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Persistence of immune responses after heterologous and homologous third COVID-19 vaccine dose schedules in the UK: eight-month analyses of the COV-BOOST trial

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SUMMARY

Background: COV-BOOST is a multicentre, randomised, controlled, phase 2 trial of seven COVID-19 vaccines used as a third booster dose in June 2021. Monovalent messenger RNA (mRNA) COVID-19 vaccines were subsequently widely used for the third and fourth-dose vaccination campaigns in high-income countries. Real-world vaccine effectiveness against symptomatic infections following third doses declined during the Omicron wave. This report compares the immunogenicity and kinetics of responses to third doses of vaccines from day (D) 28 to D242 following third doses in seven study arms.

Methods: The trial initially included ten experimental vaccine arms (seven full-dose, three half-dose) delivered at three groups of six sites. Participants in each site group were randomised to three or four experimental vaccines, or MenACWY control. The trial was stratified such that half of participants had previously received two primary doses of ChAdOx1 nCov-19 (Oxford–AstraZeneca; hereafter referred to as ChAd) and half had received two doses of BNT162b2 (Pfizer–BioNtech, hereafter referred to as BNT). The D242 follow-up was done in seven arms (five full-dose, two half-dose). The BNT vaccine was used as the reference as it was the most commonly deployed third-dose vaccine in clinical practice in high-income countries. The primary analysis was conducted using all randomised and baseline seronegative participants who were SARS-CoV-2 naïve during the study and who had not received a further COVID-19 vaccine for any reason since third dose randomisation.

Results: Among the 817 participants included in this report, the median age was 72 years (IQR: 55–78) with 50.7% being female. The decay rates of anti-spike IgG between vaccines are different among both populations who received initial doses of ChAd/ChAd and BNT/BNT. In the population that previously received ChAd/ChAd, mRNA vaccines had the highest titre at D242 following their vaccine dose although Ad26. COV2. S (Janssen; hereafter referred to as Ad26) showed slower decay. For people who received BNT/BNT as their initial doses, a slower decay was also seen in the Ad26 and ChAd arms. The anti-spike IgG became significantly higher in the Ad26 arm compared to the BNT arm as early as 3 months following vaccination. Similar decay rates were seen between BNT and half-BNT; the geometric mean ratios ranged from 0.76 to 0.94 at different time points. The difference in decay rates between vaccines was similar for wild-type live virus-neutralising antibodies and that seen for anti-spike IgG. For cellular responses, the persistence was similar between study arms.

Conclusions: Heterologous third doses with viral vector vaccines following two doses of mRNA achieve more durable humoral responses compared with three doses of mRNA vaccines. Lower doses of mRNA vaccines could be considered for future booster campaigns.

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Introduction

Third and fourth doses of COVID-19 vaccines have been deployed in populations considered vulnerable or at higher risk.[1] In 2021 and 2022, two additional doses have been deployed in some regions to protect the most vulnerable against both winter and spring COVID-19 waves. Decisions about when to offer additional vaccines and which vaccines should be offered should be informed by data on differences between vaccine classes and doses. Vaccines that potentially provide longer-lasting immunity may be preferred to those that might need to be given to individuals at shorter intervals. Alternatively, different doses may be an option depending on the duration of immune response.

The Omicron variant (B.1.1.529), with a number of mutations in the spike protein, was first reported in November 2021 but fully dominant in most western countries by January 2022. Omicron has caused the largest COVID-19 infection waves since the beginning of the COVID-19 pandemic in many countries, including those with high coverage of initial COVID-19 vaccine doses.[2] The decision to predominantly use mRNA vaccines as third doses before, during, and after the omicron waves was primarily due to their high peak humoral response,[3,4] together with the potential for rare intracerebral thrombosis events associated with viral vector COVID-19 vaccines most frequent in younger subjects.[5]

Real-world data in different countries have shown that mRNA booster doses increased vaccine effectiveness against symptomatic infection, hospitalisation, and death for both Delta (B.1.617.2) and Omicron (B.1.1.529) variants,[6–9] compared with unboosted cohorts receiving two priming doses of COVID-19 vaccines alone. However, a waning of protection against infection and transmission of infection following mRNA vaccine booster doses was also seen, especially for the Omicron variant.[6] Despite waning protection against infection, third and subsequently fourth doses of mRNA vaccines appear to have maintained better overall protection against severe COVID-19 illness (i.e. hospitalisation and death).[1]

Several studies have reported the short-term immunogenicity of different vaccines as a third dose[3,4], but limited data have been available to evaluate long-term persistence of immunity. The three-month data from the COV-BOOST trial and 16-week data from a cohort study in the US[10] have both reported possible increased durability after heterologous booster with viral-vector vaccine given as the third dose following two doses of mRNA vaccines compared to three doses of mRNA vaccine.[11] The only clinical trial data beyond this timepoint is a 6-month follow-up of homologous third dose boosters with the CoronaVac whole inactivated virus vaccine which showed a 4-fold decline in neutralising antibodies,[12] and observational data showing a 4-fold decrease in spike IgG 6 months after heterologous BNT booster following 2 doses of CoronaVac.[13] To

provide further data supporting global policymaking on the choice of future boosters and to inform manufacturing and supply decision-making, we further analysed the COV-BOOST data to report the kinetics of immune responses until eight months following the third dose.

Methods

Trial design and oversight, treatments

The detailed design of the COV-BOOST trial (ISRCTN: 73765130, protocol available at https://www.covboost.org.uk/protocol) has been previously reported.[3] 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, participants were randomised with equal probability between three or four experimental vaccines, or a control vaccine (MenACWY), with equal probability. Trial recruitment was stratified by the first 2 dose vaccination schedule (ChAdOx1-nCoV19 (hereafter referred to as ChAd)/ChAd and BNT162b2 (hereafter referred to as BNT)/BNT) and age (< 70 years old and ≥70 years old). The experimental vaccines in group A were ChAd (Oxford/AstraZeneca), NVXCoV2373 (5 μg with Matrix-M1 50 μg adjuvant in 0.5ml. Novavax; hereafter referred to as NVX) or a half dose (2.5 μg with Matrix-M1 25 μg adjuvant in 0.25 mL) of NVX. Group B vaccines were BNT (30 μg, Pfizer–BioNtech), VLA2001 (33 antigen units with 1 mg CpG adjuvant in 0.5 mL, Valneva; hereafter referred to as VLA), a half dose (16.5 antigen units with 0.5 mg CpG adjuvant in 0.25 mL) of VLA, or Ad26. COV2. S (Janssen; hereafter referred to as Ad26); and group C vaccines were m1273 (100 μg, Moderna, hereafter referred to as m1273), CVnCov (CureVac; hereafter referred to as CVn), or half dose (15 μg) BNT (Fig. 1). Immunogenicity bloods were taken at day 0 (pre-boost), D28, and D84 for all study arms.

Control arm participants and those who had received VLA, half VLA, and CVn did not have D242 visits. This was due to the deployment of third doses to the general UK population over 18 years old, so participants in the control arms were instead randomised to receive three different mRNA boosters within the trial as a sub-study around 6 months after their prime vaccination. People who received third doses of VLA, half-VLA, and CVn in the trial were recommended by the Data and Safety Monitoring Board to be given an mRNA booster due to the emerging Omicron wave and were withdrawn from further blood sampling in the trial. Finally, due to UK policymakers wishing to generate safety and immunogenicity data for fourth-dose vaccines prior to any additional 2022 spring booster campaign, participants in the BNT arm were enrolled into the fourth dose substudy,[14] and their D242 blood samples were taken around 1 month earlier than the other arms as the pre-fourth dose baseline. All the participants and investigator staff were blinded to treatment allocation until the D84 visit after which time participants' received vaccines were uploaded to the relevant UK National Health Service online health record system. The laboratory staff were blinded throughout the study.

Laboratory methods

Sera were analysed at Nexelis (Laval, QC, Canada) to determine SARS-CoV-2 anti-spike IgG concentrations by ELISA (Enyzme-linked immunoassay, reported as ELISA laboratory units [ELU]/mL). The conversion factors to international standard units can be found in the appendix. Sera from D0, D84, and D242 were analysed at Porton Down, UK Health Security Agency, by ECLIA (Cobas platform, Roche

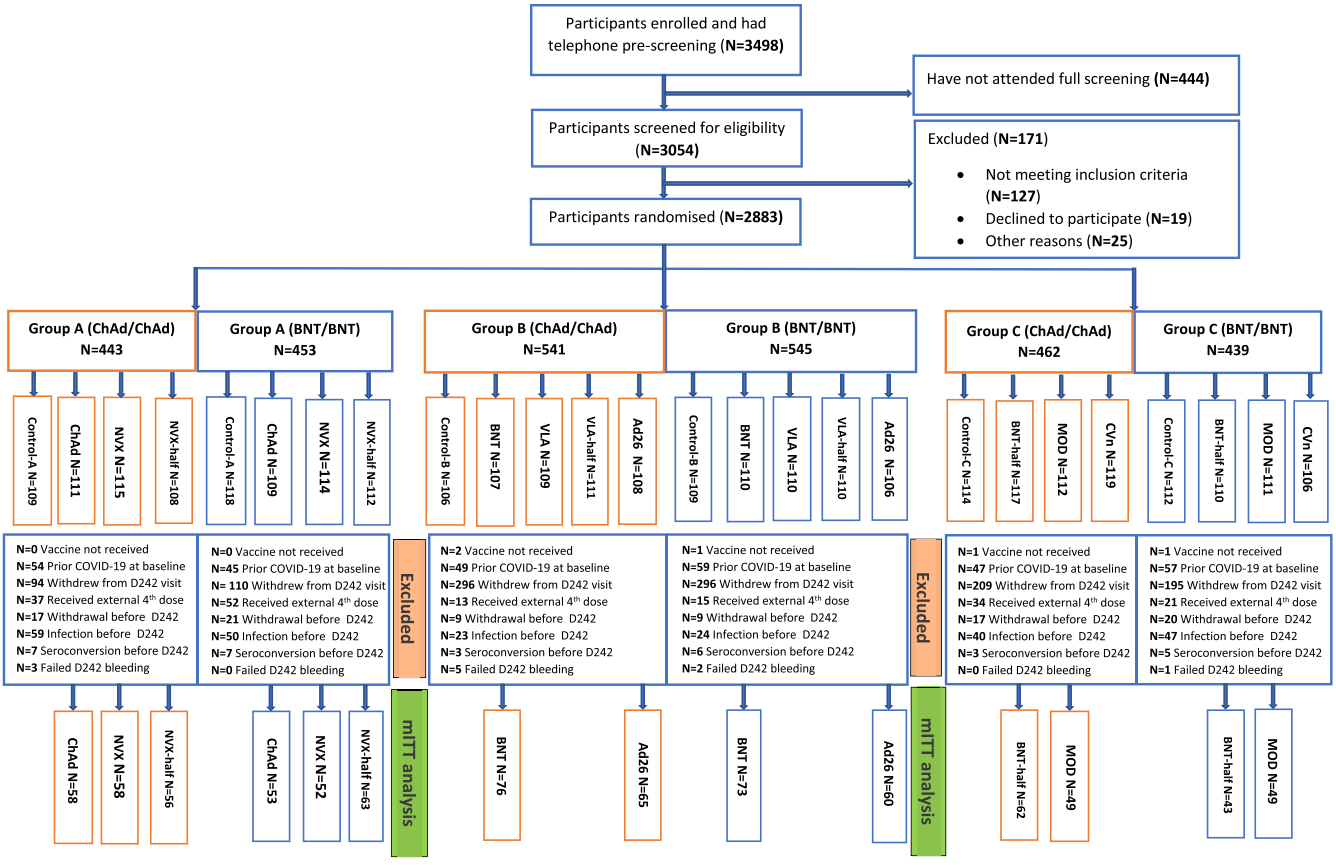

Fig. 1. CONSORT diagram.

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, D84, and D242 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 (VNA, NT_{80}) for live SARS-CoV-2 virus (wild type) by microneutralisation assays. 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 the external laboratory).[15] Gamma interferon (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 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, samples 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 secondary outcomes of immunogenicity at 28, 84, and 242 days (D28, D84, and D242) after third-dose booster vaccines for available laboratory data. The sample size calculation for the original trial was based on the primary outcome of anti-spike IgG at D28 post-booster vaccination between study vaccines and control arms.[15] This report describes the kinetics of immune responses up to 8 months after the third dose of trial COVID-19 vaccines. As BNT was the most widely used third-dose COVID-19 vaccine in the UK and most high-income countries, the analyses in the report used BNT as the reference group. We aimed to investigate the persistence of immune responses induced by COVID-19 vaccines as a third dose compared with the third dose of 30 µg BNT in populations who received ChAd/ChAd or BNT/BNT as their initial two-dose vaccine schedules.

The primary analysis population in this report was all randomised participants in the BNT, half-BNT, m1273, ChAd, Ad26, NVX, and half-NVX arms with no evidence of SARS-CoV-2 infection up until D242 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, D84, and D242 visits. Participants who received further COVID-19 vaccine doses outside the trial were also excluded from the analysis. To account for potential misreporting of infection and external vaccination, we also excluded participants with a > 2-fold rise of anti-spike IgG at any given two-time points from D28 onwards. All analyses were conducted according to the randomised arms and stratified by the initial two-dose vaccination schedules (i.e. ChAd/ChAd and BNT/BNT).

The geometric mean ratios (GMR) and 95% confidence interval (CI) of the immune responses were estimated at D28, D84 and D242 for vaccine arms compared with BNT as the reference. If the GMRs of a vaccine relative to BNT increased between D28 and D242, this meant the decay rate of this vaccine's immune response was slower than BNT within 242 days post third-dose booster. To test the difference of decay rates between arms, we also present the fold-change of immunogenicity between D242 and D28 (D242-to-D28 ratio) for each participant and the geometric mean of D242-to-D28 ratio for each vaccine arm, where a higher ratio indicates a slower decay. The GMRs of the D242-to-D28 ratio (i.e. a ratio of ratios) to BNT arm were also presented. If a GMR of the D242-to-D28 ratio is greater than one, this means the decay is slower than in the BNT reference arm. The GMRs and 95% CIs were estimated using a mixed-effect linear regression model for each time point (one model for each time point in the populations who received ChAd/ChAd or BNT/BNT), separately. The log10 transformed immunogenicity data (absolute titre) or D242-to-D28 ratios were the dependent variable and the 'sites' variable was included as a random effect in the model with age group (< 70 years, > 70 years), baseline immunogenicity, the interval between 1st and 2nd vaccines, and the interval between 2nd and boost vaccines as fixed effects. As the D242 visit for the BNT arm was around one month earlier than the other vaccine arms, time (measured as days post third-dose booster at D242) was further adjusted in the model when estimating the D242 GMRs. 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 the age group.

Because a high proportion of participants missed the D242 visits due to the long follow-up, a sensitivity analysis was conducted to check the validity of the primary results in the D242 analysis population. In contrast to fitting multiple models in the primary analysis among the D242 analysis population, one repeated measurement mixed effects model was fitted in the sensitivity analysis among the population who previously received ChAD/ChAd or BNT/BNT. In this sensitivity analysis, we included all the immunogenicity data at different study visits before the time of withdrawal, self-reported or laboratory confirmed (by anti-nucleocapsid) COVID-19 infection, or receiving an external vaccine (whichever was earlier) in the baseline seronegative population. Both participant-level and site-level random intercepts were fitted in the model with the participant-level random effects nested within study sites. The fixed effects in the mixed effects model included age group, baseline immunogenicity, the interval between 1st and 2nd vaccines, and the interval between 2nd and boost vaccines. The predicted geometric means, 95% confidence intervals, and marginal effects between all study vaccines and BNT were estimated at different time points using the same model. We made no adjustments for multiple comparisons and the significance level is two-sided 0.05. 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

Between 1st June and 30th June 2021, the study screened 3498 participants, of whom 2883 were randomised and 2878 received a third dose of COVID-19 vaccine between 10 and 26 weeks following the second dose. The median age of the < 70 years old cohort was 53.1 (43.5, 60.5) and 50.9 (41.2, 58.6) years in people who had received the first two doses of ChAd/ChAd and BNT/BNT, respectively, and 75.9 (73.4, 78.1) and 78.3 (75.1, 82.4) years respectively in the ≥ 70 years old cohort. Among the 2878 participants who received study vaccines, there were 1019 participants primed with ChAd/ChAd and 1042 participants with BNT/BNT excluded, leaving 817 participants comprising the D242 analysis population (Fig. 1).

A difference in anti-spike IgG kinetics between vaccine classes was seen for both the ChAd/ChAd and BNT/BNT cohorts (Fig. 2A & B). Among people who had ChAd/ChAd as their initial schedule, m1273 (100 µg) as the third dose had highest anti-spike IgG titres across all the three time points post booster with 3443 ELU/mL (95% CI: 2738–4331) at D242. The decay rate of Ad26 as a third dose was significantly lower than that of BNT, with the two kinetics curves converging (Fig. 2A). The GMR of Ad26 as a third dose compared to BNT increased from 0.28 (95% CI: 0.23–0.35) at D28, to 0.45 (95% CI: 0.36–0.56) at D84, and to

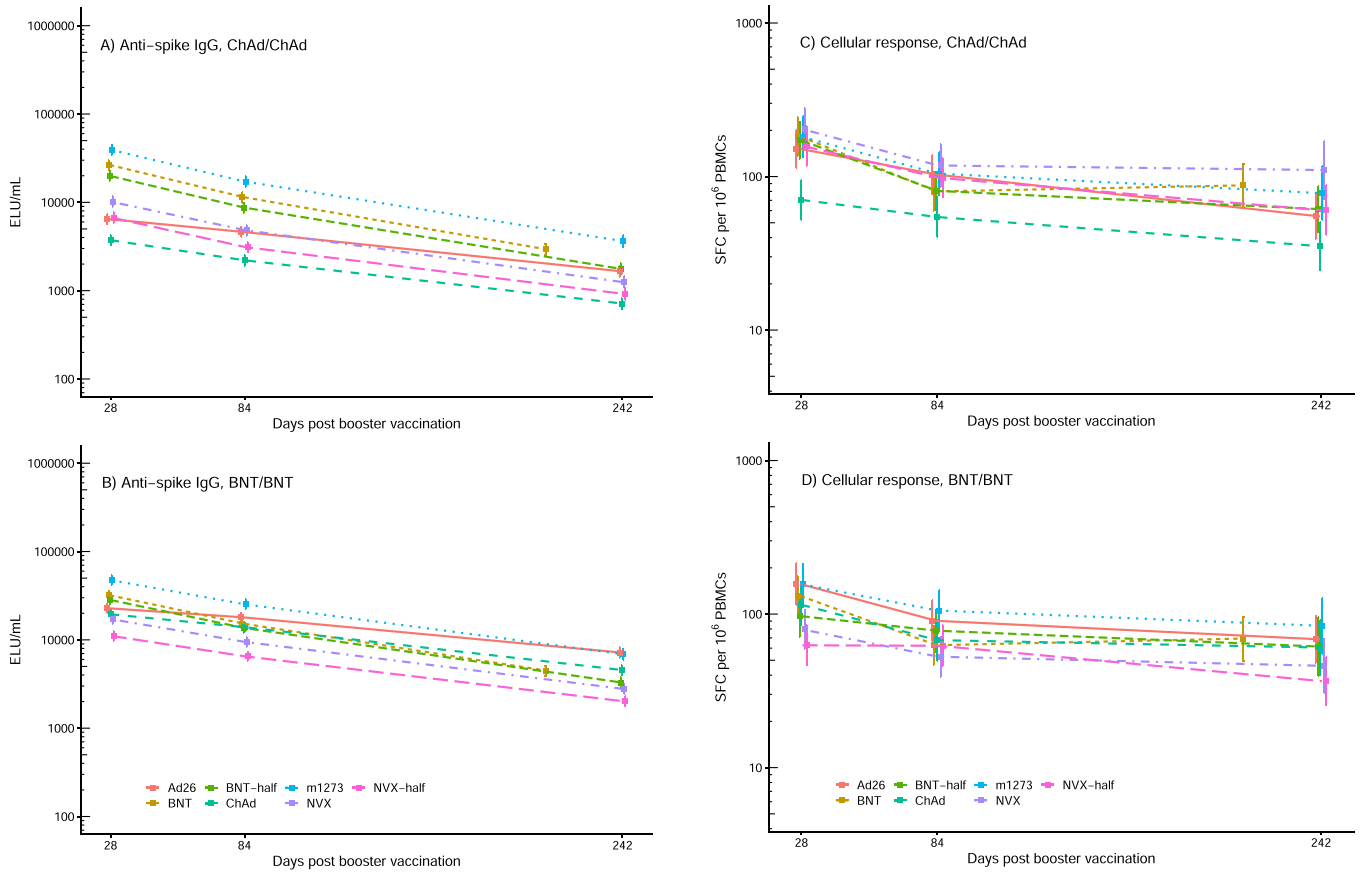

Fig. 2. Kinetics of anti-spike IgG (ELU/mL) for A) ChAD/ ChAD; B) BNT/BNT and kinetics of cellular response (SFC/10^6 PBMCs) for C) ChAD/ ChAD; D) BNT/BNT among the SARS-CoV-2 naïve population. Data presented are predicted geometric mean concentrations(or counts) and 95% confidence intervals estimated by repeated measurements mixed effects models, adjusting for immunogenicity at D0, age group (< 70 years, ≥70 years), the interval between the first and second dose and the interval between the second and the third dose as fixed effects, and study sites and participants as random effects; for A) and B), the immunogenicity at D0 is D0 anti-spike IgG; for C) and D), the immunogenicity at D0 is D0 cellular response against wild type. The number of participants contributed to the models is presented in Fig. 3A for A); Fig. 4A for B); Fig. 3C for C); and Fig. 4C for D).

0.89 (95% CI: 0.63–1.26) at D242 (Fig. 3A), with a significantly higher GMR of the D242-to-D28 ratio. Although a significant increase in GMR across the three timepoints was also seen for ChAd, NVX, and half-NVX arms, their anti-spike IgG titres were still significantly lower than that of the BNT arm at D242. For half-BNT, the GMR to BNT ranges between 0.86 and 0.94 across the three follow-up times with no significant difference (Fig. 3A). The kinetic curves between half BNT and BNT were approximately parallel (Fig. 2A).

In people receiving an initial schedule of BNT/BNT, m1273 (100 µg) induced the highest anti-spike IgG titres at D28 post third dose, but at D242 people who had received a third dose of Ad26 had the highest crude titres (m1273: 5623 ELU/mL vs. Ad26: 6361 ELU/mL) (Fig. 4A). The decay rate of Ad26 was significantly slower than that of BNT (Fig. 2B, Fig. 4A). At D28 post booster, the GMC in the Ad26 arm was significantly lower than that of BNT, but became significantly higher at D84 and D242 (Fig. 4A). A slower decay rate was also seen for ChAd compared to BNT, and ChAd as a third dose induced similar anti-Spike IgG titres to BNT from D84. The GMR between ChAd and BNT increased from 0.56 (95% CI 0.43–0.74) at D28, to 0.82 (95% CI 0.64–1.06) at D84, and to 1.10 (95% CI 0.81–1.48) at D242 (Fig. 4A). Similar decay rates were seen for BNT and half BNT (Fig. 4A). The NVX and half-NVX arms also had a significantly slower decay rate compared to BNT. For example, the GMR of D242-to-D28 ratio for NVX compared to BNT was 1.37 (95% CI: 1.04–1.82) (Fig. 4A).

Subgroup analysis by age (< 70 years and ≥ 70 years) showed the same patterns of decay for anti-spike IgG (Supplementary Figure 1). Sensitivity analysis using all available data by repeated measurements mixed-effects model showed similar results (Supplementary Figure 2). The analyses were also repeated in the baseline seropositive population, where the difference in decay rates between vaccines were similar to that seen in the seronegative population (Supplementary Figures 3 and 4).

The persistence pattern of immune response between vaccines for VNA against wild-type was similar to that for anti-spike IgG (Fig. 3B, Fig. 4B, Supplementary Figure 5), with a slower decay of ChAd, Ad26, and NVX following BNT/BNT compared with homologous BNT boost, although only Ad26 reach the statistical significance level due to small sample size overall.

There was no significant difference in decay rates of cellular responses between vaccines (Fig. 2C, Fig. 2D, Fig. 3C, Fig. 4C). Compared with anti-spike IgG, where the decay at the log scale is almost linear with time between D28 and D242, cellular responses plateaued at an earlier time before D242.

Discussion

In this report, we compared the eight-month duration of humoral and cellular responses following homologous and heterologous third COVID-19 vaccine dose schedules in populations who received ChAd/ChAd and BNT/BNT as their initial two doses. Similar to our finding at 3 months following the third dose,[11] the humoral responses after the heterologous boost of viral-vector vaccines

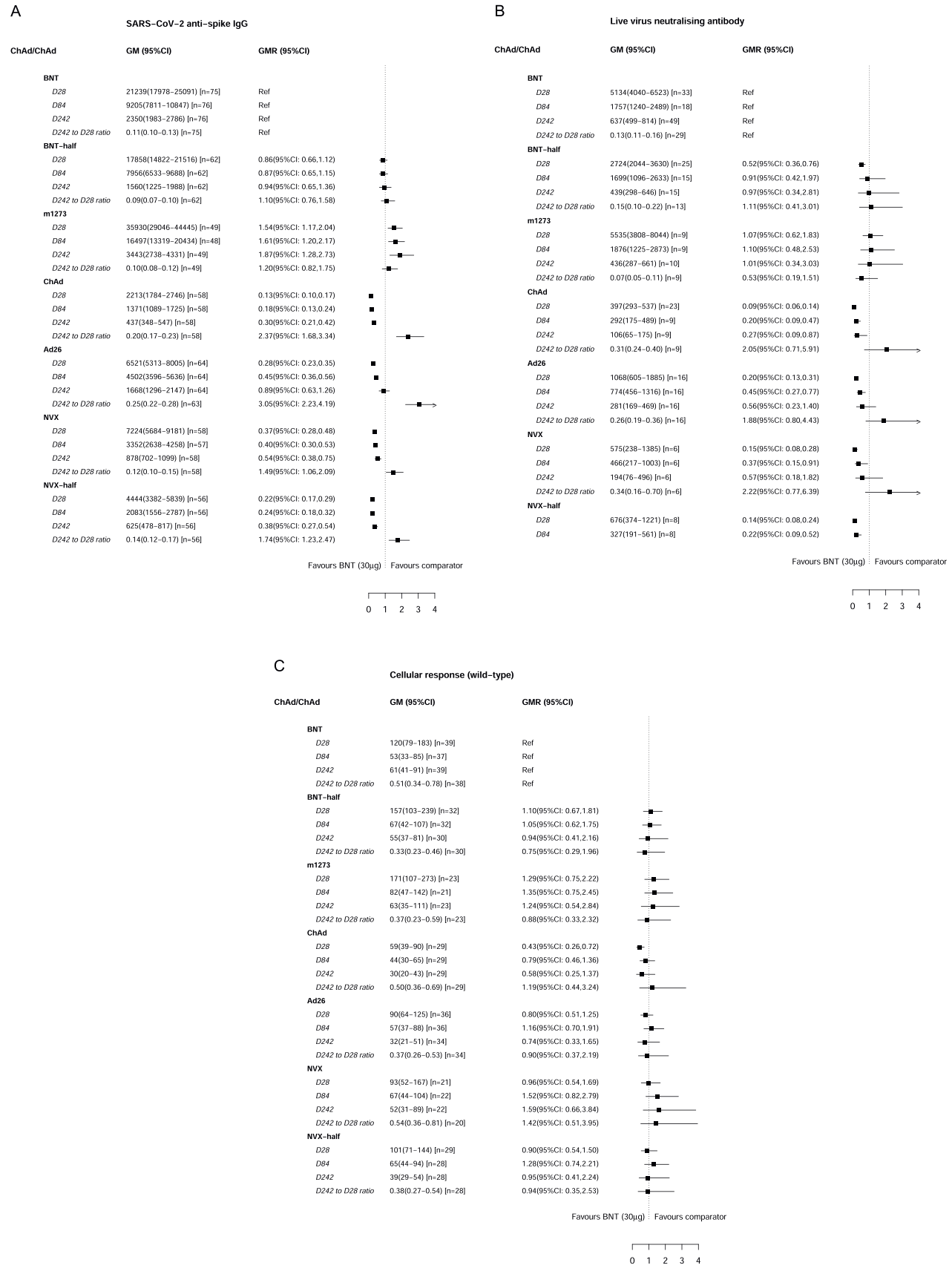

Fig. 3. Immunogenicity at D28, D84, and D242, and D242-to-D28 ratio for A) Anti-spike IgG (ELU/mL); B) Live virus neutralising antibody against wild type (NT_{80}); C) Cellular response (SFC per million PBMCs) among the SARS-CoV-2 naïve population primed with ChAD/ ChAD. GM: geometric mean; GMR: geometric mean ratio; One model was fitted for each time point; model adjusted for immunogenicity at D0, age group (< 70 years, ≥70 years), the interval between the first and second dose and the interval between the second and the third dose as fixed effects, and study sites as a random effect for D24 and D84 analyses; The visit time as days post third dose vaccination was further adjusted in the D242 and D242-to-D28 ratio analysis; For A) and B), the immunogenicity at D0 is D0 anti-spike IgG; For C), the immunogenicity at D0 is D0 cellular response against wild type.

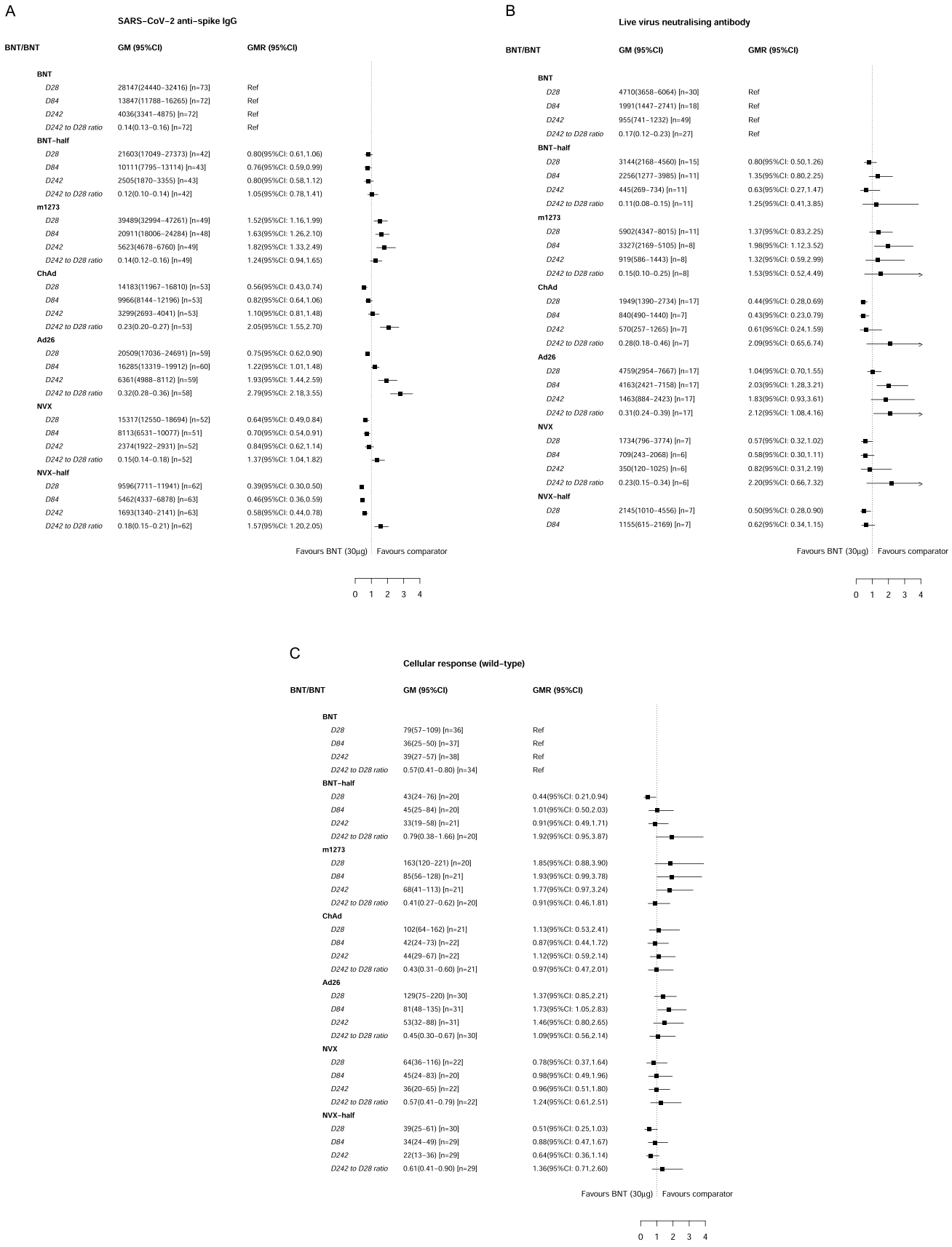

Fig. 4. Immunogenicity at D28, D84, and D242, and D242-to-D28 ratio for A) Anti-spike IgG (ELU/mL); B) Live virus neutralising antibody against wild type (NT_{80}); C) Cellular response (SFC per million PBMCs) among the SARS-CoV-2 naïve population primed with BNT/BNT. GM: geometric mean; GMR: geometric mean ratio; One model was fitted for each time point; Model adjusted for immunogenicity at D0, age group (< 70 years, ≥70 years), the interval between the first and second dose and the interval between the second and the third dose as fixed effects, and study sites as a random effect for D24 and D84 analyses; The visit time as days post third dose vaccination was further adjusted in the D242 and D242-to-D28 ratio analysis; For A) and B), the immunogenicity at D0 is D0 anti-spike IgG; For C), the immunogenicity at D0 is D0 cellular response against wild type. There was only one participant with D242 live virus neutralising antibody data available in the NVX-half arm and removed in B).

following two-dose of BNT waned more slowly than those following three doses of mRNA vaccine. Our kinetics data suggest that the anti-spike IgG following Ad26 as the third dose booster may become higher than that with BNT for people who received BNT/BNT as their initial two doses at approximately two months following vaccination. The finding is consistent with a previous cohort study, which reported a higher humoral response at 16 weeks following heterologous Ad26 booster compared with BNT in participants who received BNT/BNT.[10] That study also reported a higher CD8+ T-cell response after Ad26 than BNT. In our study, we did not find a significant difference in T-cell responses by ELISpot between viral-vector and mRNA boosters. The reason for this difference may be that we did not distinguish between CD4 + and CD8+ T-cell responses. We also found that third doses of NVX compared to BNT had a slower humoral decay during the follow-up in both people who had received ChAd/ChAd and those who received BNT/BNT. However, the absolute titres were still significantly higher for BNT than for NVX for all visits, except D242 in BNT/BNT participants. In our study, people who received ChAd/ChAd and then a non-mRNA schedule had significantly lower antibody titres than those who had received mRNA vaccines as their first doses. In the United Kingdom and elsewhere, some vulnerable people also received three doses of ChAd as part of the national immunisation campaign. These mainly homebound people were subsequently offered a fourth dose which was an mRNA vaccine.

National immunisation committees have mainly focussed on the peak antibody titres, reactogenicity, and the incidence and severity of more rare adverse events when making additional COVID-19 vaccine dose recommendations. Schedules that retain immunological protection longer may be of future advantage. Currently, many countries have decided to boost the most at-risk populations annually or more frequently where there is perceived risk. This is expensive and resource-intensive for healthcare systems and some countries may find fourth (booster) doses unaffordable.

In the future, long-term protection might become a higher priority in choosing which vaccines to use in booster programmes. In contrast to the monovalent vaccines studies here, bivalent mRNA vaccines were widely deployed in the northern hemisphere autumn/winter 2022/2023. These vaccines appear to generate similar levels of neutralising antibodies as mRNA wild-type vaccines to the wild type and currently circulating variants[16,17]. In addition, multiple studies have reported a waning of effectiveness against infection after three doses of mRNA vaccine during the Omicron wave[6,18,19]. This highlights the need to consider heterologous, possibly rotational, boost schedules given the lower decay rates seen in this study. With the U.S. FDA's decision to restrict the use of Ad26 to people who cannot receive mRNA vaccines,[20] there are minimal real-world data available to evaluate the effectiveness of mRNA prime and viral-vector booster schedules. At present, there is no certainty that viral vector vaccines against COVID-19 will be available in future years, either with wild-type or variant viral targets.

There were a number of limitations to our study. Due to the limited laboratory capacity, there were no neutralisation data available against Omicron variants. Based on previous publications,[11] there is a high correlation between neutralising antibodies against wild-type and the Omicron variant, although the VNA titres against Omicron are significantly lower than those for wild-type virus. Therefore, we expect the kinetics of neutralising antibodies against omicron would have been of a similar pattern to the responses against wild-type seen in our study. Another limitation is that the BNT arm was enrolled into a fourth dose sub-study and had their eight-month visit approximately one month earlier than other arms. As humoral responses are expected to decay over time, the crude difference between viral-vector arms and BNT may be underestimated. In addition, we adjusted the time of visit in the primary analysis when estimating the GMRs at D242 to account for the difference. Future studies are needed to evaluate the optimal booster schedules if regular doses of COVID-19 vaccine are required to protect the population, especially in participants who have had previous COVID-19 infection.

In the post-pandemic period, national immunisation committees will need to assess multiple factors including the risk of any new SARS-CoV-2 variant or variants, what is known about the overall immunity of the population as a whole and of those at most risk, and any differences between vaccines that can be used as boosters. In this study, we found that the decay of humoral responses after heterologous boost with viral vector following two doses of mRNA was slower than that after an mRNA booster. The decay rate of humoral responses following NVX was slower than BNT, although overall antibody titres were lower. This suggests that policymakers might consider non-mRNA vaccines to boost people in populations who have so far only received mRNA vaccine to maintain their antibody levels for a longer period. Formal investigation of heterologous schedules should be considered during the development of all new vaccines targeting SARS-CoV2 or other infections.

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, AW, LJ and VC designed and conducted the statistical analysis and have verified the underlying data. XL, AM, AW and SNF drafted the report. All other authors contributed to the implementation and data collection. All authors reviewed and approved the final report.

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).

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 was seconded to the Department of Health and Social Care, England until 31st March 2022. He has subsequently received lecture fees from AstraZeneca, Sanofi Pasteur and has performed paid consultancy for Janssen and Seqirus. MR has provided post marketing surveillance reports on vaccines for Pfizer and GSK for which a cost recover charge is made. MDS acted until September 2022 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. MDS became an employee of Moderna in September 2022 and holds stock options in this company. He did not perform this study in relation to his new employment and Moderna have had no a priori access to the data.

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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.2023.04.012.

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