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Reactogenicity, immunogenicity and breakthrough infections following heterologous or fractional second dose COVID-19 vaccination in adolescents (Com-COV3): A randomised controlled trial

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SUMMARY

Background: This was the first study to investigate the reactogenicity and immunogenicity of heterologous or fractional second dose COVID-19 vaccine regimens in adolescents.
Methods: A phase II, single-blind, multi-centre, randomised-controlled trial recruited across seven UK sites from September to November 2021, with follow-up visits to August 2022. Healthy 12-to-16 years olds were randomised (1:1:1) to either 30 μg BNT162b2 (BNT-30), 10 μg BNT162b2 (BNT-10), or NVX-CoV2373 (NVX), 8 weeks after a first 30 μg dose of BNT162b2. The primary outcome was solicited systemic reactions in the week following vaccination. Secondary outcomes included immunogenicity and safety. 'Breakthrough infection' analyses were exploratory.
Findings: 148 participants were recruited (median age 14 years old, 62% female, 26% anti-nucleocapsid IgG seropositive pre-second dose); 132 participants received a second dose. Reactions were mostly mild-to-

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Adolescents
Breakthrough infection
BNT162b2
NVXCoV2373

moderate, with lower rates in BNT-10 recipients. No vaccine-related serious adverse events occurred. Compared to BNT-30, at 28 days post-second dose anti-spike antibody responses were similar for NVX (adjusted geometric mean ratio [aGMR]) 1.09 95% confidence interval (CI): 0.84, 1.42] and lower for BNT-10 (aGMR 0.78 [95% CI: 0.61, 0.99]). For Omicron BA.1 and BA.2, the neutralising antibody titres for BNT-30 at day 28 were similar for BNT-10 (aGMR 1.0 [95% CI: 0.65, 1.54] and 1.02 [95% CI: 0.71, 1.48], respectively), but higher for NVX (aGMR 1.7 [95% CI: 1.07, 2.69] and 1.43 [95% CI: 0.96, 2.12], respectively). Compared to BNT-30, cellular immune responses were greatest for NVX (aGMR 1.73 [95% CI: 0.94, 3.18]), and lowest for BNT-10 (aGMR 0.65 [95% CI: 0.37, 1.15]) at 14 days post-second dose. Cellular responses were similar across the study arms by day 236 post-second dose. Amongst SARS-CoV-2 infection naïve participants, NVX participants had an 89% reduction in risk of self-reported 'breakthrough infection' compared to BNT-30 (adjusted hazard ratio [aHR] 0.11 [95% CI: 0.01, 0.86]) up until day 132 after second dose. BNT-10 recipients were more likely to have a 'breakthrough infection' compared to BNT-30 (aHR 2.14 [95% CI: 1.02, 4.51]) up to day 132 and day 236 post-second dose. Antibody responses at 132 and 236 days after second dose were similar for all vaccine schedules.

Interpretation: Heterologous and fractional dose COVID-19 vaccine schedules in adolescents are safe, well-tolerated and immunogenic. The enhanced performance of the heterologous schedule using NVX-CoV2373 against the Omicron SARS-CoV-2 variant suggests this mRNA prime and protein-subunit boost schedule may provide a greater breadth of protection than the licensed homologous schedule.

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Trial Registration: International Standard Randomised Controlled Trial Number registry: 12348322.

Introduction

Paediatric immunisation against SARS-CoV-2 has now been recommended in the majority of high-income countries, particularly in light of the sharp increase in infection rates in children and paediatric hospitalisations worldwide following the emergence of highly transmissible SARS-CoV-2 variants of concern (VOC).[1]

An increased incidence of myocarditis has been observed following receipt of a second dose of an mRNA-based COVID-19 vaccine, particularly in male adolescents, with up to 105.9 cases per million reported.[2] This risk may be reduced by using another vaccine or fractional dose for the second vaccination (a mixed schedule), or variation to dose intervals.[3]

Heterologous vaccination schedules in adults have been shown to be safe and immunogenic and have been implemented in Canada and northern Europe.[4] They have been approved by the World Health Organisation to enhance vaccination coverage, particularly where supplies are limited.[5] In the Com-COV2 trial a heterologous COVID-19 vaccine schedule utilising the Matrix-M adjuvanted recombinant nanoparticle spike protein vaccine NVX-CoV2373 (Novavax) as the second dose following BNT162b2 (Pfizer-BioNTech), was found to be less immunogenic in 50-to-70-year-olds than two doses of BNT162b2. The BNT/NXV-CoV2373 schedule was, however, still more immunogenic than two doses of the adenoviral-vectored ChAdOx1 n-CoV-19 (Oxford/AstraZeneca) vaccine, which is highly effective against hospitalisation and death.[4,6]

Fractional dose BNT162b2 schedules are now approved for 5-to-11-year-olds. A phase 2/3 study in participants aged 5 to 11 years showed a homologous two-dose regimen of 10 μg BNT162b2 induced immune responses comparable to that of a two-dose regimen of 30 μg BNT162b2 administered to 16-to-25-year-olds and was associated with a lower incidence of systemic adverse events.[7]

No data have previously been published on the safety, immunogenicity, and efficacy of mixed and fractional COVID-19 vaccine schedules in an adolescent population. Here we report a randomised controlled trial to determine the reactogenicity, immunogenicity, and number of SARS-CoV-2 infections in adolescents receiving 30 μg BNT162b2 as a first dose and a second dose of either 30 μg BNT162b2 (schedule hereafter referred to as BNT-30), 10 μg BNT162b2 (schedule hereafter referred to as BNT-10), or NVX-CoV2373 (schedule hereafter referred to as NVX) given at least 8 weeks later.

Methods

Study design

Com-COV3 is a single-blind, randomised, phase II, multi-centre study to determine the reactogenicity and immunogenicity of mixed COVID-19 vaccine schedules in adolescents. The study consists of two cohorts. This paper reports the results of the first cohort investigating the reactogenicity and immunogenicity of heterologous and fractional second-dose COVID-19 vaccine schedules in adolescents. The second cohort will examine mixed third-dose COVID-19 vaccine schedules in adolescents and will be reported separately. Recruitment for the first cohort commenced on 27th September 2021 and occurred across seven UK National Health Service and academic institutions. The study was approved by the South-Central Berkshire Research Ethics Committee (21/SC/0310) and the Medicines and Healthcare Products Regulatory Agency. The Consolidated Standards of Reporting Trials (CONSORT) guideline was followed. The study protocol is accessible at https://comcovstudy.org.uk/study-protocol.

We report here the safety, including adverse events (AEs) of special interest (AESIs) and serious AEs (SAEs), reactogenicity, immunogenicity, and breakthrough infections of mixed COVID-19 vaccine schedules following the second vaccination up until database lock on 24th March 2023.

Changes to the planned protocol

Following a change to the UK national immunisation policy on 29th November 2021 recommending that all 12-to-15-year-olds should be offered a second dose of 30 μg BNT162b2, the study design was reviewed with the Trial Steering Committee. Recruitment to the study was stopped (thus the pre-planned sample size was not met), and the study was amended to focus on the immune response to BNT162b2. After this date, enroled participants who had not yet received their second vaccination were randomised to either BNT-30 or BNT-10. Participants were no longer randomised to the NVX study arm in order to prioritise those groups more likely to inform UK immunisation policy.

Participants

Adolescents aged 12 to 16 years inclusive, who were COVID-19 vaccine naïve or had received a single dose of 30 μg BNT162b2, were

eligible. 'High-risk' individuals who were advised to receive additional doses of BNT as part of the UK COVID-19 vaccination programme (e.g., confirmed, or suspected immunosuppressive condition or serious chronic illness) were excluded. Previous SARS-CoV-2 infection was not an exclusion criterion. (See https://comcovstudy.org.uk/study-protocol for protocol eligibility criteria).

Randomisation and masking

Computer-generated randomisation lists were prepared by the study statistician. Participants were randomised 1:1:1 at the time of their second vaccination to BNT-30, BNT-10, or NVX. After 29th November 2021, when UK national immunisation policy changed to offer all 12-to-15-year-olds a second dose of BNT162b2, a protocol amendment was implemented and participants who had already received their first dose of BNT162b2 within the study were randomised 1:1 to receive 30 µg BNT162b2 or 10 µg BNT162b2 as a second dose.

Randomisation was performed using block randomisation. Block sizes of three and six were used before 29th November 2021, and block sizes of two and four were used thereafter. Randomisation was stratified by the study site and baseline anti-nucleocapsid IgG serostatus.

Participants were blinded to allocation until one month after the second dose. To maintain the blind, vaccines were prepared out of sight of the participant, and masking tape applied to the vaccine syringe. Laboratory staff were blinded to the study arm, staff involved in the study delivery were not. Statisticians were unblinded throughout the trial.

Procedures

Informed consent was obtained from participants aged 16 years or from their parents or guardians if younger than 16 years and written assent was obtained from participants aged 12 to 15 years. All participants and parents had the opportunity to read the participant information sheet (customised versions available for parents, participants aged 16 years, and 12 to 15 years to enhance comprehensibility) and to discuss trial participation with a member of the study team before signing the consent form. COVID-19 vaccine naïve participants attended a screening/enrolment visit and those eligible received a 30 µg BNT162b2 first dose. Participants who had received 30 µg BNT162b2 in the community attended a screening visit 8 weeks afterwards. All participants were randomised and vaccinated at least 8 weeks after their first dose. Two vaccines were used in the study and administered by intramuscular injection in the upper arm. 30 µg BNT162b2 was given as 0.3 ml, 10 µg BNT162b2 as 0.1 ml, and NVXCoV2373 as 0.5 ml injection.

At the time of this study, community testing for SARS-CoV-2 was free, widely available and conducted either in response to symptoms or as screening. Participants recorded in electronic diaries all SARS-CoV-2 infections (classified as AESIs) detected by community-based self-testing with either PCR or rapid antigen test, along with all solicited and unsolicited AEs (Fig. 1), hospital visits and vigorous exercise (to aid interpretation of cardiac marker results).

Sera were analysed using electrochemiluminescence immunoassays (ECLIA) at the UK Health Security Agency, Porton Down, UK Health Security Agency. Anti-nucleocapsid antibodies were determined using Roche Elecsys® Anti-SARS-CoV-2 ECLIA with a cut-off index value of 1.0 or greater considered positive. Antibodies (total Ig) against the SARS-CoV-2 spike (S) receptor binding domain were measured using the Elecsys® anti-SARS-CoV-2 spike assay, specifically targeting the RBD domain of the SARS-CoV-2 spike protein. Samples ≥0.8 U/ml were considered positive, with results 1:1 to Binding Antibody Units/ml (BAU/ml).[8] Serum neutralising ability against SARS-CoV-2 Victoria (a Wuhan-related strain isolated early in the pandemic), Omicron BA.1 or BA.2 strains was measured using Focus Reduction Neutralisation Test ($FRNT_{50}$) as previously described.[9] Blood sample collection took place at baseline (day 0), immediately prior to the second dose, and at days 14, 28, 132, and 236 following the second dose.

IFN-γ secreting T-cells specific to whole spike protein epitopes, designed based on the Wuhan-Hu-1 sequence (YP_009724390.1), were detected using T-SPOT-*Discovery*, ELISpot Test 14 (full spike, Wuhan) at Oxford Immunotec (Abingdon, UK) using peripheral blood mononuclear cells (PBMCs) within 32 h of venepuncture (T-cell Xtend reagent added to extend PBMC survival). T-cell frequencies were reported as spot-forming cells (SFC) per 250,000 PBMCs per well with a lower limit of detection (LLOD) of one in 250,000 PBMCs.

Serum samples were kept frozen at -80^0 C prior to analysis and measured for NT-proBNP and troponin I using the Abbott Architect i2000 analyser (Abbott Laboratories Ltd., Maidenhead, UK). The LLOD for NT-proBNP was 8.2 ng/L and 2.0 ng/L for troponin.[10]

Outcomes

The primary outcome was solicited systemic reactions for seven days after the second immunisation of mixed COVID-19 vaccine schedules. Secondary outcomes included solicited local reactions, immunogenicity (anti-spike immunoglobulins [total Ig], cellular responses by ELISpot), safety (AEs, SAEs and AESIs), cardiac markers (NT-proBNP and troponin), and characterisation of anti-nucleocapsid IgG seropositivity at baseline and subsequent seroconversion. The incidence of self-reported SARS-CoV-2 infections was determined as an exploratory objective, as were neutralising antibodies (NAb) against the ancestral Wuhan strain and variants of concern.

Statistical analysis

The primary outcome analysis was conducted on the safety analysis population and included participants who received a second vaccine in the study. The maximum severity for each solicited systemic AE across seven days after the second vaccination was derived for each participant and summarised by group. Analyses were conducted similarly for local reactogenicity.

Immunogenicity analyses were conducted on the modified intention-to-treat (mITT) populations at 28, 132 and 236 days following the second vaccination overall and stratified by pre-second dose serostatus (defined by anti-nucleocapsid value pre-second dose or pre-first dose if missing). The mITT populations excluded participants who withdrew, had no blood sample, received a third dose in the community before their visit or self-reported a SARS-CoV-2 infection within 14 days after the second vaccination. Immunogenicity outcomes were summarised using geometric mean concentrations (GMCs) and 95% confidence intervals (CIs). Adjusted geometric mean ratios (aGMRs) and 95% CIs were calculated comparing groups to BNT-30 as the reference, adjusting for study site in the linear regression models.

Immunogenicity secondary and sensitivity analyses were conducted on anti-spike antibodies 28 days after the second vaccination. Secondary analyses were further adjusted for pre-second dose anti-spike antibodies and intervals between two doses. Sensitivity analyses were conducted on the per-protocol population, excluding those randomised after 29th November 2021, and excluding those who self-reported a SARS-CoV-2 infection within 28 days after second vaccination. Immunogenicity sensitivity analyses were conducted on anti-spike antibodies at 132 and 236 days after second vaccination excluding participants who were considered to have had an infection before their visit. A 'breakthrough infection' between the second dose and day 236 visit was defined as either: a self-reported SARS-CoV-2 infection > 14 days after second dose, a two-fold

Fig. 1. Severity of solicited adverse reactions in days 0–7 after second vaccination by study arm as self-reported in participant electronic diaries in the safety analysis population. BNT-30: BNT162b2 30 µg; BNT-10: BNT162b2 10 µg; NVX: NVX-CoV2373. 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 two self-reported SARS-CoV-2 infections in days 0–7 after the second vaccination both occurring in the NVX-CoV2373 study arm. The first participant self-reported 6 days after second vaccination had a grade 1 headache on day 6. The second participant self-reported 7 days after the second vaccination had a grade 1 headache and grade 1 fatigue on day 5.

rise in anti-nucleocapsid IgG, a two-fold rise in anti-spike antibodies, 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.

Exploratory survival analyses were conducted and included self-reported SARS-CoV-2 infections which occurred during follow-up using Kaplan-Meier curves and Cox regression models. Infections from 14 days after the second vaccination were considered events. Participants were censored at the date of either: self-reported SARS-CoV-2 infection within 14 days of second dose inclusive, third dose vaccination in the community, withdrawal, visit date, or either 132 or 236 days after the second vaccination if the visit was missed and no infection was self-reported, whichever came first. Survival analyses were conducted separately for participants randomised to three study arms before 29th November 2021 and for participants randomised to BNT-30 or BNT-10 study arms for the entire recruitment period.

Analyses on AEs and cardiac markers were conducted using the safety analysis population including all participants who received a study vaccine. The proportions above the LLOD and individual profiles were presented. The proportion of participants with at least one safety event was reported by the study arm.

The primary analysis was descriptive therefore no formal sample size calculation was conducted. The sample size was up to 270 participants (90 per arm); however, on the advice of the Trial Steering Committee, recruitment stopped following the UK Joint Committee on Vaccination and Immunisation (JCVI) recommendation for routine administration of a second BNT162b2 dose for all 12-to-16-year-olds. No formal significance tests were conducted. Statistical analyses were performed using R version 4.1.3 and SAS version 9.4.

Results

Between 27th September and 29th November 2021, 179 volunteers were screened across seven UK sites, and 148 participants were enroled. Of these participants, 81 received their first vaccination in the trial. Sixteen participants withdrew prior to randomisation before second vaccination. Prior to 29th November, 117 participants were randomised to three study arms (Fig. 1, Supplement). Following an amendment to remove the NVX arm, a further 15 participants were randomised to two study arms. In total, 132 participants were randomised and received a second dose in the trial. Recruitment occurred prior to a period of increased SARS-CoV-2 infections, initially due to the Delta Variant, and subsequently Omicron BA.1 and BA.2 (Fig. 2, Supplement).

Of all 148 participants enroled, the median age was 14 years (range 12–17), 62% were female, and six participants (4%) were from an ethnic minority group (Table 2, Supplement). Forty-eight participants were randomised to BNT-30, 47 to BNT-10 and 37 to NVX. The median interval between two doses was 59 days (range 56–109) and was similar across the study arms. Of 132 participants randomised, 65 received their first dose in the trial, of whom 19% were positive for SARS-CoV-2 anti-nucleocapsid IgG prior to their first dose. Seropositivity increased to 30% prior to the second dose.

Generally, solicited systemic adverse reactions occurred more frequently in BNT-30 and NVX groups compared to BNT-10, while solicited local reactions were least common in the NVX group (Fig. 1). Most reactions were mild-to-moderate, with no clear difference in the frequency of severe reactions across the groups. There was no clear difference in the frequency or severity of reactions when stratified by serostatus (Fig. 3, Supplement). These findings were reflected in paracetamol usage after the second dose (Table 3, Supplement).

Two SAEs occurred: the first 4 months after the second vaccination (toxic substance ingestion, considered unrelated to immunisation), the second seven months after vaccination (anorexia nervosa, also considered unrelated to immunisation) (Table 4, Supplement). There were 65 AESIs, all of which were self-reported SARS-CoV-2 infections (Table 5, Supplement). Unsolicited AEs are reported in Table 6, Supplement. Almost all participants had a troponin value below the LLOD after the second vaccination (Table 7, Supplement). At 14 days post-second vaccination, detectable troponin levels were seen in seven participants, with all but one participant (3.5 ng/L) reporting prior vigorous exercise (Tables 7 and 8, Supplement and Fig. 4, Supplement). NT-proBNP values were similar before and after second vaccination and were comparable across the study arms (Fig. 5, Supplement).

Overall, BNT-30 and NVX groups had the highest and comparable anti-spike antibody concentrations post-immunisation with GMC of 19,005 BAU/ml (95% CI: 15,916, 22,694) and 20,172 (95% CI: 16,128, 25,230) respectively, at 28 days post-second dose (Fig. 2) (aGMR for NXV versus BNT-30: 1.09 [95% CI: 0.84, 1.42]). By contrast, the BNT-10 group value was 14,408 BAU/ml (95% CI: 12,438, 16,689; aGMR versus BNT-30: 0.78 [95% CI: 0.61, 0.99]). Amongst participants who were anti-nucleocapsid antibody negative prior to their second dose (hereafter referred to as seronegative participants), anti-spike antibody concentrations 28 days after the second dose were lower in BNT-10 compared to BNT-30 recipients (aGMR 0.70 [95% CI: 0.53, 0.93]). Conversely, seronegative NVX recipients tended to have higher anti-spike antibody concentrations than BNT-30 recipients (aGMR 1.33 [95% CI: 0.98, 1.79]). Amongst seropositive pre-second dose participants (hereafter referred to as seropositive participants), BNT-10 and BNT-30 recipients had similar anti-spike antibody concentrations (aGMR 0.98 [95% CI: 0.65, 1.46]), however seropositive NVX participants had lower concentrations than BNT-30 recipients (aGMR 0.60 [95% CI: 0.37, 0.95]) and had the lowest response among any serostatus and study arm subgroup (GMC 11,723 BAU/ml [95% CI: 7573, 18,146]). Similar results were observed across sensitivity and secondary analyses (Table 9, Supplement).

The aGMRs between the NAb titres ($FRNT_{50}$) against the Victoria, relative to BNT-30, followed a similar pattern to those of binding antibodies at 28 days after second dose (Fig. 2). However, NVX participants demonstrated higher titres compared with BNT-30 against both Omicron strains with aGMRs of 1.7 (95% CI: 1.07, 2.69) (BA.1) and 1.43 (95% CI: 0.96, 2.12) (BA.2) (Fig. 3). This was most pronounced in seronegative NVX recipients with aGMRs of 1.95 (95% CI: 1.18, 3.23) (BA.1) and 1.74 (95% CI: 1.07, 2.84) (BA.2). For BNT-10 recipients, titres were similar to BNT-30 recipients irrespective of serostatus prior to the second dose.

Cellular immune responses against wild-type virus at 14 days after the second vaccination were greatest in the NVX group (GMC 121 SFC/10^6 PBMCs [95% CI: 73, 200]), followed by BNT-30 (GMC 75 SFC/10^6 PBMCs [95% CI: 50, 114]) (Fig. 2). Similar patterns were seen in both seropositive and seronegative subgroups; however, responses were consistently higher in seropositive participants across all groups.

Exploratory analyses were conducted on 'breakthrough infections'. Fifty-one self-reported SARS-CoV-2 infections occurred during follow-up; two within one week following the second vaccination, 36 (considered 'breakthrough infections') between 14 and 132 days after the second vaccination, and 13 after day 132 (Table 5, Supplement). In participants randomised before 29th November in the mITT population, 36 self-reported 'breakthrough infections' occurred during follow-up (n = 32/36 had serological evidence of infection) and there was a difference in proportions across groups, with rates highest in BNT-10 and lowest in NVX recipients (Table 10, Supplement and Fig. 6, Supplement). Nearly all self-reported 'breakthrough infections' occurred in seronegative participants (n = 33/36). An additional 25 participants had serological evidence of infection without self-reporting, such that the proportion of probable 'breakthrough infections' by any definition up to day 236 was 66% in BNT-30, 69% in BNT-10% and 62% in the NVX group (Table 10,

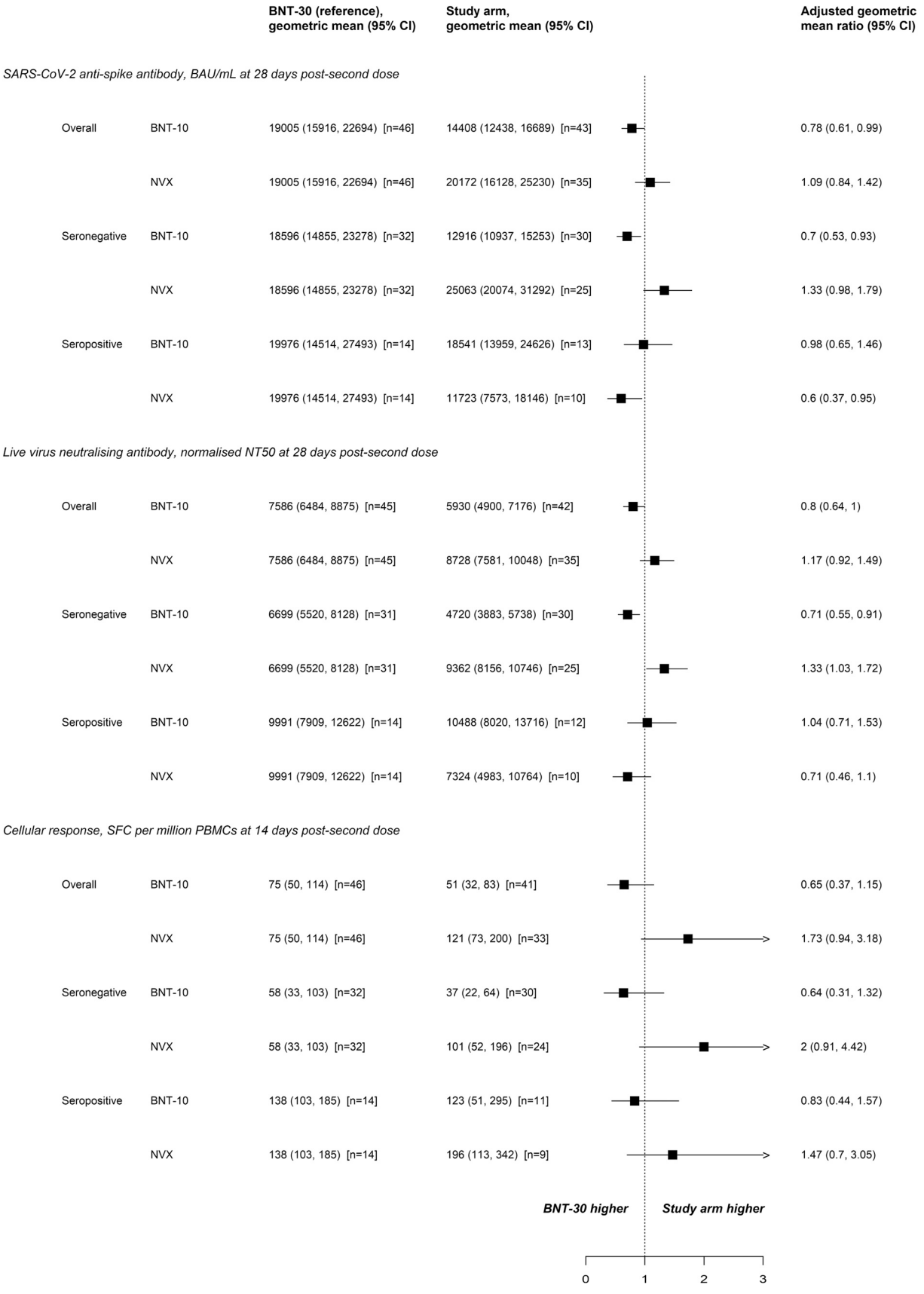

Fig. 2. Immune responses at day 28 (humoral), and day 14 (cellular) after the second vaccination, by study arm and pre-second dose serostatus in the day 28 modified intention-to-treat populations. BNT-30: BNT162b2 30 µg; BNT-10: BNT162b2 10 µg; NVX: NVX-CoV2373; CI: confidence interval. Data presented 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 between BNT-30 and either BNT-10 or NVX are adjusted for the study site as a fixed effect. 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 BNT-30 study arm.

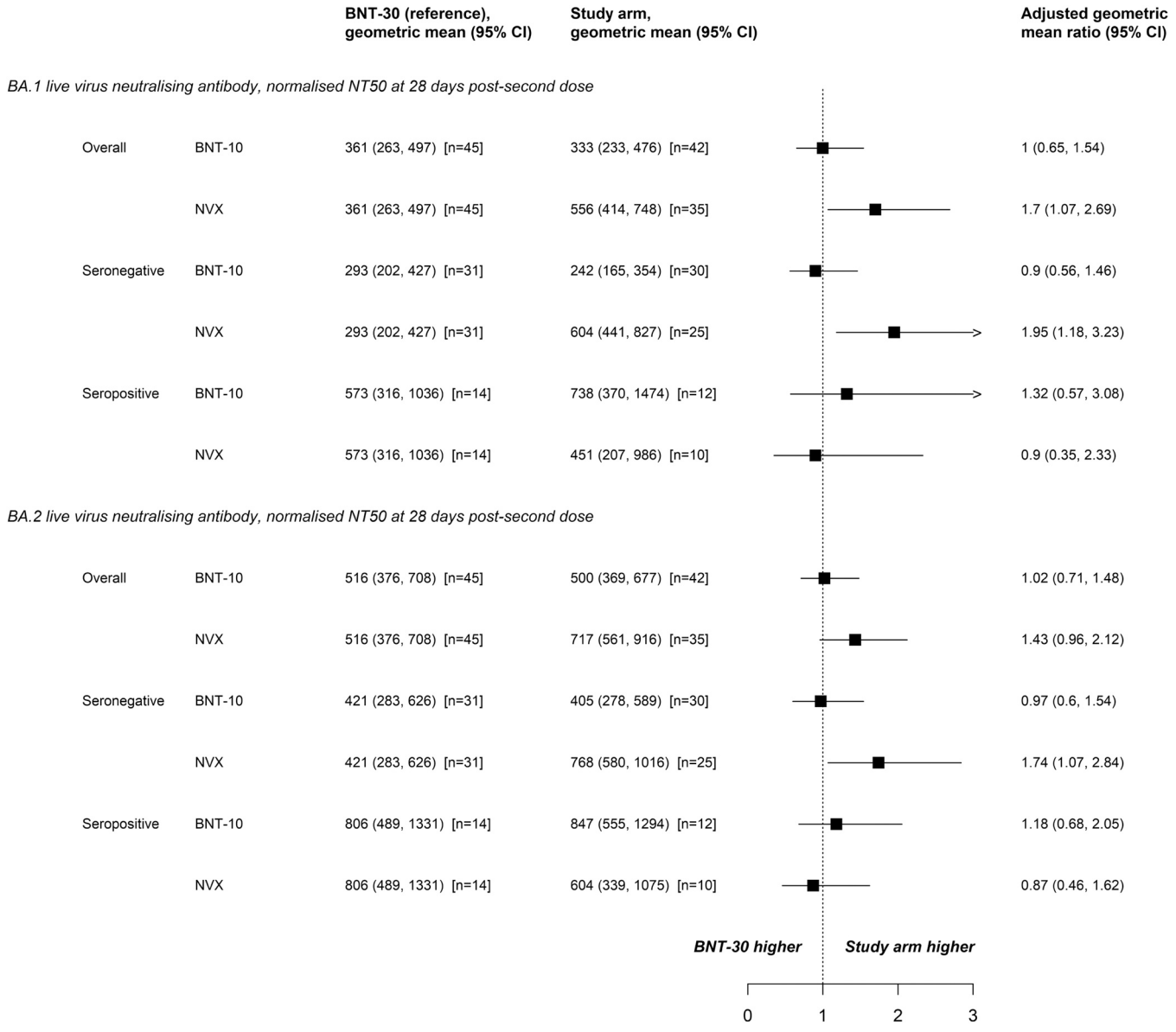

Fig. 3. Neutralising activity against Omicron BA.1 and BA.2 variants by study arm and serostatus pre-second dose at 28 days after the second vaccination in the day 28 modified intention-to-treat population. BNT-30: BNT162b2 30 µg; BNT-10: BNT162b2 10 µg; NVX: NVX-CoV2373; CI: confidence interval. Data 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 between BNT-30 and either BNT-10 or NVX are adjusted for study site as a fixed effect. 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 BNT-30 study arm.

Supplement). When limited to seronegative participants, this was 81%, 89% and 72% respectively.

There was a difference in the risk of self-reported 'breakthrough infections' across the study arms for participants randomised before 29th November in the mITT population (Fig. 4A). This difference was most evident for seronegative participants (Fig. 4B). For infections up to day 132 post second dose, seronegative NVX participants had an 89% reduction in the adjusted risk of a 'breakthrough infection' compared to BNT-30 [adjusted hazard ratio (aHR) 0.11 (95% CI: 0.01, 0.86)] (Fig. 7A, Supplement). The conclusions from the sensitivity analyses were similar (Fig. 7A, Supplement). The trends remained similar in the longer-term follow-up to day 236 (Fig.7B, Supplement).

In participants randomised to BNT-10 or BNT-30 across the whole study in the mITT population, there were 35 self-reported 'breakthrough infections' (Table 11, Supplement). The proportion was approximately half as many in the BNT-30 group (33% versus 57%). Twenty participants had serological evidence of infection without self-reporting, resulting in 55 'breakthrough infections' by any definition, 44 of which occurred in seronegative participants. For infections up to day 132 following the second dose, BNT-10 participants were more than twice as likely to have a 'breakthrough infection' compared to BNT-30 participants [aHR 2.14 (95% CI: 1.02, 4.51)] (Fig. 4D and Fig. 7A, Supplement). This was again greater for seronegative participants (aHR 2.40 [95% CI: 1.14, 5.05]) (Fig. 4E and Fig. 7A, Supplement). The conclusions from the sensitivity analyses were similar (Fig. 7A, Supplement). For infections up to day 236 post-second dose, the trend remained similar in all participants (aHR 1.97 [95% CI: 1.02, 3.81]), and seronegative participants (aHR 1.91 [95% CI: 0.97, 3.78]) (Fig. 7B, Supplement).

The persistence of humoral and cellular immune responses to immunisation was assessed at 132 and 236 days after the second

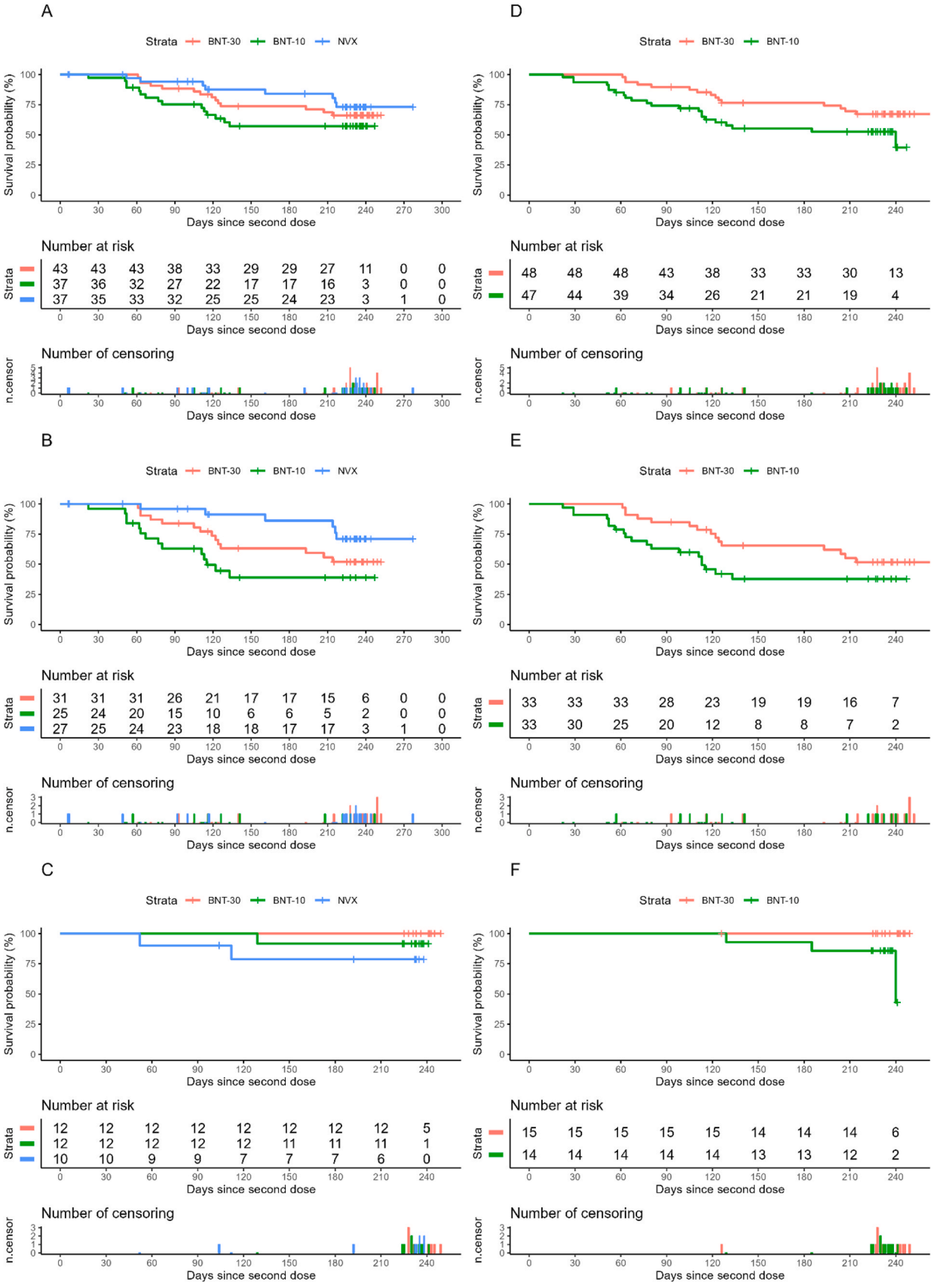

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Fig. 4. Kaplan–Meier curves for risk of self-reported SARS-CoV-2 infections during follow-up. A: participants randomised before 29th November 2021; B: seronegative participants randomised before 29th November 2021; C: seropositive participants randomised before 29th November 2021; D: participants randomised to BNT-30 or BNT-10 during the recruitment period; E: seronegative participants randomised to BNT-30 or BNT-10 during the recruitment period; F: seropositive participants randomised to BNT-30 or BNT-10 during the recruitment period. BNT-30: BNT162b2 30 μg; BNT-10: BNT162b2 10 μg; NVX: NVX-CoV2373. Self-reported SARS-CoV-2 infections occurring from > 14 days following the second dose were considered an event. Participants were censored at the date of either: self-reported SARS-CoV-2 infection within 14 days of second dose inclusive, third dose vaccination in the community, withdrawal, day 236 visit, or 236 days after the second vaccination if day 236 visit was missed and no infection was self-reported, whichever came first. A vertical step down on the curve indicates a self-reported SARS-CoV-2 infection and a tick mark on the curve indicates a censored event. Participants were randomised 1:1:1 at the time of their second vaccination to BNT-30, BNT-10, or NVX. After 29th November 2021, when UK national immunisation policy changed to offer all 12-to-15-year-olds a second dose of BNT, recruitment stopped and participants who had already received their first dose of BNT within the study were randomised 1:1 to receive 30 μg BNT162b2 or 10 μg BNT162b2 as a second dose.

dose. In the mITT population, anti-spike antibody values were similar for BNT-10 and NVX compared with BNT-30 participants overall at each timepoint. (Fig. 5, Supplementary Fig. 8). However, anti-spike antibody values were highest for seronegative NVX participants at both timepoints. There were no differences in fold-changes after the second dose and the waning over time was similar across the groups (Fig. 5 and Fig. 8, Supplement). In seropositive participants, convergence of the humoral immune response was observed by 132 days after the second dose, with anti-spike antibodies returning to pre-second dose values (Fig. 5C).

However, sensitivity analyses for participants in the day 132 mITT population with no 'breakthrough infections, and therefore, no boosting by infection, showed seronegative BNT-10 participants to have lower anti-spike antibody concentrations compared with BNT-30 participants (aGMR 0.54 [95% CI: 0.31, 0.94]) (Fig. 5D and Fig. 9, Supplement). Across the three study groups, amongst seronegative participants with 'breakthrough infections' no waning of anti-spike antibody responses was evident from the second vaccination to day 236 (Fig. 5F).

The cellular immune response against wild-type virus at 132 days after the second vaccination was similar across the groups (Fig. 8, Supplement); however, responses tended to be highest in seropositive BNT-10 and NVX participants compared with BNT-30. Conversely, seronegative BNT-30 participants tended to have higher responses compared with BNT-10 and NVX participants. Cellular responses across the study arms were similar at day 236. Responses for NVX participants were almost halved from day 14 (GMC 121 SFC/10^6 [95% CI: 73, 200]) (Fig. 3) to 236 after the second dose (GMC 75 [95% CI: 49, 114], fold-change 0.4 [95% CI: 0.3, 0.6]) (Fig. 8, Supplement).

Discussion

This study demonstrated that NVX following a first dose of 30 μg BNT162b2 elicited robust humoral and cellular immune responses, with higher neutralising titres against Omicron BA.1 and BA.2 variants than BNT-30. While the lowest antibody response occurred in the BNT-10 group, seropositive BNT-10 participants demonstrated antibody responses comparable to BNT-30 and, irrespective of serostatus, elicited similar NAb titres to BNT-30 against Omicron BA.1 and BA.2 variants. BNT-10 recipients had the least reactogenic profile, and no safety concerns were identified in any group. However, during a wave of predominantly Omicron variant infections, differences in the risk of self-reported SARS-CoV-2 infection were evident across the study arms. Amongst participants naïve to SARS-CoV-2 infection at the time of the second dose, the lowest risk of SARS-CoV-2 infection was observed in the NVX group, which elicited the highest humoral and cellular immune response overall across the study groups.

The NVX and, especially, BNT-10 schedules studied here had favourable side-effect profiles compared to BNT-30, with the NVX reactogenicity findings consistent with studies in adults.[4,11] This was reassuring in this adolescent study given the increased reactogenicity previously observed in younger versus older COVID-19 vaccine recipients.[12] Although increased reactogenicity has been reported in those with previous SARS-CoV-2 infection, we found no clear difference in reactogenicity when stratified by serostatus.[13] There was no evidence of myocardial inflammation in any study arm clinically or by troponin measurement, although population-based studies are required to definitively assess very rare side effects.

We found BNT-10 was immunogenic in adolescents. However, in participants who were infection naïve (i.e., seronegative to nucleocapsid antigen prior to the second dose), point estimates of binding antibody concentrations were lower than in BNT-30 participants. Furthermore, higher rates of self-reported breakthrough infections were observed in seronegative BNT-10 participants and, once participants experiencing breakthrough infections were excluded, lower antibody concentrations remained evident at day 132. This is consistent with a more rapid loss of protection from infection against VOCs observed following two doses of 10 μg BNT162b2 in 5-to-11-year-olds than following 30 μg BNT162b2 in 12-to-17-year-olds.[14] However, consideration of its use (or that of any COVID-19 vaccine regimen) in infection-naïve adolescents is now largely irrelevant. The current UK and the global situation is that of near-universal prior infection with SAR-CoV-2,[15] and in our study among participants previously infected with SARS-CoV-2 prior to their second COVID-19 immunisation, anti-SARS-CoV-2 antibodies were similar between BNT-10 and BNT-30 groups, with few breakthrough infections in either group and comparable antibody concentrations at day 236.[16] This is consistent with recent studies showing that "hybrid immunity" afforded through prior SARS-CoV-2 infection, provides enhanced protection against symptomatic re-infection.[17] These findings highlight the important role of antigen encounters in shaping the immune response to vaccination and support the potential use of fractional dosing when providing the third (or fourth) antigen exposure. This approach of reduced dosing for post-primary immunisation has been adopted by the mRNA vaccine manufacturer Moderna for its monovalent booster vaccines, albeit at a dose (50 μg) that remains above that of the full dose BNT162b2 vaccine studied here, and for its bivalent Omicron containing variant vaccines (which contain 25 μg for each of its two target strains).[18] The potential for 10 μg BNT162b2 to be used as a third dose is currently being assessed in an extension to this Com-COV3 study.[19] In the meantime, the utility of homologous 10 μg BNT162b2 schedules for primary immunisation in adolescents remains under investigation and will be further informed by an ongoing phase I adolescent study of homologous 10 μg BNT162b2.[20]

Overall, the highest humoral (including neutralising antibody titres) and cellular immune responses, were observed in the NVX group; this pattern persisted out to day 132 even when participants with SARS-CoV-2 infections following vaccination were excluded from the analysis. Correspondingly, the lowest rate of self-reported and serologically confirmed infections was recorded in this group. Furthermore, when compared to the number of serologically confirmed infections, a lower number of self-reported infections were reported in the NVX group, suggesting these participants also experienced milder symptoms on infection. The majority of breakthrough infections for the NVX group occurred later in the study compared to BNT-30 and BNT-10 groups, consistent with the gradual rise in antibody responses seen from day 132 to day 236. NVX-CoV2373 has already been shown to be highly immunogenic in adult populations and to provide protection against VOCs.[21] Our findings

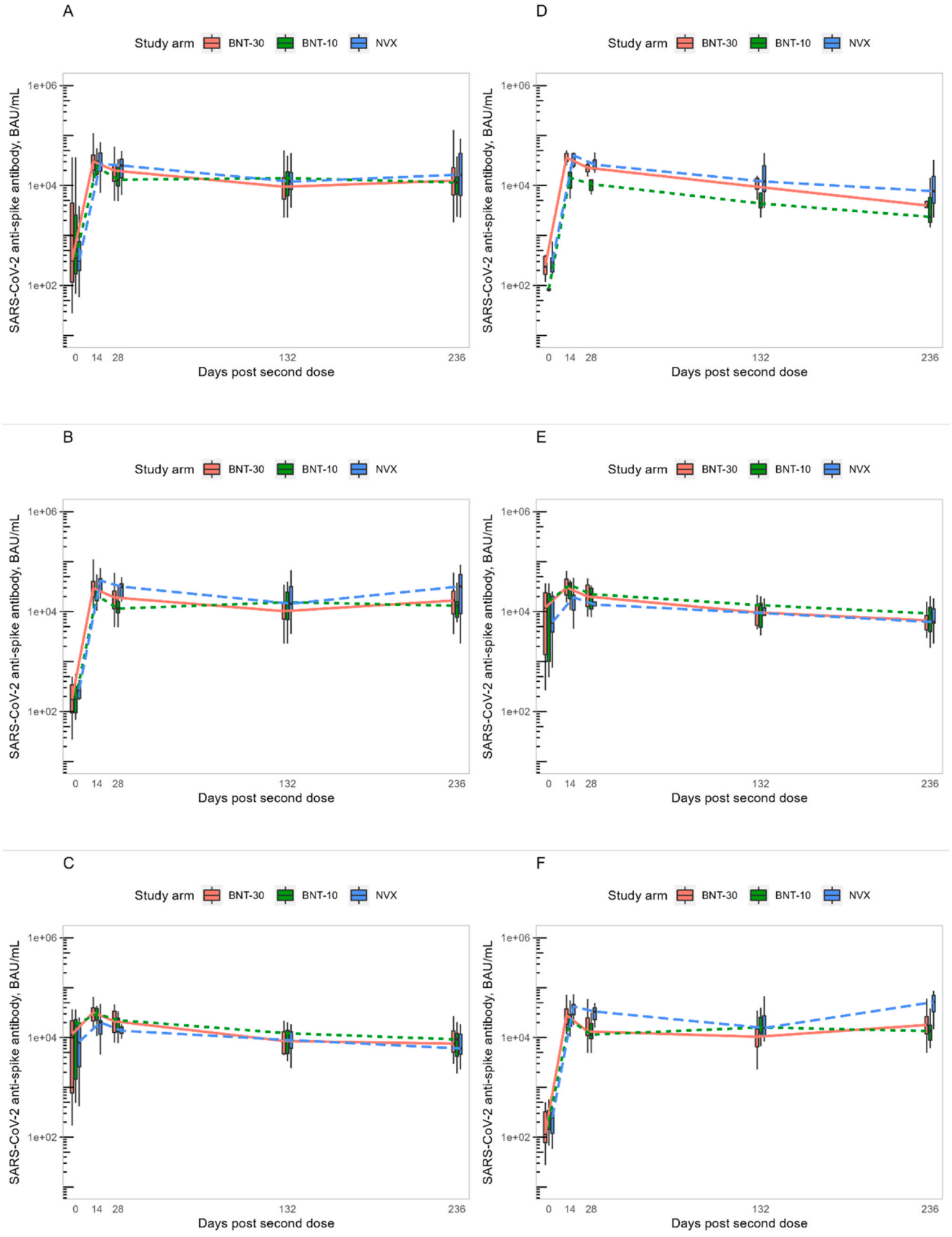

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Fig. 5. Kinetics of SARS-CoV-2 anti-spike antibodies after the second dose in the day 236 modified intention-to-treat population. A: all participants; B: seronegative participants; C: seropositive participants; D: seronegative participants with no infection between the second dose and day 236 visit; E: seropositive participants with no infection between the second dose and day 236 visit; F: seronegative participants with an infection between second dose and day 236 visit. BNT-30: BNT162b2 30 µg; BNT-10: BNT162b2 10 µg; NVX: NVX-CoV2373. Is it The boxplots display the distribution of SARS-CoV-2 anti-spike antibodies over time, outliers are not displayed. The lines display the change in the median over time. An infection could occur at any time between the second dose and the day 236 visit and was defined as either: a self-reported SARS-CoV-2 infection > 14 days after the second dose, a two-fold rise in anti-nucleocapsid IgG from the second dose to 132 or from 132 to 236 days after second dose, a two-fold rise in anti-spike antibodies from 28 to 132 or from 132 to 236 days after the second dose, or anti-nucleocapsid IgG seroconversion from second dose to day 132 or from 132 to 236 days after the second dose.

also concur with the results from the adolescent PREVENT-19 Phase 3 trial in which NVX-CoV2373 demonstrated protective efficacy of 79.5% against SARS-CoV-2% and 82% vaccine efficacy against the Delta variant.[22,23] It has been postulated that the success of the vaccine's performance may be attributable to the presence of the novel Matrix M adjuvant, previously shown to enhance immunogenicity.[24]

This is the first study to examine immune responses to mixed COVID-19 vaccine schedules in adolescents, and revealed striking differences in responses elicited by NVX compared with 50-to-70-year-olds.[4] Specifically, in the adolescent seronegative NVX group, higher anti-spike antibodies were observed compared to BNT-30 (aGMR 1.33), whereas in seronegative adults, this schedule-induced concentrations that failed non-inferiority compared to BNT-30 (aGMR 0.53).[4] Cellular immune responses to NVX also differed, with a relatively low frequency of SARS-CoV-2 specific T-cells in adults (29 SFC/10^6, aGMR 0.6 compared to BNT-30), versus adolescents (121 SFC/10^6, aGMR 1.73).[4] An age-related decline in immunogenicity ('immunosenescence') for COVID-19 and non-COVID-19 vaccines is well recognised,[25–27] and is further evidenced by geometric mean NAb titres against the ancestral strain being 4-fold higher following BNT-30 in seronegative adolescents (Com-COV3) versus adults (Com-COV2) and the observation that two doses of 10 µg BNT162b2 in children elicits an immune response similar to BNT-30 in young adults.[6,7] Nevertheless, the relatively better immune response to NVX compared with BNT-30 in adolescents versus adults suggests that this age-related waning was more pronounced for NVX than BNT-30.

Previous SARS-CoV-2 infection may be expected to be associated with higher baseline, and hence post-vaccination spike-specific antibody levels. However, we found markedly greater binding and neutralising antibody responses in seronegative compared to seropositive NVX recipients. This unexpected finding in our NVX group should however be interpreted cautiously because of the small sample size. Two NVX recipients who tested SARS-CoV-2 positive in the week following their second vaccination were excluded from the analysis to reduce the risk of confounding bias.

The limitations of this study include the use of a pragmatic approach, with no formal sample size calculations. The change to UK national immunisation policy which necessitated a change to the study design resulted in fewer participants recruited than originally planned, limiting the reliability of the conclusions which can be drawn from these data. The age and ethnicity of the study population affect the generalisability of the findings because of the limited representativeness when compared to the general population. The differences in self-reported infection observed in this study need to be interpreted with caution as the study was not powered to assess efficacy, and BNT-10 participants may have been more likely than other groups to self-test once unblinded at day 28 following vaccination. However, the pattern of infection across groups remained consistent for serologically defined infections which were not influenced by testing behaviour. Also, the formulation of BNT-10 used (a one-third dose of the adult preparation, administered in a 0.1 ml volume) differs from the licensed formulation of this vaccine (administered as a 0.2 ml dose).[28] Further clarity on the relevance of this will be provided in the second cohort of the Com-COV3 study, investigating 'third dose' COVID-19 schedules, in which both preparations of the 10 µg dose are being compared directly. Considering the varied vaccine volumes used in the study, there is also a risk that participants may have been inadvertently unblinded at the time of vaccination. However, to maintain the blind, vaccines were prepared out of sight and the syringes covered with masking tape, thereby minimising this risk.

In summary, this study shows that heterologous and fractional dose COVID-19 vaccine schedules studied are well-tolerated and immunogenic in adolescents. BNT-10 demonstrated a highly favourable reactogenic profile, however, it elicited the lowest peak immune response. Although BNT-10 neutralising activity against Omicron BA.1 and BA.2 variants was comparable to BNT-30, BNT-10 participants were more than twice as likely to have a self-reported 'breakthrough infection' compared with BNT-30. NVX demonstrated the highest peak humoral and cellular immune response and had a comparable reactogenic profile to BNT-30. Furthermore, NVX elicited the highest neutralising activity against BA.1 and BA.2 and demonstrated a reduction in risk of self-reported 'breakthrough infection' during an Omicron predominant wave. The performance of NVX in this study supports its use in heterologous COVID-19 vaccine schedules in adolescents, which could offer more flexible and efficient deployment of global COVID-19 vaccine supplies and provide important global policy-relevant data. NVX is currently under review as a third-dose option for adolescents in the second cohort of the Com-COV3 study.

Contributors

MDS 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. EK, ELP, and ST led the implementation of the study. XL, MG and LC performed the statistical analysis and have verified the underlying data. EK, MG, PdW, AMM, XL, and MDS 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.

Data Sharing

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, AstraZeneca, GlaxoSmithKline, Novavax, Seqirus, Sanofi, Medimmune, Merck 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 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 will undertake paid consulting for Moderna BioTech from 3rd May 2023. 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.2023.06.007.

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