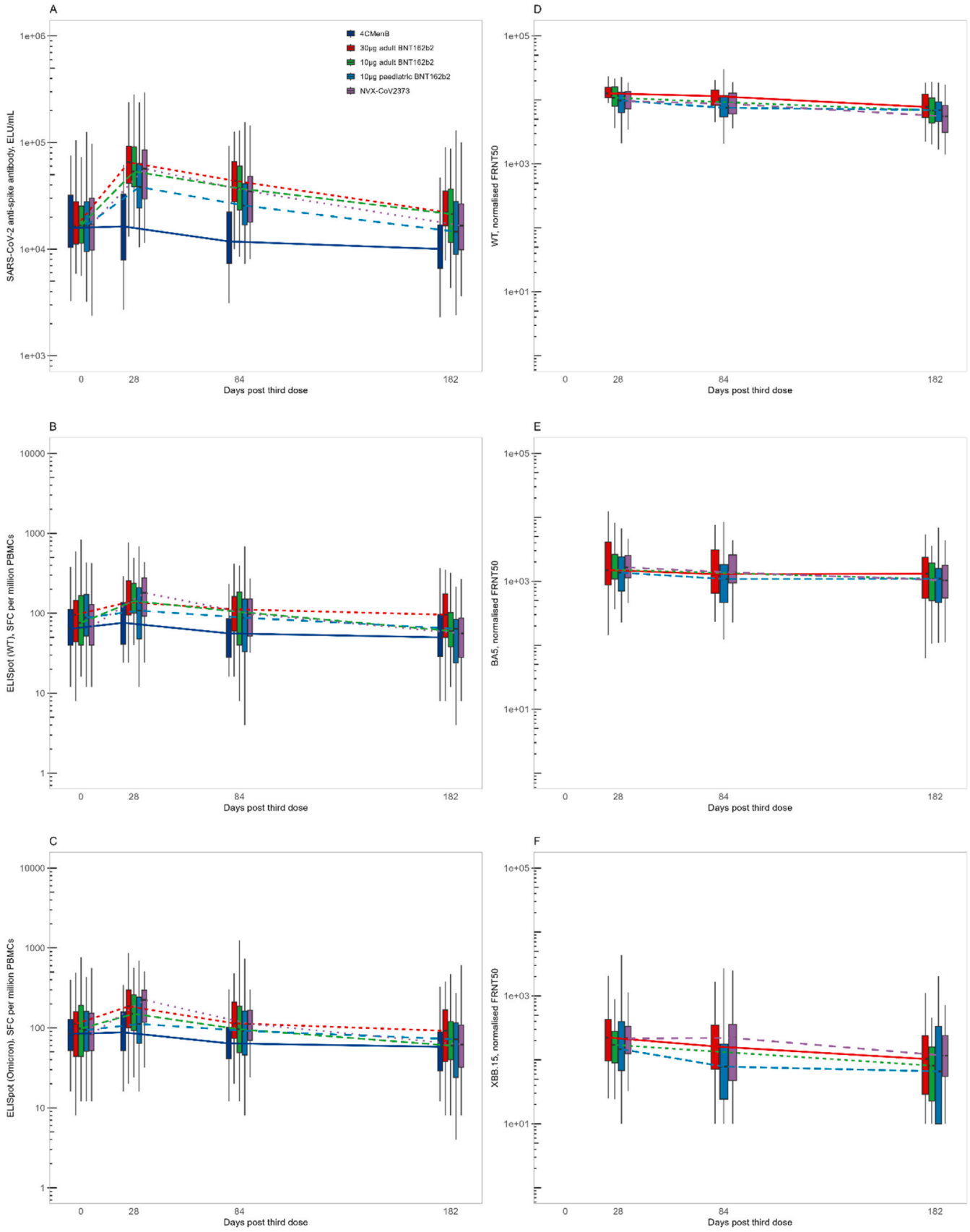


Fig. 4. Kinetics of SARS-CoV-2 anti-spike antibodies, wild-type, BA.5 and XBB.15 live virus neutralising antibodies, and cellular responses to wild-type and Omicron after the third dose in the day 182 modified intention-to-treat population in participants without breakthrough infection. Kinetics of (A) anti-spike IgG (ELU/mL); (B) cellular response to wild-type SARS-CoV-2 (SFC per million PBMCs); (C) cellular response to Omicron (SFC per million PBMCs); (D) live virus neutralising antibody against wild-type SARS-CoV-2 (FRNT50); (E) live virus neutralising antibody against Omicron BA.5 (FRNT50); (F) live virus neutralising antibody against Omicron XBB.15 (FRNT50). The boxplots display the distribution over time, outliers are not displayed. The lines display the change in the median over time. Participants with breakthrough infection were censored at the time of infection.

schedule.[21] In Cohort B, day 28 anti-spike IgG concentrations were significantly lower in the NVX group compared with BNT-30, though by day 182, anti-spike IgG concentrations were not significantly different between the groups. VNA titres and cellular responses were also similar between NVX and BNT-30. When compared with the control arm, the humoral and cellular responses induced by COVID-19 vaccines reduced over time. For example, the GMR dropped from 4.04 at day 28 to 1.88 at day 182 for BNT-30. Our data support the current policy of seasonal vaccination in adolescents at high risk.

Consistent with previous studies in adults,[14,20] we have shown that heterologous third dose vaccination in adolescents is safe, exhibits favourable reactogenicity and demonstrates similar immunogenicity when compared with the licensed homologous vaccine schedule. To our knowledge, only one other study examining heterologous third-dose intramuscular vaccination in adolescents has been published which reports immunogenicity findings after either 30 µg, 15 µg, or 10 µg BNT162b2 third dose vaccination following CoronaVac/BNT162b2 as the primary series.[22] In this study, third dose BNT162b2 vaccination induced robust neutralising activity against the Omicron variant and no significant difference in neutralising antibody titres was detected between the fractional BNT162b2 groups [GMRs of 0.82 95% CI (0.44–1.53) in 15 µg BNT162b2 arm and 0.74 95% CI (0.39–1.39) in 10 µg BNT162b2 arm, BNT-30 as the reference group]. The paediatric formulation was used to administer the 10 µg dose.[22] The findings of this study are consistent with the results reported here showing that BNT-30 and BNT-10 elicit similar neutralising antibody titres against Omicron. We have shown that robust humoral and cellular immune responses are elicited after heterologous COVID-19 vaccination and that persistence of the immune response was well maintained during the six-month follow-up period.

Similar peak humoral and cellular immune responses to the Victoria strain were observed between the bivalent Original/Omicron BA.1 and BNT-30 vaccines. However, significantly higher VNA titres against Omicron BA.5 and XBB.15 were observed in the bivalent Original/Omicron BA.1 group compared with BNT-30. In line with previous studies, these results suggest that boosting with bivalent vaccines targeting variant strains generates enhanced neutralising antibody activity against related subvariants.[23] However, the longer interval prior to vaccination and the occurrence of SARS-CoV-2 infections during this time may have influenced these findings.

This study had several limitations. Although the study achieved the total effective sample size required to fulfil the primary objective of the trial, recruitment was challenging and was stopped after one year following discussion with the TSC. We did not reach an equal number between the two BNT-10 arms (53 versus 51) for the primary analysis, but the impact on the study was negligible. Most study participants were white, and therefore not representative of the general population, limiting the potential wider applicability of the results. The age range of participants included in the study was narrow, limiting the generalisability of the results. Although we investigated the effect of vaccine interval on immunogenicity, the follow-up period for the control group was too short to assess immune persistence in this group. Similarly, a follow-up of just six months post-third dose in the vaccine arms does not allow for a longer-term assessment of immune persistence.

In conclusion, this study demonstrates that heterologous and fractional third dose COVID-19 vaccine schedules in adolescents are highly immunogenic and well-tolerated. Adult BNT-10 was shown to be superior to paediatric BNT-10 and comparably immunogenic to BNT-30. This study provides support for the use of heterologous third dose COVID-19 vaccine schedules in adolescents and for fractional adult BNT162b2 as an alternative to the paediatric formulation in adolescent booster campaigns.

Author contributions

MDS, XL and JSN-V-T conceived the trial; MDS was the chief investigator until September 2022 and subsequently AMM took over this role. MDS, PdW, XL, MG, and EK contributed to the protocol and design of the study. GM, EK, ELP, and SK led the implementation of the study. XL and MG performed the statistical analysis and have verified the underlying data. EK, MG, AMM, and XL drafted the manuscript. All other authors contributed to the implementation and data collection. All authors reviewed and approved the final report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Data availability

The study protocol is provided in the Supplement. Individual participant data will be made available when the trial is complete, upon requests directed to the corresponding author; after approval of a proposal, data can be shared through a secure online platform.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MDS acted until September 2022 on behalf of the University of Oxford as an Investigator on research studies funded or supported by the vaccine manufacturers GlaxoSmithKline, Janssen, AstraZeneca, Novavax, MCM vaccines and Pfizer. He received no direct personal benefit for this work. From September 2022 he has been an employee at Moderna Biotech and holds stock options in this company. SNF acts on behalf of University Hospital Southampton NHS Foundation Trust as an Investigator and/or providing consultative advice on clinical trials and studies of COVID-19 and other vaccines funded or sponsored by vaccine manufacturers including Janssen, Pfizer, BioNTech, AstraZeneca, GlaxoSmithKline, Sanofi, Merck, Moderna, and Valneva vaccines and antimicrobials. He receives no personal financial payment for this work. KC acts on behalf of University Hospital Southampton NHS Foundation Trust as an investigator and/or providing consultative advice on studies funded or sponsored by vaccine manufacturers including AstraZeneca, GlaxoSmithKline, Janssen, Medimmune, Merck, Pfizer, Sanofi, Iliad and Valneva. She receives no personal financial payment for this work. AMM acts on behalf of the University of Oxford as an investigator on research studies funded +/- sponsored by vaccine manufacturers including Pfizer, GlaxoSmithKline, Janssen, Valneva SE and Novavax. She receives no personal financial benefit for this work. PTH acts on behalf of St George's University of London as an Investigator on clinical trials and studies of COVID-19 vaccines funded or sponsored by vaccine manufacturers including Janssen, Pfizer, AstraZeneca, Moderna, Novavax and Valneva. He receives no personal financial payment for this work. He is a member of the JCVI. JSN-V-T was seconded to the Department of Health and Social Care (DHSC) from October 2017-March 2022 as Deputy Chief Medical Officer, England, receiving no benefits, other than salary, for this work. Since leaving DHSC he has received a lecture fee from AstraZeneca and undertaken paid consulting for Moderna BioTech. The views expressed in this paper are those of its authors and not necessarily those of DHSC or JCVI.

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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.2025.106663.

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