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3 month immunogenicity in the COV-BOOST trial

Persistence of immunogenicity after seven COVID-19 vaccines given as third dose boosters following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK: three month analyses of the COV-BOOST trial.

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Highlights

- The persistence of humoral responses are different between vaccines.
- After ChAd/ChAd, mRNA vaccines still have the highest humoral response at D84
- After BNT/BNT viral-vector vaccines have comparable or even higher humoral response at D84 compared with homologous BNT boost schedule
- Heterologous and homologous schedules have different kinetics of antibody titre decline by D84 which appears to depend both on vaccine class and order of administration.
- Half dose BNT induced comparable levels of humoral and cellular responses at D84 compared with full dose BNT

Abstract

Objectives: To evaluate the persistence of immunogenicity three months after third dose boosters.

Methods: COV-BOOST is a multicentre, randomised, controlled, phase 2 trial of seven COVID-19 vaccines used as a third booster dose. The analysis was conducted using all randomised participants who were SARS-CoV-2 naïve during the study.

Results: Among the 2883 participants randomised, there were 2422 SARS-CoV-2 naïve participants until D84 visit included in the analysis with median age of 70 (IQR: 30-94) years. In the participants who had two initial doses of ChAd, schedules using mRNA vaccines as third dose have the highest anti-spike IgG at D84 (e.g. geometric mean concentration of 8674 ELU/ml (95% CI: 7461-10085) following ChAd/ChAd/BNT). However, in people who had two initial doses of BNT there was no significant difference at D84 in people given ChAd versus BNT (geometric mean ratio (GMR) of 0.95 (95%CI: 0.78, 1.15). Also, people given Ad26.COV2.S (Janssen; hereafter referred to as Ad26) as a third dose had significantly higher anti-spike IgG at D84 than BNT (GMR of 1.20, 95%CI: 1.01,1.43). Responses at D84 between people who received BNT (15 μg) or BNT (30 μg) after ChAd/ChAd or BNT/BNT were similar, with anti-spike IgG GMRs of half-BNT (15 μg) versus BNT (30 μg) ranging between 0.74-0.86. The decay rate of cellular responses were similar between all the vaccine schedules and doses.

Conclusions: 84 days after a third dose of COVID-19 vaccine the decay rates of humoral response were different between vaccines. Adenoviral vector vaccine anti-spike IgG concentration at D84 following BNT/BNT initial doses were higher than for a three dose (BNT/BNT/BNT) schedule. Half dose BNT immune responses were similar to full dose responses. While high antibody tires are desirable in situations of high transmission of new variants of concern, the maintenance of immune responses that confer long-lasting protection against severe disease or death is also of critical importance. Policymakers may also consider adenoviral vector, fractional dose of mRNA, or other non-mRNA vaccines as third doses.

Keywords: *COVID-19 vaccine; third dose; heterologous boost; homologous boost; fractional dose; immunogenicity; persistence*

Introduction

Many countries elected to deploy 3rd dose booster vaccines against COVID-19 towards the end of 2021 as a result of waning immunity and emergence of variants with varying degrees of immune escape, (1). Results previously published from the COV-BOOST study demonstrated that most COVID-19 vaccines delivered as a 3rd dose booster provided a significant boost to both humoral and cellular immunity at 28 days following immunisation (2). Due to their very high IgG anti-spike titres by day 7 after immunisation, mRNA vaccines were deployed by most high-income countries as the third dose booster. There is emerging real world observational evidence of significantly increased protection following a 3rd dose booster of mRNA vaccine after two initial doses of both mRNA (BNT162b2 (Pfizer–BioNtech, hereafter referred to as BNT); and mRNA1273 (Moderna, hereafter referred to as m1273)) and two doses of adenoviral vector (ChAdOx1 nCov-19 (Oxford–AstraZeneca, hereafter referred to as ChAd)) vaccines (3). It is currently unclear how rapidly the protection from a 3rd dose booster wanes over time.

In November 2021 reports emerged of a new variant of SARS-CoV-2 with a large number of mutations, in particular to the receptor binding domain of the spike antigen against which most currently approved vaccines are targeted. Omicron has a significant transmission advantage over previous variants due to intrinsically enhanced transmissibility and immune evasion (4). Studies have demonstrated extremely limited neutralisation of omicron from sera following two doses of vaccine or in convalescent individuals (5, 6, 7). A third dose of vaccine (or two doses plus infection) augments neutralisation against omicron in laboratory studies (8, 9). T cell responses appears to be preserved (10, 11, 12) (similar to other Variants of Concern (VOC) (2)) which may help protect against severe disease. Observational studies also suggest a third dose significantly improves protection from symptomatic infection compared to two doses (13, 14).

Although a substantial number of people worldwide have already been given third dose boosters, many low and middle-income countries are still working towards administering first doses. It is, therefore, important to characterise differences in the longitudinal immune response following different vaccines given as third doses to inform possible flexible mixed vaccine third dose programmes.

There are limited data on immunogenicity beyond one month following third doses (15, 16), and none from randomised controlled trials. To provide further data supporting global policymaking, we conducted this day (D) 84 post-boost analysis to compare immune responses of study vaccines to the corresponding ChAd/ChAd/BNT or BNT/BNT/BNT schedule as BNT is currently the most commonly used booster in clinical practice in high income countries. Due to the emergence of omicron, commonly deployed clinical schedules tested in the trial were also analysed by viral neutralisation assays and are reported here.

Methods

Trial Design & Oversight, Treatments

The COV-BOOST trial (ISRCTN: 73765130, protocol available at https://www.covboost.org.uk/protocol) has been previously reported (2). In brief, the trial is a multicentre, randomised, controlled, phase 2 trial of third dose booster vaccination against COVID-19. The 18 study sites were split into three site groups (A, B, and C). Within each site group, the participants were randomised to three or four experimental vaccines, or a control vaccine (MenACWY), with equal probability. Trial recruitment was stratified by the first 2 dose vaccination schedule (ChAd/ChAd and BNT/BNT) and age (30-69 years old and ≥70 years old). The experimental vaccines in group A were ChAd, NVX-CoV2373 (Novavax; hereafter referred to as NVX) or a half dose of NVX; BNT, VLA2001 (Valneva; hereafter referred to as VLA), a half dose of VLA, Ad26.COV2.S (Janssen; hereafter referred to as Ad26) in group B; and m1273, CVnCov (CureVac; hereafter referred to as CVn), a half dose of BNT in Group C (Figure 1). Immunogenicity bloods were taken at day 0 (pre-boost), D28 and D84 post-boost for all the participants. All the participants and investigator staff were blinded to treatment allocation until the D84 visit.

Due to the general population being recommended third doses, participants in the control arms were then randomised to receive half-BNT, BNT, or half-m1273 around 6 months after their first two doses of ChAd/ChAd or BNT/BNT. Additional immunogenicity bloods were taken in this group at D0, D28 and D84 post the boost vaccine.

Laboratory Methods

Sera were analysed at Nexelis (Laval, QC, Canada) to determine SARS-CoV-2 anti-spike IgG concentrations by ELISA (reported as ELISA laboratory units [ELU]/mL), and for SARS-CoV-2 pseudotype virus neutralisation (PNA) assay, using a vesicular stomatitis virus backbone adapted to exhibit the SARS-CoV-2 spike protein, reported as 50% neutralising antibody titres (NT_{50}). The conversion factors to international standard units can be found in the appendix. Sera from D0 and D84 were analysed at Porton Down, Public Health England, by ECLIA (Cobas platform, Roche Diagnostics) to determine anti-SARS-CoV-2 nucleocapsid IgG status (reported as negative if below a cut-off index (COI) of 1.0). The sera at D28 and D84 from a subset of participants with anti-SARS-CoV-2 nucleocapsid COI <1.0

at baseline (n=~25) were also tested at Porton Down, UK Health Security Agency to measure the normalised 80% neutralising antibody titre (NT_{80}) for live SARS-CoV-2 virus (wild type) by microneutralisation assays. The sera from those with the UK deployed vaccine schedules (ChAd prime and ChAd/BNT/half-m1273 third dose boost, BNT prime and BNT/ half-m1273 third dose boost) were also analysed by microneutralisation assays (MNA) to determine 50% focus reduction neutralisation titres ($FRNT_{50}$) for live SARS-CoV-2 virus lineages (Victoria/01/2020, Delta variant B.1.617.1, and Omicron variant B.1.1.529) at the University of Oxford, Oxford, UK. The reduction in the number of infected foci was compared with a negative control well without an antibody. All assays were conducted in duplicate at minimum.

The cellular immunology samples were collected from nine sites based on logistical reasons (i.e. proximity to external laboratory)(2). IFN-γ secreting T cells specific to whole spike protein epitopes designed based on the Wuhan-Hu-1 sequence (YP_009724390.1) were detected by modified TSPOT-Discovery test within 32 hours (h) of venepuncture, using the addition of T-Cell Xtend reagent to extend peripheral blood mononuclear cell (PBMC) survival, at Oxford Immunotec (Abingdon, UK). 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, and these results were multiplied by four to express frequencies per million PBMCs. For the rest of the study sites, sample were not taken as the sample integrity can be affected due to the long distance to the processing laboratory.

Statistical analysis

We conducted analyses on the immunogenicity outcomes at 28 and 84 days after third dose booster vaccines for available laboratory data. The sample size calculation was described previously (2). The COV-BOOST trial was originally designed to investigate the immune responses by different third dose boost vaccines in ChAd and BNT primed participants. With the rollout of third doses worldwide based on the data generated by the COV-BOOST trial and others, the comparison to control arm has become less relevant to policymaking. BNT has become the most widely used third dose boost vaccine in the UK and most high-income countries. The analysis in this report aims to address the most relevant clinical question of the persistence of immune responses induced by other vaccines as a third dose compared with a third dose of BNT in populations who received ChAd/ChAd and BNT/BNT as their initial two dose vaccine schedules. Since BNT was only used in group B, we joined the three groups in one analysis, and the three control arms were combined into one arm.

The analysis population was all randomised participants with no evidence of SARS-CoV-2 infection up until 84 days post third dose. This was defined as self-reported SARS-CoV-2 infection or anti-nucleocapsid COI ≥1 by the Roche Elecsys anti-Sars-CoV-2 assay at baseline or D84 visit. All the analyses were conducted according to the randomised arms and stratified by first doses (ChAd/ChAd and BNT/BNT). To compare changes overtime, we presented the geometric mean ratios (GMR) and 95% confidence interval (CI) of the absolute immune responses at D28 and D84, respectively, for the study vaccines compared with BNT as the reference. If the GMRs of a vaccine to BNT increased between D28 and D84, it means the decay rate of this vaccine is slower between D28 and D84 than for BNT. We also calculated the fold-change of immunogenicity between D28 and D84 (D84 to D28 ratio) for each participant and presented the geometric mean of D84 to D28 ratio for each vaccine arm with a higher ratio indicating a slower decay. The GMRs of the D84 to D28 ratio (i.e. a ratio of ratios) were also presented with 95% CIs using BNT as the reference. The GMRs and 95% CIs were estimated using a mixed-effect linear regression model. The log10 transformed immunogenicity data (absolute titre or D84 to D28 ratio) was the dependant variable and the 'sites' variable was included as a random effect in the model with age group (<70 years, ≥70 years), baseline immunogenicity, the duration between 1st and 2nd vaccine, and the duration between 2nd and boost vaccine as fixed effects. The GMR was calculated as the antilogarithm of the adjusted difference between arms in the model. Subgroup analyses by age (<70 years, ≥70 years) were carried out using the above model after removing the fixed effect of age group. Sensitivity analyses were also conducted to check the validity of the pooled analysis by comparing the GMR of each vaccine to the control arm estimated by the simple analysis within each group with the GMR estimated after pooling group A-C and combining all three control arms. Statistical analyses were conducted using R version 4.1.1.

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

The baseline characteristics of the trial was reported previously (2). In summary, between 1st June and 30th June 2021, the study screened 3498 participants, of whom 2883 were randomised and 2878 received a third dose boost vaccine between 10 and 26 weeks following the second dose. Recruitment was stratified by age group (30-69 years and ≥ 70 years). The median age of the younger cohort was 53 and 51 years in the ChAd/ChAd and BNT/BNT primed participants, and, respectively, 76 and 78 years in the older cohort. Among the 2878 participants receiving the study vaccines, there were 228 participants primed with ChAd/ChAd and 228 participants with BNT/BNT excluded, leaving 2422 participants in this analysis (CONSORT Figure 1). This report focuses on the results for the trial vaccines with current UK and European Union use authorization, but presents results for all vaccines for transparency.

Overall, a significant drop between D28 and D84 was seen in all study arms for anti-spike IgG, live virus neutralising antibody and cellular responses (Figure 2, Figure 3).

In the population who had ChAd/ChAd as first doses, full dose (100 μg) m1273 as the third dose had highest titres but, due to reactogenicity, half dose (50μg) has been deployed worldwide. BNT standard dose (30 μg) as third dose induced higher anti-spike IgG at D28 and D84 than other vaccines deployed clinically (Figure 2A). The decay rate of Ad26 as a third dose was lower than BNT between D28 and D84, with a D84 to D28 ratio of 0.72 (95%CI: 0.68-0.77) for Ad26 and 0.43 (95%CI: 0.41-0.46) for BNT (adjusted GMR for Ad26 versus BNT of 1.66 (95%CI: 1.45-1.90)), although the anti-spike IgG concentration at D84 in Ad26 recipients (GMC: 4105 ELU/ml , 95%CI: 3438-4903) was still significantly lower than BNT (GMC: 8674 ELU/ml, 95%CI: 7461-10085) (Figure 2A). Similar to Ad26, ChAd also showed a slower decay but with significant lower anti-spike IgG concentrations at D28 and D84 compared with BNT. For NVX, the decay rate of anti-spike IgG was similar to BNT with D84 to D28 ratio of 0.50 (95%CI: 0.44-0.55). The pseudotype virus neutralising and live viral neutralising antibody GMRs at D28 and D84, and the D84 to D28 ratio, of ChAd and Ad26 compared to BNT were similar to that seen for anti-Spike IgG (Figure 2B & 2C). This was not the case for NVX, where a significant lower decay (higher D28 to D84 ration) of the live virus neutralising antibody was observed. For anti-spike IgG (Figure 2A), the D84 to D28 ratios were 0.43 (95%CI: 0.41-0.46) and 0.50 (95%CI: 0.44-0.55) for BNT and NVX, respectively, with adjusted GMR of 1.14 (95%CI: 0.97, 1.34) between NVX and BNT, while the GMR of D84 to D28 ratios for live virus neutralising antibody (Figure 2C) was 1.83 (95%CI: 1.13, 2.96) when comparing NVX (0.63, 95%CI: 0.46-0.84) to BNT (0.36, 95%CI: 0.26-0.48). All vaccines induced similar or lower level of cellular responses against wild-type at both D28 and D84 compared with BNT (Figure 2D). The cellular response was also more persistent in the Ad26 arm compare with BNT (adjusted GMR: 1.81, 95%CI: 1.13, 2.92). Significantly less decay was also observed in ChAd recipients (adjusted GMR: 1.88, 95% CI: 1.16, 3.07), but the level of cellular responses was significantly lower than for BNT recipients at D28 (adjusted GMR: 0.39, 95% CI: 0.25, 0.59).

For participants primed with BNT/BNT, the pattern of anti-spike IgG between vaccine arms at day 28 was similar to people primed with ChAd/ChAd, with BNT 30μg as third dose inducing the highest concentration besides 100 μg m1273 (Figure 3A). Whilst ChAd and Ad26 arms had significantly lower anti-spike IgG than BNT at D28 with adjusted GMR of 0.62 (95%CI: 0.51, 0.76) and 0.72 (95%CI: 0.61, 0.85), this was no longer the case at D84 with adjusted GMR increasing to 0.95 (95%CI: 0.78, 1.15) and 1.20 (95%CI: 1.01,1.43), respectively. The concentration of anti-spike IgG at D28 and D84 was significantly lower for NVX compared to BNT. Apart from BNT-half (15 μg) and m1273 (100 μg), the D84 to D28 ratios in the ChAd, Ad26, and NVX arms were significantly higher than the BNT arm, showing the anti-spike decays slower in these arms compared with BNT. Among these arms, Ad26 has the highest D84 to D28 ratio (GM: 0.80, 95%CI: 0.73-0.88) indicating the slowest decline. In addition, the absolute level of the anti-spike IgG was significantly higher at D84 for Ad26 (14214 ELU/ml, 95%CI: 11910-16958) than BNT (13025, 95%CI: 11291-15025). Similarly, the D84 to D28 ratios for the pseudotype virus neutralising and live neutralising antibody were highest for Ad26, indicating the slowest decay for Ad26 (GM: 0.83, 95% CI: 0.71, 0.96 and GM: 0.85, 95% CI: 0.69, 1.05 respectively). The absolute neutralising antibody titres at D84 were also significantly higher for Ad26 than for BNT (Figure 3B & 3C). The decay rates of the pseudotype neutralising antibody for ChAd (GMR of D84 to D28 ratio: 1.67, 95%CI: 1.38, 2.02) and NVX (GMR of D84 to D28 ratio: 1.22, 95%CI: 1.01, 1.47) were significantly higher than for BNT, but the decay rates were not statistically significant for the live neutralising antibody due to the small number. For cellular responses, m1273 (100 □g) had the highest cellular responses at D84 (75, 95%CI: 51-110), though not reaching the significance level when comparing with BNT. The cellular responses at D28 and D84, as well as the D84 to D28 ratio in the ChAd and Ad26 arms were similar to the BNT arm (Figure 3D).

In the subgroup analysis, similar patterns of immunogenicity were observed in the two age groups in both ChAd/ChAd and BNT/BNT first doses populations (Figure 4, Figure 5, Figure 6).

BNT-half induced similar humoral and cellular responses compared with BNT at D28 and D84 (Figure 2 & 3). This was seen in populations primed with both ChAd/ChAd and BNT/BNT, and in both age groups (Figure 4, 5 &6).

The live neutralising antibody data were available in five UK deployed schedules, including ChAd/ChAd/ChAd, ChAd/ChAd/BNT and BNT/BNT/BNT with a 3-month interval between second and third doses, and ChAd/ChAd/half-m1273(50μg) and BNT/BNT/half-m1273 (50□□g) with a 6-month interval between second and third doses. Significant reductions in neutralising titres against delta and omicron variants were observed when compared with the wild type strain at 28 days post boost dose (Figure 7, supplementary table 3). The drops in neutralisation against delta and omicron were consistent across the schedules (Supplementary table 3). In ChAd/ChAd/ChAd arm, only 2 out of 24 participants showed detectable neutralisation against omicron, whilst neutralisation against omicron was detected in most participants of the other four schedules.

Discussion

We report D84 immunogenicity data after seven different boost vaccines in participants following ChAd/ChAd and BNT/BNT as first doses. In the ChAd/ChAd primed population, the anti-spike IgG remained highest in the mRNA vaccine arms at D84, although people given Ad26 had antibody levels that declined at a slower rate than that following mRNA vaccines between D28 and D84. In people who received BNT/BNT first doses, the anti-spike IgG at D28 had been significantly lower for ChAd and Ad26 compared with BNT as a third dose, but by D84 there was no significant difference between ChAd and BNT, and the concentration of anti-spike IgG was significantly higher for Ad26 than BNT. As reported for D28 (2), live viral neutralisation against wild type correlates with anti-spike IgG levels at day 84 and the overall pattern between arms was similar to that of anti-spike IgG for D28, D84 and the D84 to D28 ratio. T cell responses remain broad to wild type, delta and beta variants tested at D84 (supplementary tables 1 and 2).

The anti-spike IgG and live neutralising antibody were significantly lower for NVX at both D28 and D84 in people given ChAD/ChAd and BNT/BNT as first doses compared with BNT, but a slower decay was observed between D28 and D84 than for BNT.

In both ChAd/ChAd and BNT/BNT primed populations, the GMR of anti-spike IgG induced by half-BNT (15µg) was over 0.7 (ranging between 0.74 to 0.88) compared with BNT standard dose (30µg), indicating that the anti-spike IgG levels were similar by three months following a third dose of standard or half dose BNT. Although recent data suggest using two first doses of 10 mcg BNT in children 5-11 years is less effective than two doses of 30 mcg BNT in 12-16 year olds (17, 18), our data suggests the kinetics of immune responses after a third doses might be different to the first two (priming) doses. Fractional dosing for third and potentially subsequent dosing may well offer benefit in adults by increasing global vaccine supply and an important question is whether using a lower dose could potentially reduce the incidence of the very rare associated adverse effect of myocarditis/pericarditis. To explore this further, we have initiated a non-inferiority trial in 18-30 year olds to investigate fractional dosing of both BNT (10µg) and m1273 (50 µg and 25 µg) compared with BNT 30 µg (https://www.covboost.org.uk/participate-substudy).

To our best knowledge, this is the first study reporting persistence of immunogenicity for homologous and heterologous boost schedules from a randomised controlled trial. In December 2021, the European Medicines Agency (EMA) published its regulatory considerations on heterologous primary and booster COVID-19 vaccination (19), based on evidence generated from short-term immunogenicity studies and a vaccine effectiveness study (2, 20, 21). The EMA concluded the immunogenicity of heterologous boost schedule is as good as, or better than, homologous schedules. Our data at D84 post third dose further support the EMA's statement. The mRNA vaccine arms still have the highest anti-spike IgG in the ChAd/ChAd first doses population, although the heterologous boost schedule anti-spike IgG with Ad26 after ChAd/ChAd appears to decay slower than ChAd/ChAd followed by mRNA. Based on limited available data, the EMA also suggested (19) that heterologous schedules with adenoviral vector vaccine first doses and mRNA vaccine third dose is more immunogenic than the reverse. However, based on our data other vaccines may be as immunogenic by D84 following third dose. The anti-spike IgG in adenoviral vector vaccine arms (ChAd and Ad26) after the BNT/BNT prime are the most persistent schedules up to D84. The immunogenicity at D84 post boost for ChAd and Ad26 was similar to, or higher than, the three dose BNT schedule (BNT/BNT/BNT), especially in older people. Although the WHO does not yet recommend third doses for healthy adults due to the inequity of vaccine distribution worldwide (22), the data from our study also supports WHO recommendations to consider using adenoviral vector vaccines for third doses in countries implementing mRNA vaccine as initial doses. The use of fractional mRNA dosing may be another solution to accelerate the worldwide vaccine coverage rate. The anti-spike IgG level in the half BNT arm was >70% compared with that in the full dose BNT arm, whilst the difference was even smaller in the BNT/BNT prime population.

In the UK, mRNA vaccines were initially chosen for third doses to achieve the highest possible peak antibody levels given a likely resurgent wave in autumn/winter 2021. As maximum antibody levels following third mRNA doses are achieved by day seven after the third dose (2), our previous data also supported acceleration of the UK third dose programme to try to control omicron transmission. A third dose mRNA vaccine given as a boost to people who received BNT/BNT (23) and ChAd/ChAd (21) has also shown increased effectiveness compared to two doses to prevent symptomatic, severe and hospitalised COVID-19 infection. These data highlight the particular need to use third doses in vulnerable populations to reduce the mortality and burden to healthcare systems. Although a third dose of viral vector vaccine was not a widespread deployed schedule, recent UK data have shown good long term protection against hospitalisation and death for Omicron even in the population who received ChAd/ChAd/ChAd for logistical reasons (14). Given the high correlation observed between humoral responses and vaccine efficacy following two doses (24), it is likely that the two doses of mRNA vaccine with an adenoviral vector 3rd dose will achieve similar protection as three doses of mRNA vaccine. Importantly, our antibody decay rate data suggest that two doses of mRNA followed by an adenoviral vector vaccine is likely to achieve more sustainable protection. Our 8-month follow up visit will further investigate the longer-term immunogenicity persistence. Using adenoviral vector vaccines as third doses following two doses of mRNA vaccine will not only make more mRNA vaccine available for people who have not yet received their first two doses, but could also delay any potential need for a fourth dose. In countries that have not yet implemented third doses, and where omicron has already passed through the population, policymakers will need to assess the risk/benefit of a potentially longer lasting third dose schedule balanced against the possibility of the extremely rare side effect of thrombosis with thrombocytopenia syndrome (TTS) which has not been observed after second doses and is not detected across all ethnicities and geographies.

Preliminary data on cross reactive neutralisation against omicron suggest that, among the combinations so far evaluated, a lower neutralising response with ChAd/ChAd/ChAd and highest responses where half (50 μg) dose m1273 has been used as third dose, irrespective of primary schedule. The neutralising antibody levels against omicron at D28 following a third dose of mRNA vaccine in people who had received ChAd/ChAd and BNT/BNT were between 125 and 756 ($FRNT_{50}$). This lies between levels of antibodies against wild type after priming with two-doses of ChAd or BNT ($FRNT_{50}$: 109 and 1501 respectively) (25). Both assays were run by the same laboratory following the same procedure. Our data suggest that protection against omicron infection after a third dose of mRNA vaccine is likely be the same as that against wild type after two doses of ChAd/ChAd and BNT/BNT. The vaccine effectiveness after three doses of mRNA vaccine were 82% and 90% for severe and hospitalised Omicron predominated COVID-19 infections, which is consistent with our immunogenicity findings (23).

There are some limitations of this analysis. The original trial included 10 candidate third dose vaccines, and the trial was designed by splitting the study sites into three groups to randomise participants into control vaccine and three or four study vaccine arms. This means that the study vaccines were not all randomised within the same study populations, making the comparison of vaccines between groups more complicated than our original report, which compared to the control arm within each group. Little difference was observed in a sensitivity analysis on the GMR to the control arm that was conducted by comparing the results from simple analysis within group (used in the primary endpoint paper) with the results from the combined approach in this analysis (Supplementary Figure 1). Secondly, m1273 was used at full dose (100 μg) as a boost in this study, as the decision (and international regulatory approval) to use 50 μg was made after the start of the study; therefore, the data presented for m1273 third dose cannot be directly used to inform policy making. However, participants in the control arms within the original trial were subsequently randomised to third doses with half-BNT (15 μg), BNT (30 μg), and half-m1273 (50 μg) at a 6-month interval, following UK policymaker advice. These data will provide evidence on the optimal interval of mRNA boost and the immunogenicity of 50 μg mRNA1273 as a boost. Finally, this analysis was done in a seronegative population to inform the policy making in September 2021, when the majority of worldwide population were SARS-CoV-2 naïve. This population no longer representative of most global populations, where a substantial proportion of people will have had at least one SARS-CoV2 infection. Subsequent analysis will include the impact of prior infection on post third dose responses over the length of the study.

In conclusion, substantial differences in the decay rates of humoral responses between study vaccines used as third doses were observed. The heterologous schedule with mRNA vaccine first two doses followed by adenoviral vector vaccine third dose showed more persistent humoral responses as well as comparable or higher antibody responses at D84 post third dose. 15 μg BNT also showed comparable immune response compared with standard 30 μg dose BNT when used as a third dose.

Using vaccines in heterologous manner (“mix and match”) is relatively novel, as are the vaccines being used in the mixed platforms investigated in this study and using different dosing schedules. This analysis has demonstrated that there is much to be learnt about these and other heterologous vaccine combinations for SARS-CoV2, and vaccines against other infectious pathogens.

Contributors

SNF, MDS, XL and JSN-V-T conceived the trial and SNF is the chief investigator. SNF, AM, MDS and XL contributed to the protocol and design of the study. AM, GB and SS led the implementation of the study. XL, SF, LJ and VC designed and conducted the statistical analysis and have verified the underlying data. XL, AM, SF and SNF drafted the report. All other authors contributed to the implementation and data collection. All authors reviewed and approved the final report.

Declaration of Competing Interest

KC acts on behalf of University Hospital Southampton as an investigator 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. 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. ALG is named as an inventor on a patent covering use of a particular promoter construct that is often used in ChAdOx1-vectored vaccines and is incorporated in the ChAdOx1 nCoV-19 vaccine. ALG may benefit from royalty income paid to the University of Oxford from sales of this vaccine by AstraZeneca and its sublicensees under the University's revenue sharing policy. JH has received payments for presentations for AstraZeneca, Boehringer Ingelheim, Chiesi, Ciple & Teva. VL acts on behalf of University College London Hospitals NHS Foundation Trust as an Investigator on clinical trials of COVID-19 vaccines funded or sponsored by vaccine manufacturers including Pfizer, AstraZeneca and Valneva. He receives no personal financial payment for this work. PM acts on behalf of University Hospital Southampton NHS Foundation Trust and The Adam Practice as an investigator on studies funded or sponsored by vaccine manufacturers including AstraZeneca, GlaxoSmithKline, Novavax, Medicago and Sanofi. He received no personal financial payment for this work. JSN-V-T is seconded to the Department of Health and Social Care, England until 31st March 2022. MR has provided post marketing surveillance reports on vaccines for Pfizer and GSK for which a cost recover charge is made. MDS acts on behalf of the University of Oxford as an investigator on studies funded or sponsored by vaccine manufacturers including AstraZeneca, GlaxoSmithKline, Pfizer, Novavax. Janssen, Medimmune and MCM vaccines. He received no personal financial payment for this work.

Data sharing

The study protocol is provided in the appendix. Individual participant data will be made available when the study is complete upon reasonable requests made to the corresponding author; data can be shared through secure online platforms after proposals are approved. All the sequence datasets used in the T-cell analysis are available in the public GISAID database (https://www.gisaid.org).

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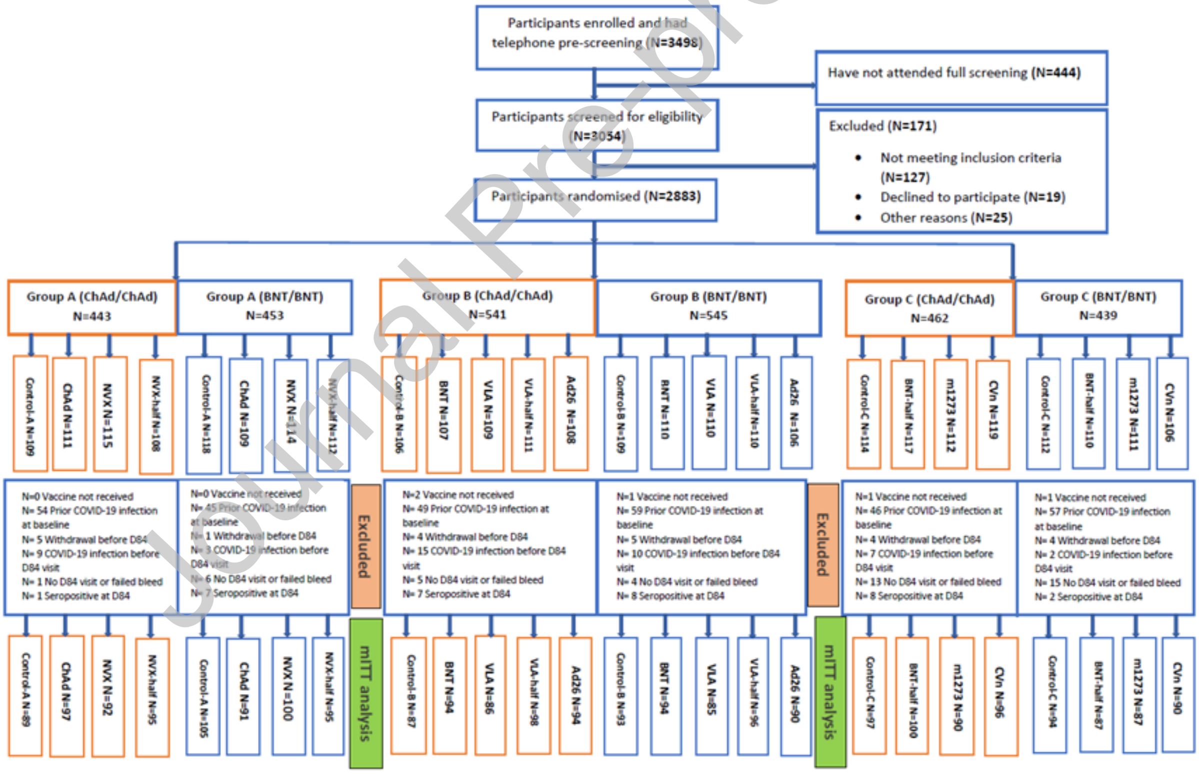
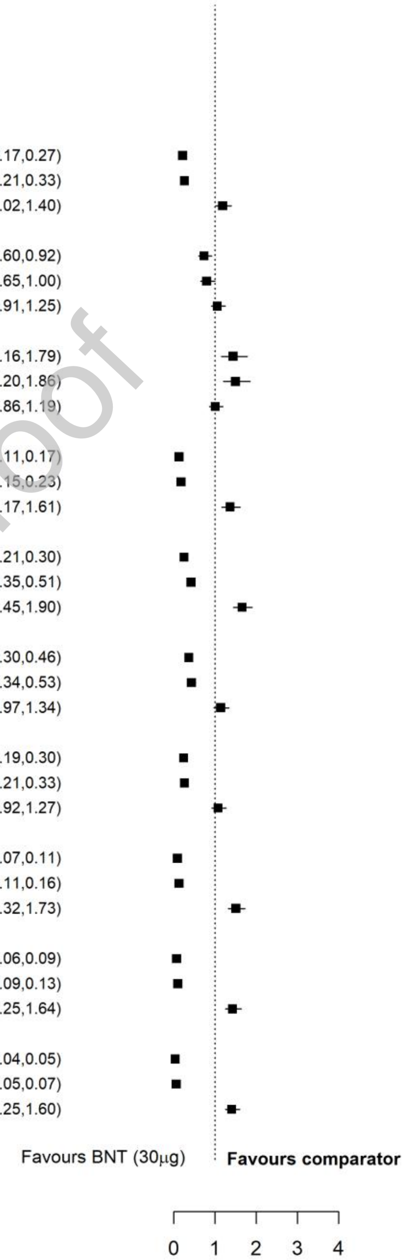


Figure 1. Consort diagram

A)

SARS-CoV-2 anti-spike IgG

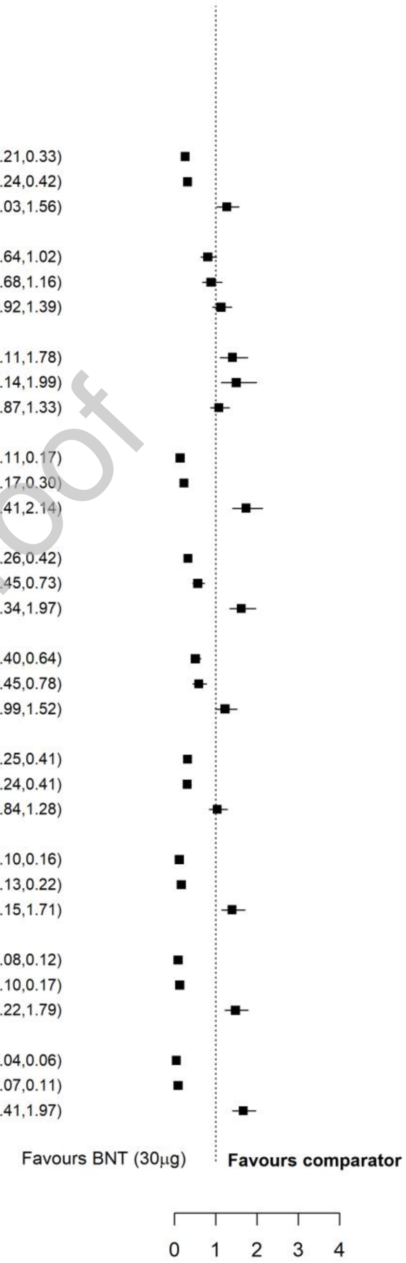
ChAd/ChAd	GM (95%CI)	GMR (95%CI)
BNT		
D28	20556(17725-23839) [n=92]	Ref
D84	8674(7461-10085) [n=94]	Ref
D84/D28 ratio	0.43(0.41-0.46) [n=92]	Ref
CVn		
D28	3880(3342-4505) [n=96]	0.22(95%CI: 0.17,0.27)
D84	2068(1769-2418) [n=96]	0.26(95%CI: 0.21,0.33)
D84/D28 ratio	0.53(0.49-0.58) [n=96]	1.19(95%CI: 1.02,1.40)
BNT-half		
D28	15492(12927-18567) [n=98]	0.74(95%CI: 0.60,0.92)
D84	7308(6277-8508) [n=100]	0.80(95%CI: 0.65,1.00)
D84/D28 ratio	0.47(0.41-0.54) [n=98]	1.06(95%CI: 0.91,1.25)
m1273		
D28	31387(26294-37467) [n=89]	1.44(95%CI: 1.16,1.79)
D84	14489(12185-17229) [n=90]	1.50(95%CI: 1.20,1.86)
D84/D28 ratio	0.45(0.40-0.51) [n=89]	1.01(95%CI: 0.86,1.19)
ChAd		
D28	2388(1996-2857) [n=96]	0.13(95%CI: 0.11,0.17)
D84	1411(1172-1700) [n=97]	0.18(95%CI: 0.15,0.23)
D84/D28 ratio	0.59(0.55-0.64) [n=96]	1.37(95%CI: 1.17,1.61)
Ad26		
D28	5780(4893-6827) [n=92]	0.25(95%CI: 0.21,0.30)
D84	4105(3438-4903) [n=94]	0.42(95%CI: 0.35,0.51)
D84/D28 ratio	0.72(0.68-0.77) [n=92]	1.66(95%CI: 1.45,1.90)
NVX		
D28	6883(5724-8278) [n=92]	0.37(95%CI: 0.30,0.46)
D84	3407(2795-4154) [n=92]	0.43(95%CI: 0.34,0.53)
D84/D28 ratio	0.50(0.44-0.55) [n=92]	1.14(95%CI: 0.97,1.34)
NVX-half		
D28	4571(3725-5608) [n=95]	0.24(95%CI: 0.19,0.30)
D84	2143(1721-2668) [n=95]	0.26(95%CI: 0.21,0.33)
D84/D28 ratio	0.47(0.43-0.51) [n=95]	1.08(95%CI: 0.92,1.27)
VLA		
D28	1745(1429-2132) [n=85]	0.09(95%CI: 0.07,0.11)
D84	1156(950-1407) [n=86]	0.13(95%CI: 0.11,0.16)
D84/D28 ratio	0.65(0.60-0.71) [n=85]	1.51(95%CI: 1.32,1.73)
VLA-half		
D28	1423(1189-1703) [n=97]	0.07(95%CI: 0.06,0.09)
D84	893(737-1081) [n=98]	0.10(95%CI: 0.09,0.13)
D84/D28 ratio	0.62(0.58-0.66) [n=97]	1.43(95%CI: 1.25,1.64)
Control		
D28	799(713-897) [n=268]	0.04(95%CI: 0.04,0.05)
D84	496(441-559) [n=272]	0.06(95%CI: 0.05,0.07)
D84/D28 ratio	0.62(0.58-0.66) [n=267]	1.41(95%CI: 1.25,1.60)



B)

Pseudotype virus neutralising antibody

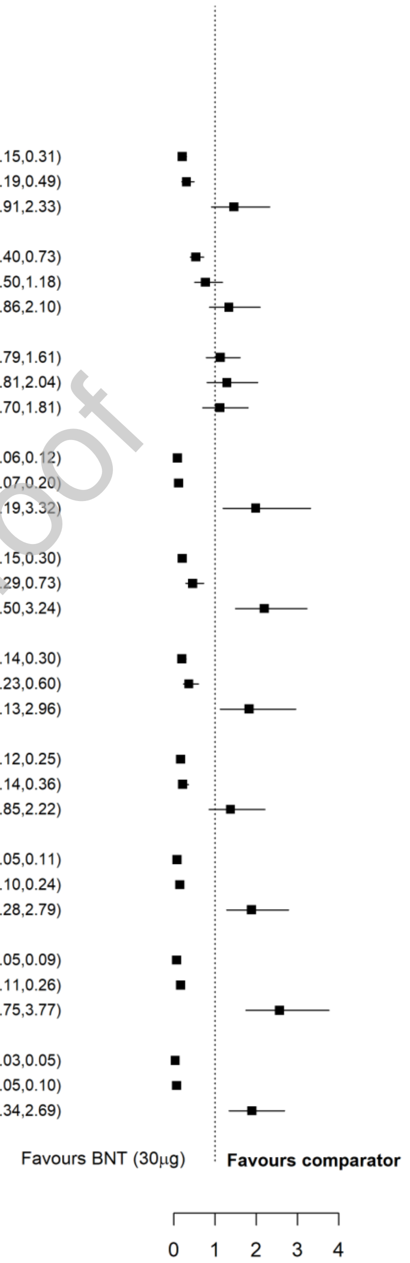
ChAd/ChAd	**GM (95%CI)**	**GMR (95%CI)**
BNT		
D28	1623(1313-2006) [n=92]	Ref
D84	639(531-770) [n=93]	Ref
D84/D28 ratio	0.40(0.34-0.48) [n=91]	Ref
CVn		
D28	372(313-443) [n=90]	0.26(95%CI: 0.21,0.33)
D84	188(158-225) [n=96]	0.32(95%CI: 0.24,0.42)
D84/D28 ratio	0.52(0.44-0.61) [n=90]	1.27(95%CI: 1.03,1.56)
BNT-half		
D28	1304(1092-1557) [n=98]	0.81(95%CI: 0.64,1.02)
D84	585(482-710) [n=100]	0.89(95%CI: 0.68,1.16)
D84/D28 ratio	0.45(0.39-0.53) [n=98]	1.13(95%CI: 0.92,1.39)
m1273		
D28	2334(2009-2712) [n=89]	1.41(95%CI: 1.11,1.78)
D84	1061(877-1284) [n=90]	1.50(95%CI: 1.14,1.99)
D84/D28 ratio	0.44(0.39-0.50) [n=89]	1.08(95%CI: 0.87,1.33)
ChAd		
D28	191(159-230) [n=96]	0.14(95%CI: 0.11,0.17)
D84	127(105-153) [n=97]	0.23(95%CI: 0.17,0.30)
D84/D28 ratio	0.67(0.61-0.74) [n=96]	1.74(95%CI: 1.41,2.14)
Ad26		
D28	605(491-745) [n=89]	0.33(95%CI: 0.26,0.42)
D84	410(334-504) [n=94]	0.57(95%CI: 0.45,0.73)
D84/D28 ratio	0.66(0.58-0.74) [n=89]	1.62(95%CI: 1.34,1.97)
NVX		
D28	718(588-877) [n=84]	0.51(95%CI: 0.40,0.64)
D84	346(279-430) [n=92]	0.59(95%CI: 0.45,0.78)
D84/D28 ratio	0.47(0.41-0.54) [n=84]	1.23(95%CI: 0.99,1.52)
NVX-half		
D28	465(371-581) [n=84]	0.32(95%CI: 0.25,0.41)
D84	182(145-229) [n=95]	0.31(95%CI: 0.24,0.41)
D84/D28 ratio	0.40(0.36-0.45) [n=84]	1.04(95%CI: 0.84,1.28)
VLA		
D28	196(160-240) [n=82]	0.12(95%CI: 0.10,0.16)
D84	110(90-134) [n=85]	0.17(95%CI: 0.13,0.22)
D84/D28 ratio	0.57(0.50-0.64) [n=81]	1.40(95%CI: 1.15,1.71)
VLA-half		
D28	151(127-180) [n=89]	0.09(95%CI: 0.08,0.12)
D84	84(69-103) [n=97]	0.13(95%CI: 0.10,0.17)
D84/D28 ratio	0.60(0.53-0.66) [n=88]	1.48(95%CI: 1.22,1.79)
Control		
D28	77(68-87) [n=269]	0.05(95%CI: 0.04,0.06)
D84	51(45-59) [n=272]	0.09(95%CI: 0.07,0.11)
D84/D28 ratio	0.66(0.61-0.72) [n=268]	1.67(95%CI: 1.41,1.97)



C)

Live virus neutralising antibody

ChAd/ChAd	GM (95%CI)	GMR (95%CI)
BNT		
D28	4816(3915-5924) [n=42]	Ref
D84	1767(1279-2442) [n=23]	Ref
D84/D28 ratio	0.36(0.26-0.48) [n=22]	Ref
CVn		
D28	830(528-1306) [n=19]	0.21(95%CI: 0.15,0.31)
D84	447(291-688) [n=18]	0.31(95%CI: 0.19,0.49)
D84/D28 ratio	0.54(0.28-1.04) [n=18]	1.46(95%CI: 0.91,2.33)
BNT-half		
D28	2521(1964-3236) [n=38]	0.54(95%CI: 0.40,0.73)
D84	1379(954-1994) [n=24]	0.77(95%CI: 0.50,1.18)
D84/D28 ratio	0.46(0.36-0.58) [n=22]	1.34(95%CI: 0.86,2.10)
m1273		
D28	5276(4049-6875) [n=21]	1.13(95%CI: 0.79,1.61)
D84	2076(1572-2743) [n=19]	1.29(95%CI: 0.81,2.04)
D84/D28 ratio	0.40(0.33-0.49) [n=17]	1.12(95%CI: 0.70,1.81)
ChAd		
D28	338(266-430) [n=37]	0.09(95%CI: 0.06,0.12)
D84	178(115-277) [n=16]	0.12(95%CI: 0.07,0.20)
D84/D28 ratio	0.74(0.53-1.04) [n=14]	1.99(95%CI: 1.19,3.32)
Ad26		
D28	1061(687-1638) [n=22]	0.21(95%CI: 0.15,0.30)
D84	867(580-1295) [n=21]	0.46(95%CI: 0.29,0.73)
D84/D28 ratio	0.81(0.65-0.99) [n=21]	2.20(95%CI: 1.50,3.24)
NVX		
D28	837(536-1307) [n=18]	0.20(95%CI: 0.14,0.30)
D84	546(329-906) [n=17]	0.37(95%CI: 0.23,0.60)
D84/D28 ratio	0.63(0.46-0.84) [n=17]	1.83(95%CI: 1.13,2.96)
NVX-half		
D28	731(494-1082) [n=19]	0.17(95%CI: 0.12,0.25)
D84	356(249-509) [n=18]	0.22(95%CI: 0.14,0.36)
D84/D28 ratio	0.48(0.39-0.59) [n=18]	1.38(95%CI: 0.85,2.22)
VLA		
D28	319(195-520) [n=21]	0.08(95%CI: 0.05,0.11)
D84	244(172-345) [n=20]	0.15(95%CI: 0.10,0.24)
D84/D28 ratio	0.68(0.55-0.83) [n=20]	1.89(95%CI: 1.28,2.79)
VLA-half		
D28	299(211-425) [n=25]	0.07(95%CI: 0.05,0.09)
D84	264(180-386) [n=23]	0.17(95%CI: 0.11,0.26)
D84/D28 ratio	0.94(0.75-1.18) [n=23]	2.57(95%CI: 1.75,3.77)
Control		
D28	158(133-187) [n=105]	0.04(95%CI: 0.03,0.05)
D84	107(84-135) [n=57]	0.07(95%CI: 0.05,0.10)
D84/D28 ratio	0.67(0.60-0.76) [n=54]	1.90(95%CI: 1.34,2.69)



D)

Cellular response (wild-type)

ChAd/ChAd	GM (95%CI)	GMR (95%CI)
BNT		
D28	116(82-163) [n=50]	Ref
D84	43(29-65) [n=48]	Ref
D84/D28 ratio	0.40(0.28-0.57) [n=48]	Ref
CVn		
D28	52(38-72) [n=44]	0.45(95%CI: 0.30,0.70)
D84	35(23-53) [n=39]	0.87(95%CI: 0.50,1.51)
D84/D28 ratio	0.56(0.40-0.77) [n=39]	1.48(95%CI: 0.89,2.46)
BNT-half		
D28	140(99-196) [n=48]	0.97(95%CI: 0.64,1.48)
D84	64(46-90) [n=48]	1.28(95%CI: 0.76,2.17)
D84/D28 ratio	0.50(0.39-0.64) [n=47]	1.25(95%CI: 0.77,2.01)
m1273		
D28	138(93-204) [n=39]	0.95(95%CI: 0.61,1.49)
D84	79(51-121) [n=39]	1.56(95%CI: 0.90,2.71)
D84/D28 ratio	0.61(0.39-0.95) [n=37]	1.59(95%CI: 0.95,2.65)
ChAd		
D28	55(39-77) [n=46]	0.39(95%CI: 0.25,0.59)
D84	36(26-48) [n=46]	0.69(95%CI: 0.41,1.18)
D84/D28 ratio	0.69(0.51-0.94) [n=44]	1.88(95%CI: 1.16,3.07)
Ad26		
D28	102(76-136) [n=50]	0.84(95%CI: 0.57,1.24)
D84	67(46-99) [n=47]	1.54(95%CI: 0.98,2.42)
D84/D28 ratio	0.69(0.52-0.91) [n=47]	1.81(95%CI: 1.13,2.92)
NVX		
D28	111(76-160) [n=45]	1.11(95%CI: 0.72,1.70)
D84	60(42-85) [n=47]	1.50(95%CI: 0.88,2.58)
D84/D28 ratio	0.53(0.37-0.77) [n=44]	1.38(95%CI: 0.84,2.26)
NVX-half		
D28	98(73-130) [n=48]	0.88(95%CI: 0.58,1.35)
D84	55(37-79) [n=49]	1.20(95%CI: 0.70,2.04)
D84/D28 ratio	0.56(0.41-0.77) [n=46]	1.49(95%CI: 0.92,2.44)
VLA		
D28	54(37-79) [n=41]	0.46(95%CI: 0.30,0.69)
D84	34(23-49) [n=40]	0.81(95%CI: 0.50,1.29)
D84/D28 ratio	0.71(0.49-1.01) [n=39]	1.79(95%CI: 1.09,2.96)
VLA-half		
D28	55(40-75) [n=49]	0.42(95%CI: 0.29,0.63)
D84	27(19-37) [n=49]	0.53(95%CI: 0.34,0.82)
D84/D28 ratio	0.49(0.34-0.70) [n=48]	1.23(95%CI: 0.76,1.98)
Control		
D28	43(35-52) [n=134]	0.32(95%CI: 0.23,0.45)
D84	32(25-40) [n=132]	0.61(95%CI: 0.41,0.92)
D84/D28 ratio	0.76(0.61-0.94) [n=129]	1.85(95%CI: 1.25,2.75)

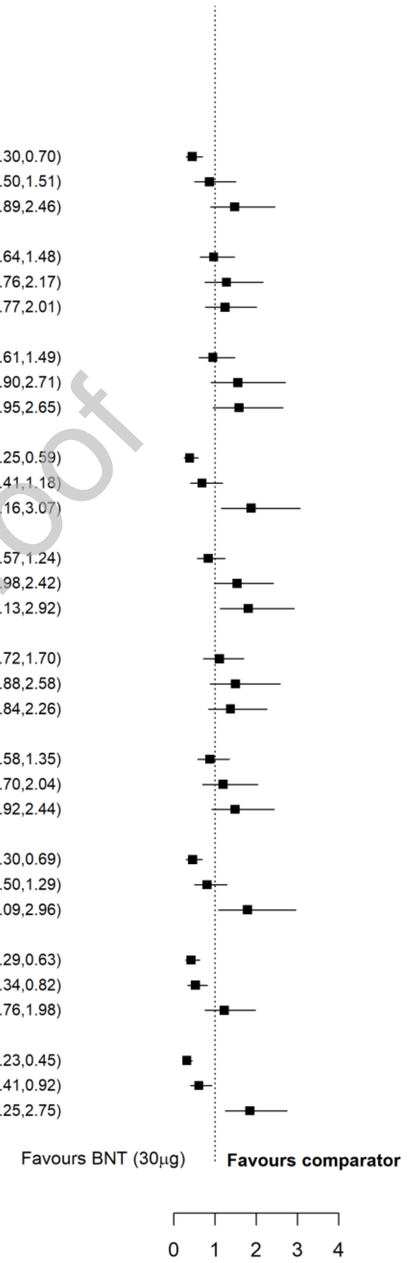
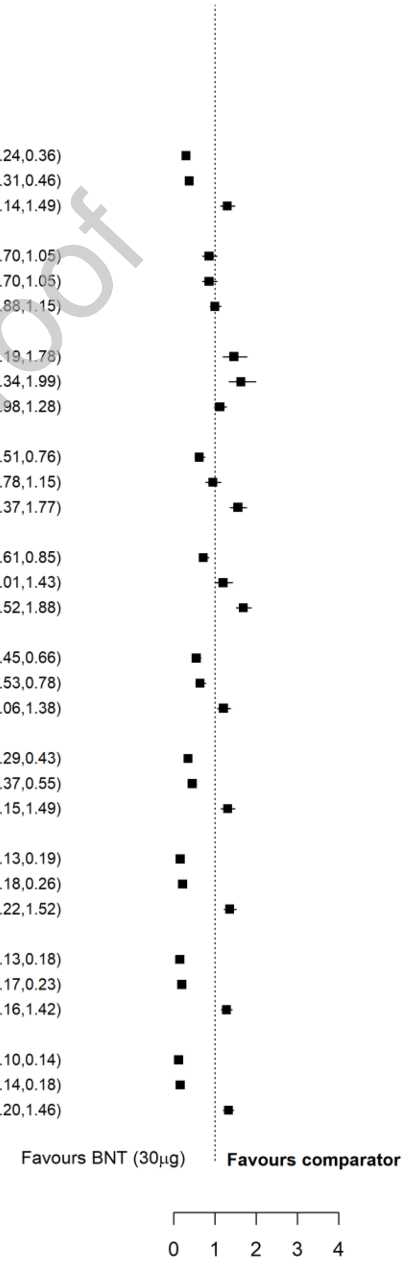


Figure 2. Immunogenicity A) Anti-spike IgG (ELU/mL); B) Pseudotype virus neutralising antibody (NT_{50}); C) Live virus neutralising antibody (NT_{80}); D) Cellular response (SFC per million PBMCs) at D28 and D84 among the SARS-CoV-2 naïve population primed with ChAD/ ChAD

A)

SARS-CoV-2 anti-spike IgG

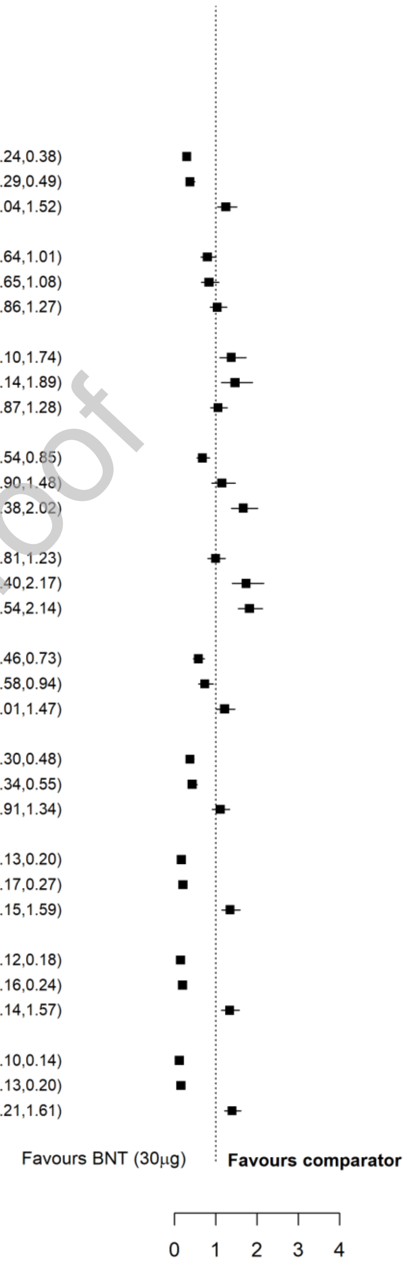
BNT/BNT	GM (95%CI)	GMR (95%CI)
BNT		
D28	27307(24182-30835) [n=94]	Ref
D84	13025(11291-15025) [n=93]	Ref
D84/D28 ratio	0.48(0.44-0.51) [n=93]	Ref
CVn		
D28	7602(6467-8937) [n=88]	0.30(95%CI: 0.24,0.36)
D84	4649(3956-5464) [n=90]	0.38(95%CI: 0.31,0.46)
D84/D28 ratio	0.62(0.57-0.67) [n=88]	1.30(95%CI: 1.14,1.49)
BNT-half		
D28	23337(20072-27132) [n=86]	0.86(95%CI: 0.70,1.05)
D84	11488(9739-13550) [n=85]	0.86(95%CI: 0.70,1.05)
D84/D28 ratio	0.49(0.45-0.53) [n=84]	1.00(95%CI: 0.88,1.15)
m1273		
D28	33690(27547-41202) [n=87]	1.46(95%CI: 1.19,1.78)
D84	17718(14594-21512) [n=86]	1.63(95%CI: 1.34,1.99)
D84/D28 ratio	0.53(0.50-0.57) [n=86]	1.12(95%CI: 0.98,1.28)
ChAd		
D28	13361(11593-15398) [n=91]	0.62(95%CI: 0.51,0.76)
D84	9685(8215-11419) [n=91]	0.95(95%CI: 0.78,1.15)
D84/D28 ratio	0.72(0.67-0.79) [n=91]	1.56(95%CI: 1.37,1.77)
Ad26		
D28	17816(15036-21109) [n=88]	0.72(95%CI: 0.61,0.85)
D84	14212(11910-16958) [n=90]	1.20(95%CI: 1.01,1.43)
D84/D28 ratio	0.80(0.73-0.88) [n=88]	1.69(95%CI: 1.52,1.88)
NVX		
D28	10511(8704-12693) [n=98]	0.55(95%CI: 0.45,0.66)
D84	5850(4827-7089) [n=100]	0.64(95%CI: 0.53,0.78)
D84/D28 ratio	0.56(0.52-0.60) [n=98]	1.21(95%CI: 1.06,1.38)
NVX-half		
D28	8449(7097-10060) [n=94]	0.35(95%CI: 0.29,0.43)
D84	5051(4163-6129) [n=95]	0.45(95%CI: 0.37,0.55)
D84/D28 ratio	0.60(0.55-0.65) [n=94]	1.31(95%CI: 1.15,1.49)
VLA		
D28	4176(3570-4884) [n=85]	0.16(95%CI: 0.13,0.19)
D84	2703(2305-3170) [n=84]	0.22(95%CI: 0.18,0.26)
D84/D28 ratio	0.64(0.60-0.69) [n=84]	1.36(95%CI: 1.22,1.52)
VLA-half		
D28	3687(3163-4299) [n=96]	0.15(95%CI: 0.13,0.18)
D84	2229(1907-2605) [n=96]	0.20(95%CI: 0.17,0.23)
D84/D28 ratio	0.60(0.54-0.68) [n=96]	1.28(95%CI: 1.16,1.42)
Control		
D28	2881(2593-3201) [n=289]	0.12(95%CI: 0.10,0.14)
D84	1795(1613-1996) [n=291]	0.16(95%CI: 0.14,0.18)
D84/D28 ratio	0.62(0.60-0.64) [n=289]	1.33(95%CI: 1.20,1.46)



B)

Pseudotype virus neutralising antibody

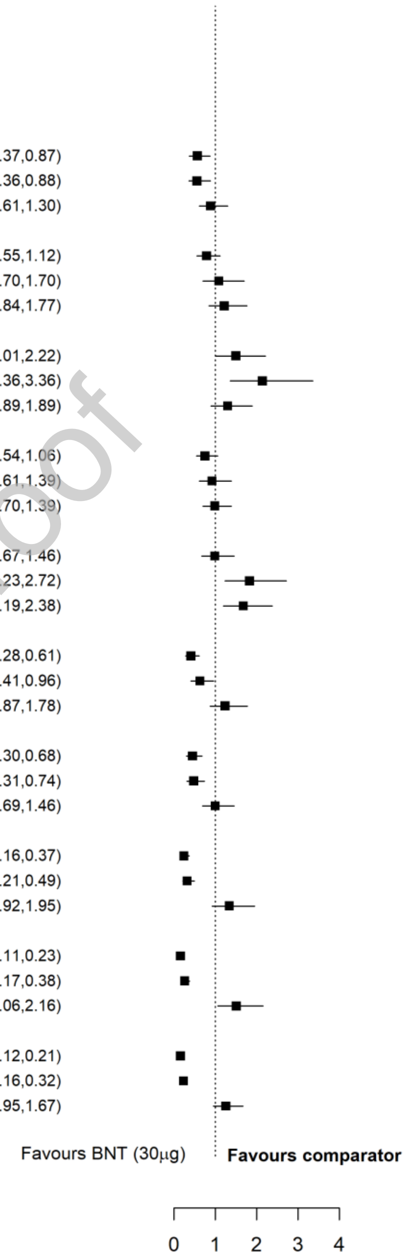
BNT/BNT	GM (95%CI)	GMR (95%CI)
BNT		
D28	1767(1502-2080) [n=94]	Ref
D84	789(656-948) [n=94]	Ref
D84/D28 ratio	0.45(0.39-0.51) [n=94]	Ref
CVn		
D28	479(403-570) [n=87]	0.30(95%CI: 0.24,0.38)
D84	277(227-337) [n=90]	0.38(95%CI: 0.29,0.49)
D84/D28 ratio	0.58(0.52-0.64) [n=87]	1.25(95%CI: 1.04,1.52)
BNT-half		
D28	1370(1142-1643) [n=85]	0.80(95%CI: 0.64,1.01)
D84	691(564-847) [n=86]	0.84(95%CI: 0.65,1.08)
D84/D28 ratio	0.51(0.44-0.58) [n=85]	1.04(95%CI: 0.86,1.27)
m1273		
D28	2022(1606-2545) [n=86]	1.38(95%CI: 1.10,1.74)
D84	971(775-1217) [n=85]	1.47(95%CI: 1.14,1.89)
D84/D28 ratio	0.49(0.43-0.55) [n=84]	1.06(95%CI: 0.87,1.28)
ChAd		
D28	956(800-1143) [n=91]	0.68(95%CI: 0.54,0.85)
D84	718(589-876) [n=90]	1.15(95%CI: 0.90,1.48)
D84/D28 ratio	0.76(0.68-0.84) [n=90]	1.67(95%CI: 1.38,2.02)
Ad26		
D28	1521(1242-1862) [n=77]	1.00(95%CI: 0.81,1.23)
D84	1252(986-1590) [n=90]	1.74(95%CI: 1.40,2.17)
D84/D28 ratio	0.83(0.71-0.96) [n=77]	1.82(95%CI: 1.54,2.14)
NVX		
D28	738(601-908) [n=91]	0.58(95%CI: 0.46,0.73)
D84	406(330-499) [n=100]	0.74(95%CI: 0.58,0.94)
D84/D28 ratio	0.53(0.48-0.59) [n=91]	1.22(95%CI: 1.01,1.47)
NVX-half		
D28	591(480-728) [n=86]	0.38(95%CI: 0.30,0.48)
D84	290(237-355) [n=94]	0.43(95%CI: 0.34,0.55)
D84/D28 ratio	0.48(0.42-0.56) [n=85]	1.11(95%CI: 0.91,1.34)
VLA		
D28	285(240-340) [n=78]	0.17(95%CI: 0.13,0.20)
D84	161(132-196) [n=85]	0.21(95%CI: 0.17,0.27)
D84/D28 ratio	0.60(0.53-0.67) [n=78]	1.35(95%CI: 1.15,1.59)
VLA-half		
D28	230(197-269) [n=85]	0.15(95%CI: 0.12,0.18)
D84	135(115-159) [n=96]	0.20(95%CI: 0.16,0.24)
D84/D28 ratio	0.61(0.54-0.68) [n=85]	1.34(95%CI: 1.14,1.57)
Control		
D28	176(156-198) [n=288]	0.12(95%CI: 0.10,0.14)
D84	110(98-123) [n=291]	0.16(95%CI: 0.13,0.20)
D84/D28 ratio	0.63(0.59-0.66) [n=288]	1.40(95%CI: 1.21,1.61)



C)

Live virus neutralising antibody

BNT/BNT	GM (95%CI)	GMR (95%CI)
BNT		
D28	4644(3697-5834) [n=35]	Ref
D84	1958(1522-2520) [n=23]	Ref
D84/D28 ratio	0.49(0.38-0.64) [n=23]	Ref
CVn		
D28	1994(1185-3355) [n=17]	0.57(95%CI: 0.37,0.87)
D84	906(605-1356) [n=17]	0.56(95%CI: 0.36,0.88)
D84/D28 ratio	0.45(0.35-0.60) [n=17]	0.89(95%CI: 0.61,1.30)
BNT-half		
D28	3264(2595-4106) [n=34]	0.79(95%CI: 0.55,1.12)
D84	2300(1452-3644) [n=20]	1.09(95%CI: 0.70,1.70)
D84/D28 ratio	0.67(0.50-0.90) [n=19]	1.22(95%CI: 0.84,1.77)
m1273		
D28	5356(4150-6913) [n=22]	1.50(95%CI: 1.01,2.22)
D84	3009(2245-4033) [n=16]	2.14(95%CI: 1.36,3.36)
D84/D28 ratio	0.62(0.52-0.76) [n=16]	1.30(95%CI: 0.89,1.89)
ChAd		
D28	2575(2052-3231) [n=40]	0.75(95%CI: 0.54,1.06)
D84	1366(1009-1850) [n=23]	0.92(95%CI: 0.61,1.39)
D84/D28 ratio	0.48(0.42-0.56) [n=23]	0.99(95%CI: 0.70,1.39)
Ad26		
D28	4045(2781-5883) [n=21]	0.99(95%CI: 0.67,1.46)
D84	3439(2244-5271) [n=21]	1.83(95%CI: 1.23,2.72)
D84/D28 ratio	0.85(0.69-1.05) [n=21]	1.68(95%CI: 1.19,2.38)
NVX		
D28	1374(1009-1872) [n=23]	0.41(95%CI: 0.28,0.61)
D84	799(565-1131) [n=21]	0.63(95%CI: 0.41,0.96)
D84/D28 ratio	0.54(0.45-0.66) [n=21]	1.24(95%CI: 0.87,1.78)
NVX-half		
D28	1850(1265-2706) [n=19]	0.45(95%CI: 0.30,0.68)
D84	848(580-1239) [n=18]	0.48(95%CI: 0.31,0.74)
D84/D28 ratio	0.47(0.37-0.61) [n=18]	1.00(95%CI: 0.69,1.46)
VLA		
D28	794(539-1169) [n=18]	0.24(95%CI: 0.16,0.37)
D84	596(408-870) [n=17]	0.32(95%CI: 0.21,0.49)
D84/D28 ratio	0.72(0.55-0.93) [n=17]	1.34(95%CI: 0.92,1.95)
VLA-half		
D28	555(401-767) [n=22]	0.16(95%CI: 0.11,0.23)
D84	419(299-585) [n=21]	0.26(95%CI: 0.17,0.38)
D84/D28 ratio	0.79(0.68-0.92) [n=20]	1.51(95%CI: 1.06,2.16)
Control		
D28	553(457-668) [n=112]	0.16(95%CI: 0.12,0.21)
D84	343(280-420) [n=67]	0.23(95%CI: 0.16,0.32)
D84/D28 ratio	0.63(0.52-0.77) [n=67]	1.26(95%CI: 0.95,1.67)



D)

Cellular response (wild-type)

BNT/BNT	GM (95%CI)	GMR (95%CI)
BNT		
D28	82(64-105) [n=48]	Ref
D84	37(28-48) [n=50]	Ref
D84/D28 ratio	0.47(0.37-0.60) [n=48]	Ref
CVn		
D28	44(30-63) [n=43]	0.58(95%CI: 0.35,0.94)
D84	33(22-52) [n=42]	0.74(95%CI: 0.45,1.21)
D84/D28 ratio	0.84(0.58-1.22) [n=40]	1.57(95%CI: 0.92,2.66)
BNT-half		
D28	79(55-115) [n=41]	0.84(95%CI: 0.51,1.39)
D84	58(38-88) [n=39]	1.08(95%CI: 0.65,1.80)
D84/D28 ratio	0.67(0.45-0.99) [n=38]	1.23(95%CI: 0.72,2.10)
m1273		
D28	106(67-168) [n=41]	1.22(95%CI: 0.75,2.00)
D84	75(51-110) [n=42]	1.58(95%CI: 0.97,2.58)
D84/D28 ratio	0.69(0.51-0.96) [n=41]	1.37(95%CI: 0.82,2.29)
ChAd		
D28	93(63-136) [n=45]	0.93(95%CI: 0.57,1.50)
D84	49(31-77) [n=44]	0.89(95%CI: 0.55,1.45)
D84/D28 ratio	0.53(0.38-0.75) [n=43]	1.01(95%CI: 0.60,1.69)
Ad26		
D28	111(73-168) [n=45]	1.15(95%CI: 0.75,1.77)
D84	59(37-93) [n=45]	1.27(95%CI: 0.82,1.97)
D84/D28 ratio	0.50(0.36-0.69) [n=44]	1.05(95%CI: 0.65,1.71)
NVX		
D28	56(36-86) [n=48]	0.64(95%CI: 0.40,1.03)
D84	36(24-55) [n=47]	0.77(95%CI: 0.47,1.24)
D84/D28 ratio	0.63(0.42-0.96) [n=46]	1.26(95%CI: 0.75,2.09)
NVX-half		
D28	36(24-53) [n=46]	0.52(95%CI: 0.32,0.84)
D84	30(21-43) [n=46]	0.86(95%CI: 0.53,1.41)
D84/D28 ratio	0.81(0.58-1.14) [n=45]	1.62(95%CI: 0.97,2.70)
VLA		
D28	32(23-45) [n=44]	0.40(95%CI: 0.26,0.63)
D84	23(15-33) [n=43]	0.61(95%CI: 0.39,0.96)
D84/D28 ratio	0.73(0.52-1.01) [n=43]	1.56(95%CI: 0.95,2.56)
VLA-half		
D28	37(25-53) [n=50]	0.42(95%CI: 0.28,0.64)
D84	27(18-40) [n=50]	0.65(95%CI: 0.43,1.00)
D84/D28 ratio	0.75(0.52-1.08) [n=50]	1.55(95%CI: 0.97,2.48)
Control		
D28	29(23-36) [n=141]	0.35(95%CI: 0.24,0.50)
D84	23(18-29) [n=140]	0.54(95%CI: 0.37,0.79)
D84/D28 ratio	0.80(0.65-0.97) [n=137]	1.63(95%CI: 1.09,2.43)

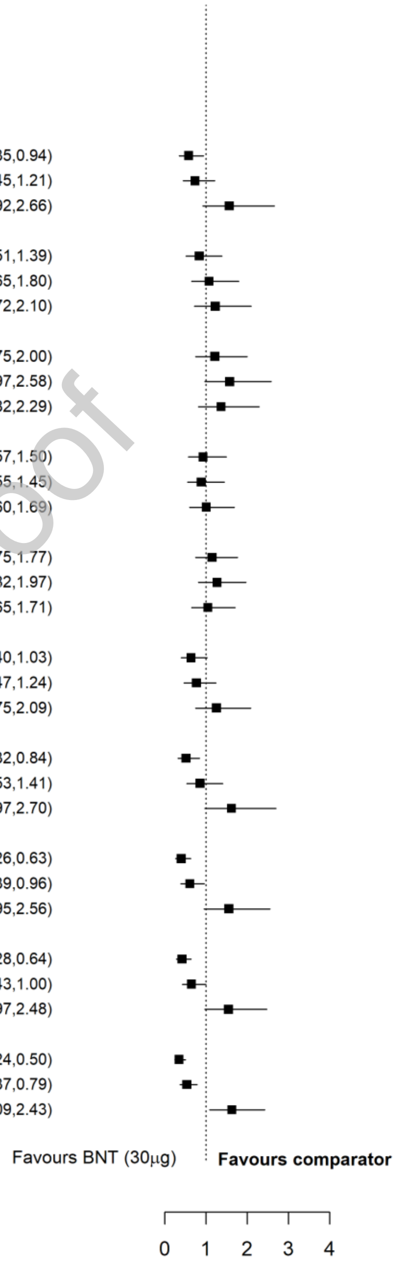
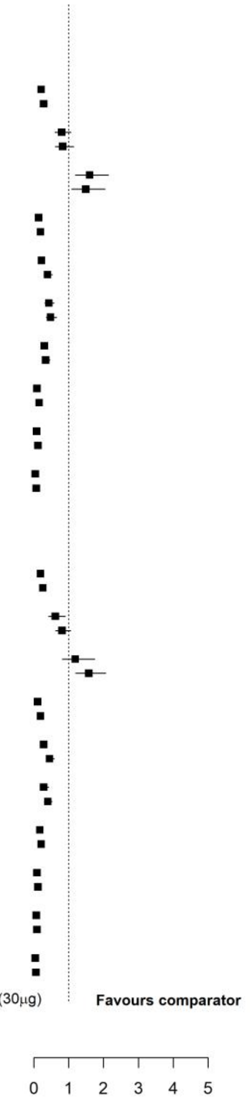


Figure 3. Immunogenicity A) Anti-spike IgG (ELU/mL); B) Pseudotype virus neutralising antibody (NT_{50}); C) Live virus neutralising antibody (NT_{80}); D) Cellular response (SFC per million PBMCs) at D28 and D84 among the SARS-CoV-2 naïve population primed with BNT/ BNT

A) ChAd/ChAd Primed Population.

ChAd/ChAd

Age group	Vaccine	Day	GM (95%CI)	GMR (95%CI)
<70 years				
	BNT	*D28*	22630(18310-27968) [n=40]	Ref
		D84	8986(7181-11246) [n=41]	Ref
	CVn	*D28*	4025(3368-4810) [n=47]	0.21(95%CI: 0.16,0.28)
		D84	2218(1801-2732) [n=47]	0.28(95%CI: 0.21,0.38)
	BNT-half	*D28*	16497(13630-19968) [n=41]	0.80(95%CI: 0.60,1.06)
		D84	7183(5908-8733) [n=43]	0.83(95%CI: 0.61,1.14)
	m1273	*D28*	37115(29957-45985) [n=38]	1.60(95%CI: 1.19,2.14)
		D84	15055(11434-19822) [n=39]	1.49(95%CI: 1.08,2.04)
	ChAd	*D28*	2739(2165-3466) [n=46]	0.14(95%CI: 0.11,0.19)
		D84	1557(1210-2003) [n=47]	0.19(95%CI: 0.14,0.26)
	Ad26	*D28*	5818(4545-7448) [n=41]	0.22(95%CI: 0.17,0.28)
		D84	4163(3292-5263) [n=42]	0.39(95%CI: 0.29,0.53)
	NVX	*D28*	8257(6434-10595) [n=45]	0.43(95%CI: 0.32,0.57)
		D84	3826(2839-5157) [n=45]	0.48(95%CI: 0.35,0.65)
	NVX-half	*D28*	6500(4876-8665) [n=47]	0.30(95%CI: 0.22,0.39)
		D84	3045(2280-4068) [n=47]	0.34(95%CI: 0.25,0.46)
	VLA	*D28*	1596(1199-2124) [n=38]	0.09(95%CI: 0.07,0.11)
		D84	1145(899-1457) [n=38]	0.15(95%CI: 0.11,0.20)
	VLA-half	*D28*	1713(1359-2160) [n=41]	0.08(95%CI: 0.06,0.10)
		D84	1136(901-1432) [n=41]	0.12(95%CI: 0.09,0.16)
	Control	*D28*	841(720-981) [n=117]	0.04(95%CI: 0.03,0.05)
		D84	535(446-641) [n=119]	0.07(95%CI: 0.05,0.09)
>=70 years				
	BNT	*D28*	19091(15554-23432) [n=52]	Ref
		D84	8440(6877-10359) [n=53]	Ref
	CVn	*D28*	3746(2949-4757) [n=49]	0.19(95%CI: 0.13,0.29)
		D84	1933(1532-2440) [n=49]	0.26(95%CI: 0.20,0.34)
	BNT-half	*D28*	14807(11188-19596) [n=57]	0.62(95%CI: 0.42,0.90)
		D84	7403(5919-9260) [n=57]	0.81(95%CI: 0.62,1.05)
	m1273	*D28*	27702(21337-35966) [n=51]	1.19(95%CI: 0.81,1.75)
		D84	14071(11249-17601) [n=51]	1.58(95%CI: 1.20,2.06)
	ChAd	*D28*	2105(1614-2745) [n=50]	0.11(95%CI: 0.08,0.17)
		D84	1287(980-1690) [n=50]	0.19(95%CI: 0.14,0.24)
	Ad26	*D28*	5750(4579-7220) [n=51]	0.28(95%CI: 0.21,0.36)
		D84	4060(3127-5270) [n=52]	0.45(95%CI: 0.35,0.58)
	NVX	*D28*	5783(4441-7530) [n=47]	0.28(95%CI: 0.19,0.42)
		D84	3049(2348-3961) [n=47]	0.40(95%CI: 0.30,0.52)
	NVX-half	*D28*	3238(2500-4193) [n=48]	0.17(95%CI: 0.12,0.26)
		D84	1519(1124-2052) [n=48]	0.21(95%CI: 0.16,0.28)
	VLA	*D28*	1876(1418-2482) [n=47]	0.09(95%CI: 0.07,0.12)
		D84	1166(866-1570) [n=48]	0.12(95%CI: 0.09,0.16)
	VLA-half	*D28*	1242(961-1606) [n=56]	0.07(95%CI: 0.05,0.09)
		D84	751(569-990) [n=57]	0.09(95%CI: 0.07,0.12)
	Control	*D28*	769(652-907) [n=151]	0.04(95%CI: 0.03,0.05)
		D84	468(400-548) [n=153]	0.06(95%CI: 0.05,0.07)



B) BNT/BNT Primed Population

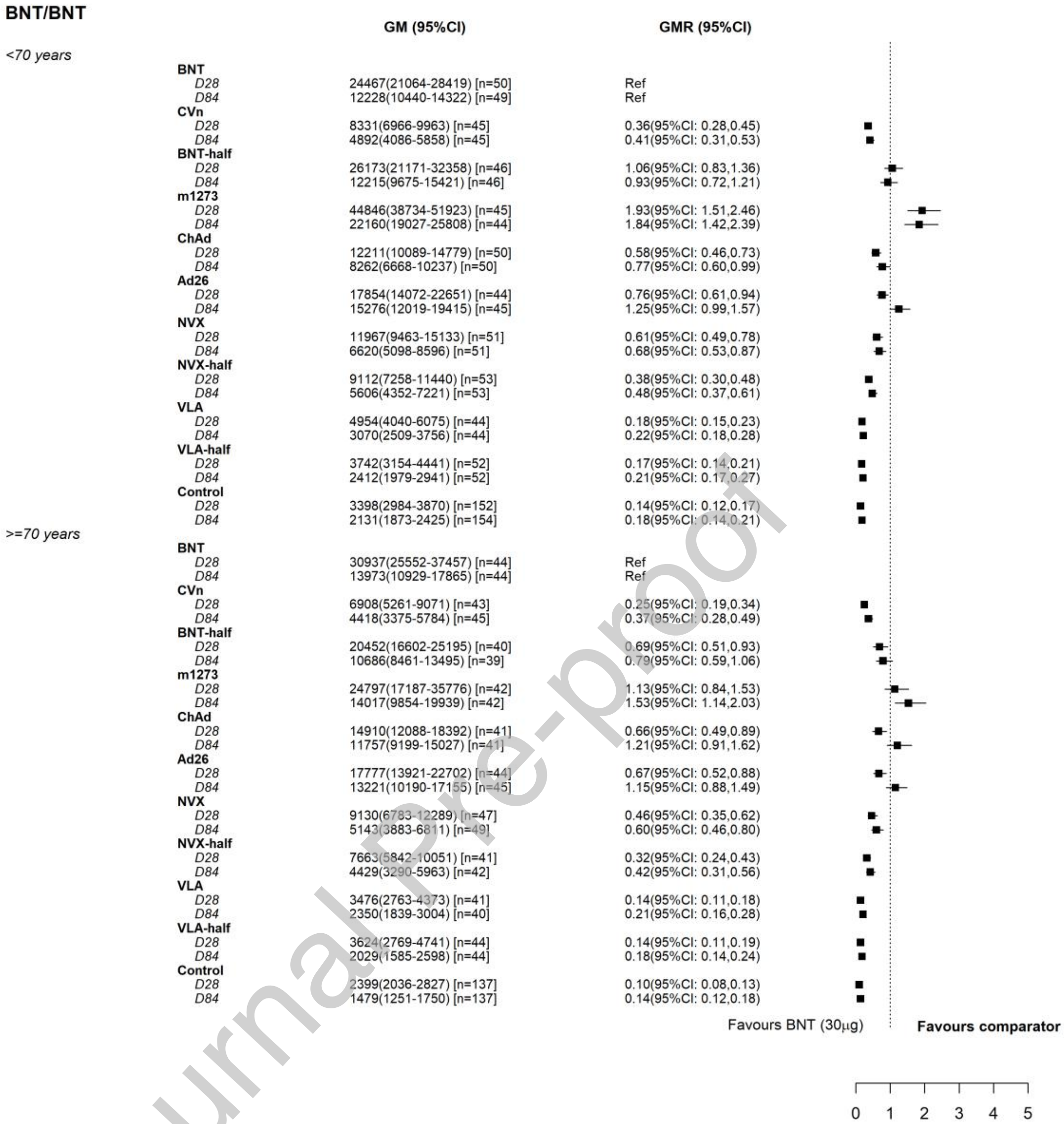
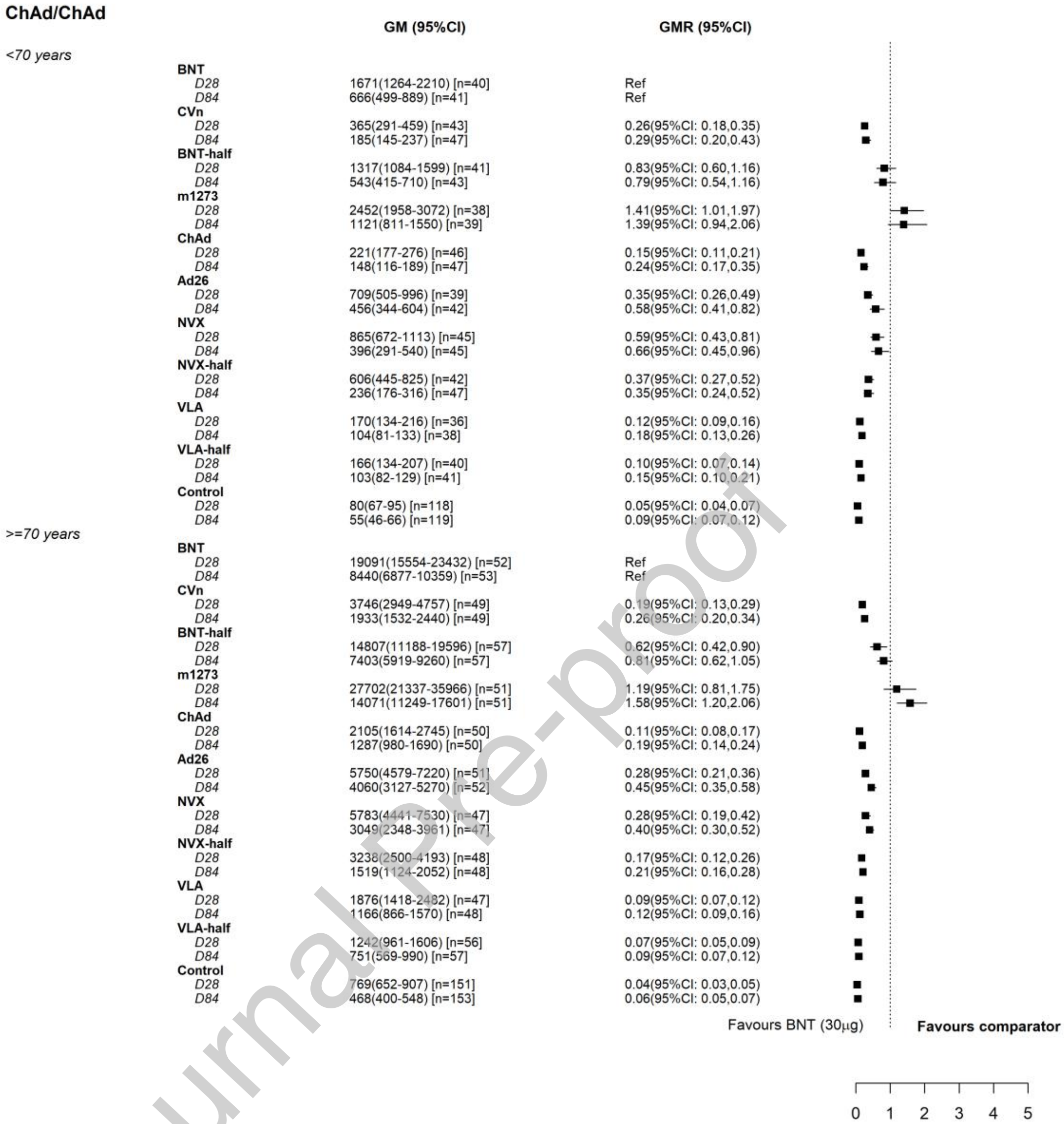


Figure 4. Anti-spike IgG (ELU/mL) at D28 and D84 among the SARS-CoV-2 naïve population by age group A) ChAD/ChAd, B) BNT/BNT

A) ChAd/ChAd Primed Population



B) BNT/BNT Primed Population

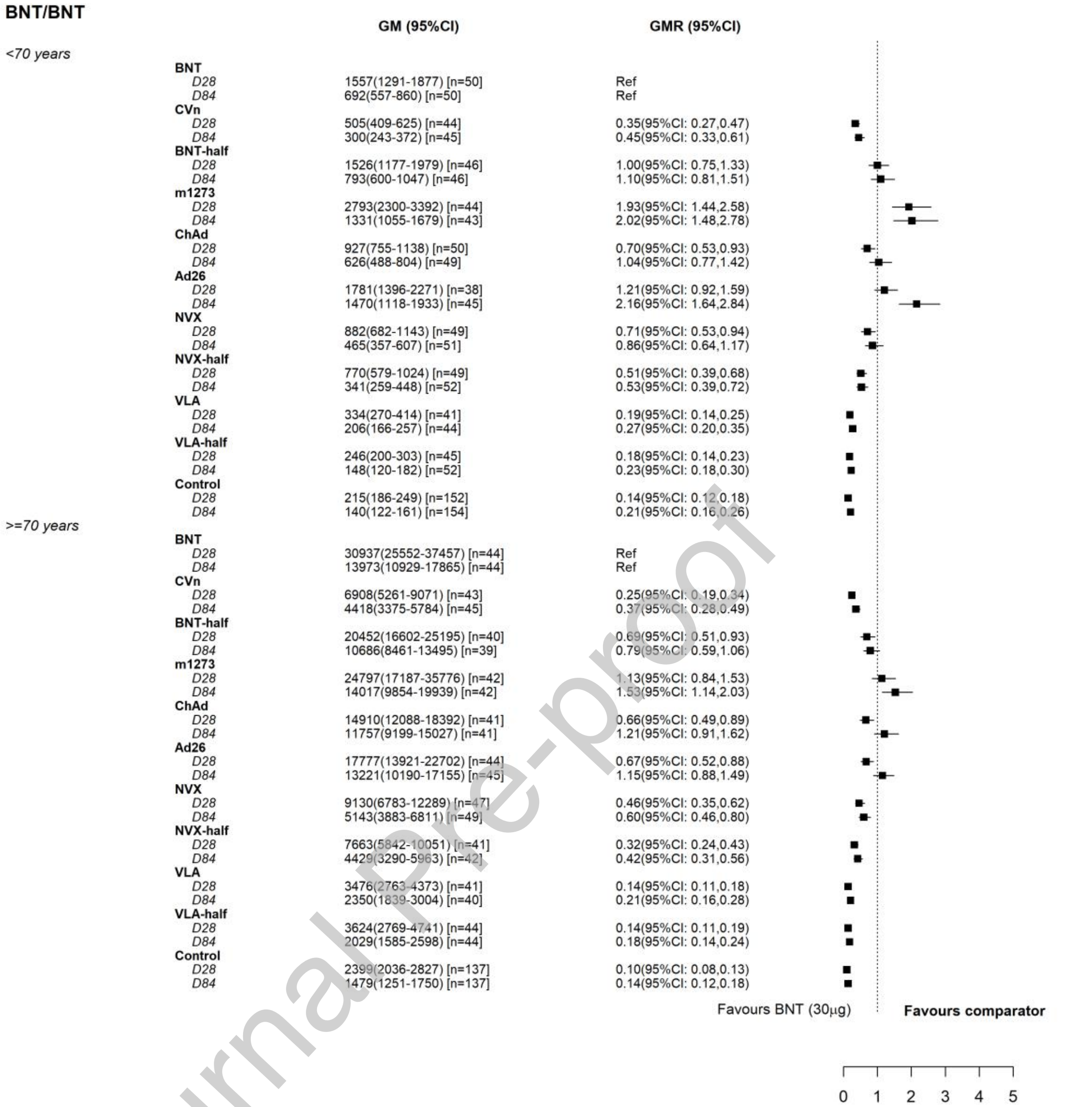
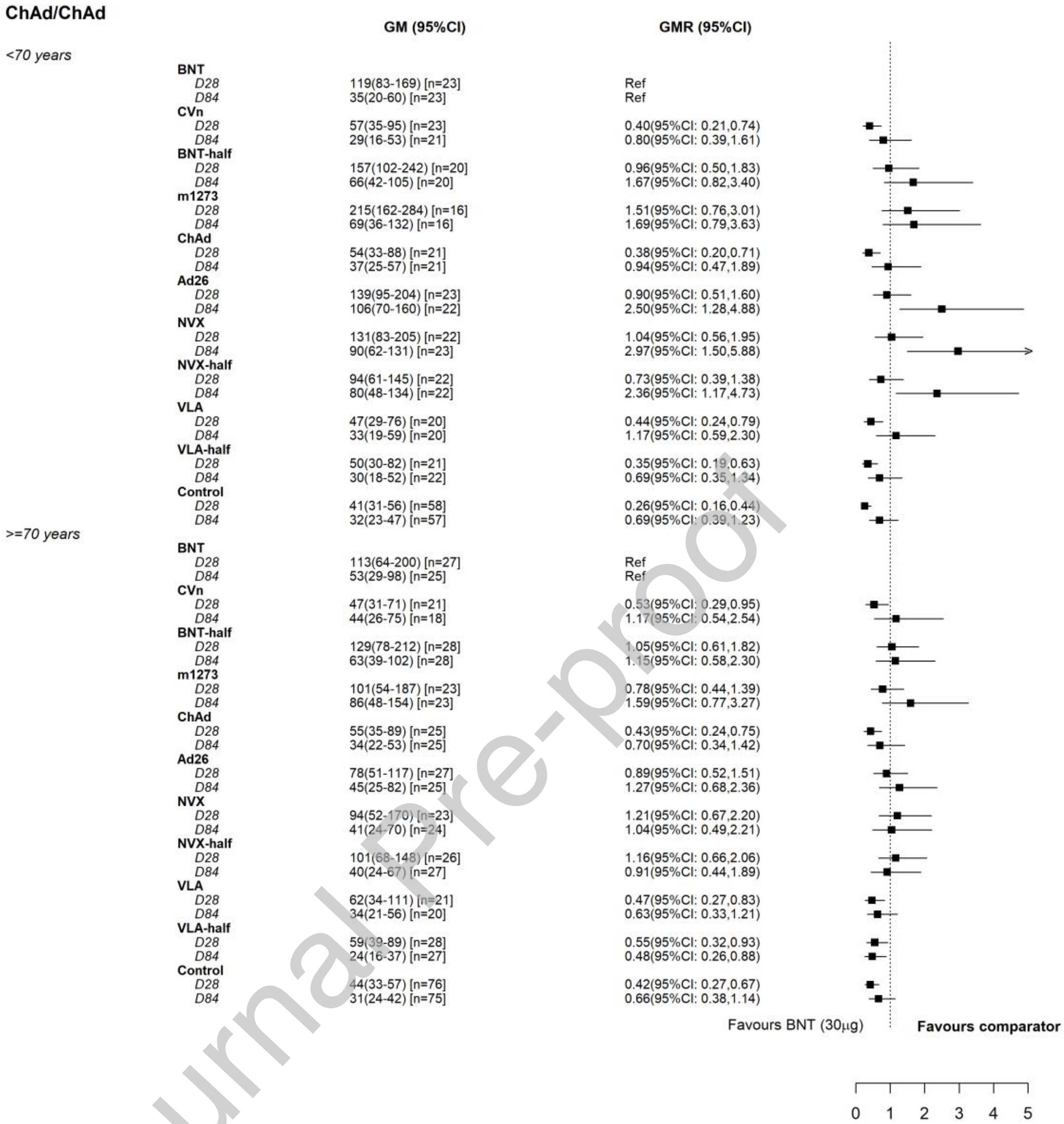


Figure 5. Pseudotype virus neutralising antibody (NT_{50}) at D28 and D84 among the SARS-CoV-2 naïve population by age group A) ChAD/ChAd, B) BNT/BNT

A) ChAd/ChAd Primed Population



B) BNT/BNT Primed Population

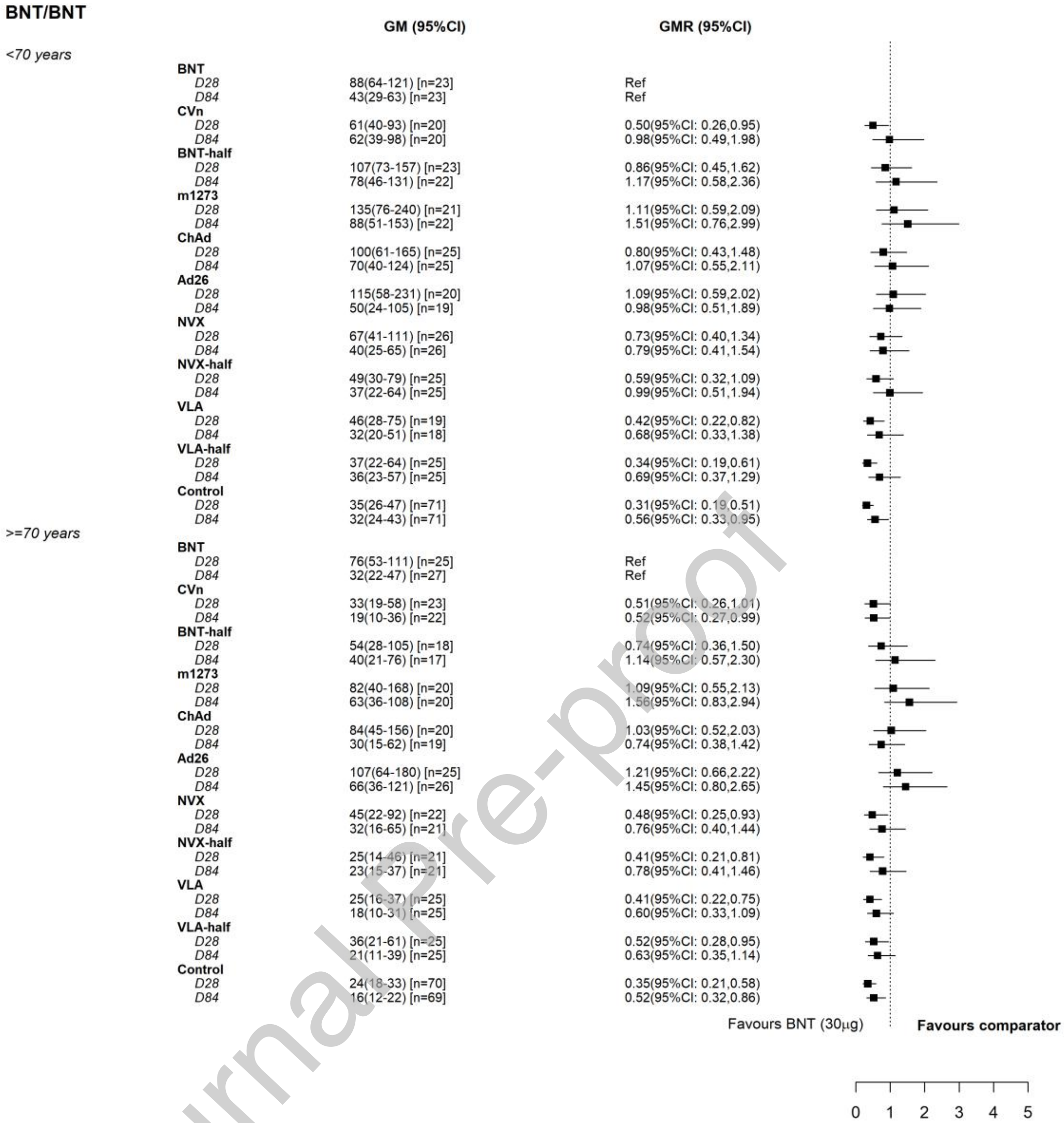


Figure 6. Cellular response (SFC per million PBMCs) at D28 and D84 among the SARS-CoV-2 naïve population by age group A) ChAD/ChAd, B) BNT/BNT

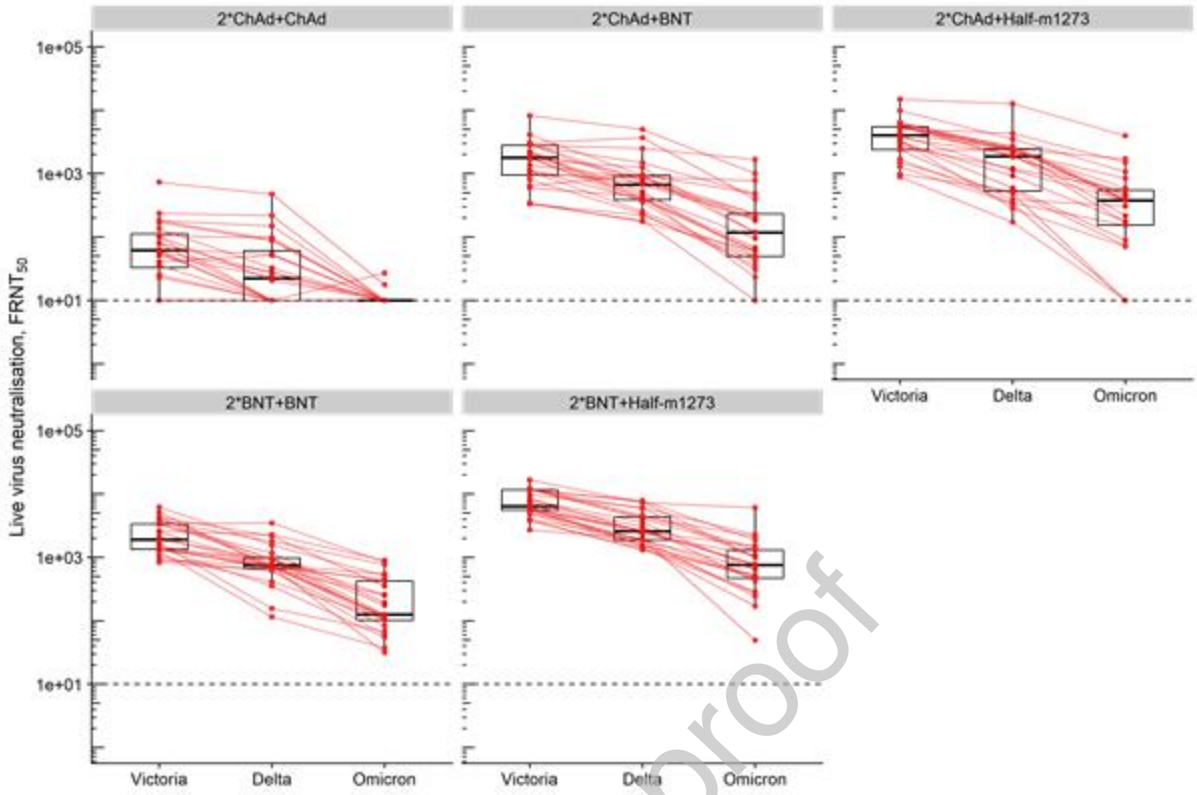


Figure 7. Live neutralising antibodies against wild type, Delta and Omicron at 28 days post boost