Tolerability and immunogenicity after a late second dose or a third dose of ChAdOx1 nCoV-19 (AZD1222)

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ABSTRACT

Background: COVID-19 vaccine supply shortages are causing concerns about compromised immunity in some countries as the interval between first and second dose extends. Conversely, countries with no supply constraints are considering administering a third dose. We assessed the persistence of immunogenicity after a single dose, the immunity after an extended interval between the first and second dose of ChAdOx1 nCoV-19(AZD1222), and the response to a third dose as a late booster.

Methods: Volunteers aged 18-55 years who were enrolled in a Phase 1/2 or Phase 2/3 clinical trial of ChAdOx1 nCoV-19 and had received either a single dose or two doses of 5×10^{10} viral particles were invited back for vaccination. Reactogenicity and immunogenicity of a delayed second dose or a third dose are reported here.

Findings: Antibody titres after a single dose and measured on d362 remain higher than the titres measured on d0 (62.61 EU; 95% CI 47.43-82.64 vs 1 EU 95% CI 1-16). 30 participants received a late second dose of ChAdOx1 nCoV-19 (median 44 weeks after first dose), antibody titres were higher in those with a longer interval between first and second dose (median EU for 8-12, 15-25, and 44-46 weeks were 923 [IQR 525-1764], 1860 [IQR 917-4934] and 3738 [IQR 1824-6625] respectively). 90 participants received a third dose and antibody titres were significantly higher following a third dose ($FRNT_{50}$ 612 [IQR 351-920]) when compared with the response 28 days after a second dose ($FRNT_{50}$ 319 [IQR 176-591].

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T-cell responses were also boosted after a third dose. Reactogenicity after a late second dose or a third dose was lower than reactogenicity after a first dose.

Interpretation: A longer delay before the second dose of ChAdOx1 nCoV-19 leads to an increased antibody titre after the second dose. A third dose of ChAdOx1 nCoV-19 induces antibodies to a level that correlate with high efficacy after second dose and boosts T-cell responses.

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Research in Context

Evidence before this study

Multiple vaccines against SARS-CoV-2 have now been authorised for use in multiple countries. The majority of the vaccines are given in a two-dose primary schedule, and it is possible that further doses may be required to maintain protective immunity or control emerging variants. We searched PubMed for research articles published between database inception and June 23rd, 2021 using the search terms 'SARS-CoV-2', 'vaccine', 'clinical trial', and 'third dose' or 'late boost' with no language restrictions. We identified animal studies using combinations of three-dose vaccine delivery in prime-boost schedules[1]. In addition, there were two clinical trials of three-dose delivery, including one in solid organ transplant recipients[2]. In this study antibody titres increased after the third dose of either 162b2 (Pfizer/BioNTech), or mRNA-1273 (Moderna) vaccine in one third of patients who had negative antibody titres and in all patients who had low-positive antibody titres[2]. In a phase 1 and 2 trial of a protein subunit vaccine ZF2001, the safety and immunogenicity data support the use of the 25µg dose in a three-dose schedule[3]. A number of ongoing clinical studies are measuring the impact of third dose vaccination, including a Phase 1 study of 144 participants who have received a homologous third dose of BNT162b2, 6 or 12 months after the second dose (ClinicalTrials.gov Identifier: NCT04368728).

Added Value of this study

We report immune responses to ChAdOx1 nCoV-19 following a second dose after an extended interval between first and second dose, or after a third dose with an extended interval between the second and third dose. The extended interval between the first two doses resulted in higher antibody titres after the second dose. A third dose given 44-45

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weeks after the primary series increased the antibody titres further. Reactogenicity was lower after the second or third dose than after the first.

Implications of the available evidence

Vaccine shortages have resulted in some people receiving a first dose of ChAdOx1 nCoV-19 without receiving the second dose within the recommended 4-12 week period. We report that increasing the interval as far as 45 weeks results in an increased antibody titre after the second dose, offering greater flexibility in vaccination schedules. A third dose at an extended interval after the second dose resulted in a further increase in antibody titres, mitigating concerns that antibodies raised against the ChAdOx1 vector would limit repeated use of the vaccine.

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INTRODUCTION

The SARS-CoV-2 pandemic continues to place a significant burden on healthcare systems and a massive global effort is underway to protect populations through vaccination. COVID-19 vaccine supply shortages in low- and middle-income countries are causing concerns about compromised immunity as the interval until the second dose extends beyond 12 weeks[4]. The World Health Organisation recommends that the second dose is given 8-12 weeks after the first dose since the clinical trial data provide support for good levels of protection with this dose interval[5,6]. However, many countries cannot obtain second doses by 12 weeks leading to even longer intervals and uncertainty from policymakers about whether protection against COVID-19[5,6] will be maintained, as there are no data on intervals between the first and second dose that extend beyond this limit.

Conversely, some high-income countries with highly vaccinated populations are considering administration of a third dose of a COVID-19 vaccine because of uncertainty about duration of immunity following the first two doses, and the possible risk of breakthrough infection as new variants emerge.

ChAdOx1 nCoV-19 (AZD1222), a replication deficient adenoviral vectored vaccine, which encodes the SARS-CoV-2 spike protein, is one of the most widely used vaccines globally. More than half a billion doses have been distributed to more than 168 countries across six continents, including provision through the CoVax facility. The issues considered here are especially pertinent for ChAdOx1 nCoV-19 given its global reach.

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Here we describe the tolerability and immune response to a late second dose of ChAdOx1 nCoV-19, and after a third dose. We also report the persistence of cellular and antibody responses at 6 months and approximately one year after a first dose of ChAdOx1 nCoV-19.

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METHODS

Participants/Study Design/administering doses

COV001 and COV002 are ongoing single-blind randomised controlled trials of ChAdOx1 nCoV-19 in the UK, in which participants were randomised to receive ChAdOx1 nCoV-19 or a Group ACWY meningococcal vaccine (MenACWY) as a control. Safety, immune responses, and efficacy have been previously published[5,7,8]. The trials were originally intended to be single dose vaccine studies, but the strong neutralising titres seen in COV001 induced by a second dose of vaccine[7] prompted a protocol amendment to allow the addition of booster doses to most study participants across both trials. The timing of the second dose varied and the initial phase 1 group in COV001 was retained as a single dose cohort in order to observe the persistence of immune responses after a single dose. Baseline characteristics as described in Supplementary Table 1.

As a comparison cohort for those with a long interval between first and second doses in COV001, a subset of participants from COV001 and COV002 who had received two doses of ChAdOx1 nCoV-19 with varying prime-boost intervals were selected for inclusion in analyses. Blood samples from participants who were PCR+ to SARS-CoV-2 were removed from the analysis if the infection occurred before the blood draw. Baseline characteristics as described in Supplementary Table 2.

A substudy was added to the COV001 trial as a protocol amendment on 1 March 2021, to investigate the immunogenicity and tolerability of a third dose. 90 participants who had previously received two doses of ChAdOx1 nCoV-19 were recruited, along with 40 control participants to maintain blinding of reactogenicity data. 66 participants from the single dose

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cohort were also offered a second dose at this time (44 ChAdOx1 nCoV-19 recipients and 22 control group participants). Seven days after vaccination, participants were unblinded and those in the control group were offered the vaccine. Participants were targeted for inclusion in the substudies if they had not previously been unblinded or offered a vaccine as part of the national government COVID-19 vaccine programme. Baseline characteristics as described in Supplementary Table 3.

Participants were asked to complete a diary card for 7 days after each vaccination, to record solicited local and systemic adverse reactions. In the UK, the COV001 and COV002 studies were approved by the South Central Berkshire Research Ethics Committee (COV001 reference 20/SC/0145, March 23, 2020; and COV002 reference 20/SC/0179; conditional approval April 8, full approval April 19, 2020).

Immunogenicity assessment

A standardised single dilution total IgG ELISA was performed as previously described[8]. This assay was used to measure antibody responses pre and post vaccination to Victoria/01/2020 SARS-CoV-2 spike protein and adapted to measure responses to B.1.351 (Beta) SARS-CoV-2 protein. Meso Scale Discovery (MSD) multi-plex immunoassay was used to assess antibody titres against spike proteins from different variants. V-PLEX SARS-CoV-2 Panel 6 (IgG) kits were used following manufacturer's instructions (Meso Scale Discovery, K15433U). Full details are provided in the Supplementary Appendix. *Ex vivo* IFN-γ ELISpot was performed as previously described[8] to assess T-cell responses to Victoria/01/2020 SARS-CoV-2 spike overlapping peptide pools pre and post vaccination. Focus reduction neutralisation assays were performed as described previously[9] to measure neutralising

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antibody titres against Alpha (B.1.1.7), Beta (B.1.351) and Delta (B.1.617.2) SARS-CoV-2 viral variants.

Statistical Analysis

Summary statistics are presented as median and interquartile range, or geometric mean titre with 95% confidence intervals. Wilcoxon rank sum and Kruskal Wallis tests were used for comparisons between independent groups. Wilcoxon sign rank tests were used to compare paired data.

The decay of antibody over time after a single dose was modelled using an unadjusted mixed effects regression (SAS *proc mixed*) with participant-level random intercepts fitted to log-transformed antibody values. GMRs and GMTs were estimated from the linear combination of model parameters. A linear model was chosen after comparison with a polynomial model and a generalised additive (smoothed) model (GAM). The polynomial (squared) term was non-significant and the GAM was similar and did not substantially improve the model fit from the linear model therefore the linear model was retained.

All analyses were restricted to those aged 18 – 55 years inclusive. Statistical analyses were performed using R version 4.0.2 or later and SAS version 9.2. *P* values of <0.05 were considered significant and no adjustments were made for multiple comparisons.

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RESULTS

Participants

Between 11th and 21st March 2021, 90 participants were enrolled into the COV001 third dose boost substudy and vaccinated with ChAdOx1 nCoV-19. Ten participants from this substudy were excluded from reactogenicity summaries as they were enrolled from an open label subgroup. A further 5 participants were excluded from immunogenicity assessments as their prime-boost interval was outside the defined range of 8 to 16 weeks (Supplementary Figure 1).

321 participants from COV001 and COV002 with prime-boost intervals between 8-12, 15-25 or 44-45 weeks had reactogenicity data available and were included in analyses, along with 261 that had immunogenicity data available. All exclusions are shown in Supplementary Figure 2.

Tolerability and Reactogenicity

The severity of local and systemic solicited adverse reactions after a second dose were mostly mild to moderate irrespective of the interval between doses. Local symptoms occurred after a second dose in 201 (75%) of 267 participants in the 8-12 week group, 15 (62%) of 24 participants in the 15-25 week group and 23 (77%) of 30 participants in the 44-45 week (Figure 1A, Supplementary Tables 4 & 5). Systemic reactions occurred in 190 (71%) of 267 participants in the 8-12 week group, 18 (75%) of 24 participants in the 15-25 week group and 26 (87%) of 30 participants in the 44-45 week (Figure 1A, Supplementary Tables 4

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& 5); 65 (81%) of 80 participants in the third dose group reported at least one local symptom after a third dose (Figure 1B, Supplementary Tables 6 & 7).

Second dose vaccinations in the long interval cohort were less reactogenic than first dose vaccination. 72 (22%) of 321 participants reported more than two moderate to severe systemic symptoms after first vaccination compared with 21 (7%) of 321 participants after second vaccination (Supplementary Tables 4 & 5). Third dose vaccinations were also less reactogenic than first doses; 4 (5%) of 80 participants in the third dose cohort reported more than two moderate to severe systemic symptoms after a third dose compared to 27 (34%) of 80 participants after a first dose (Supplementary Tables 6 & 7).

Persistence of the immune response after a single dose of ChAdOx1 nCoV-19

Antibody responses after a single dose of vaccine declined during the year but were maintained above baseline levels. At day 180, geometric mean antibody levels were half the levels observed at the day 28 peak (GMR 0.54, 95% CI 0.47, 0.61), and by day 320 were 0.30 as high as the peak (GMR 0.30, 95% CI 0.24, 0.39) (Figure 2A, Supplementary Table 8).

Vaccine-induced cellular immune responses after a single dose of ChAdOx1 nCoV-19 were maintained above baseline levels at day 182 after vaccination (median 237 SFUx10^6 PBMC [IQR 109-520]; Figure 2B, Supplementary Table 9).

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Immunogenicity after a late second dose

The median age of participants in the long interval antibody immunogenicity cohort with an 8–12 week V1-V2 interval was 39 years (IQR 30–49 years), in the 15-25 week interval group was 36 years (IQR 30–43 years), and in the 44-45 week interval group was 32 years (IQR 25–44 years).

Antibody levels 28 days after second dose were higher with longer intervals between doses: median tIgG EU in those with 8-12 week , 15-25 week and 44-45 week intervals were 923 [IQR 525-1764], 1860 [IQR 917-4934] and 3738 [IQR 1824-6625] respectively (Kruskal-Wallis test P <0.001) (Figure 3, Supplementary Table 10).

Six months after second dose, antibody levels remained significantly higher in the group with 15-25 week interval between doses compared with 8-12 week interval (median 1240 [IQR 432-2002] and 278 [IQR 166-499], respectively; $P < 0.001$, Wilcoxon rank sum test with continuity correction) (Figure 3, Supplementary Table 10).

IgG binding titres to all four variants tested (D614G, Alpha (B.1.1.7), Beta (B.1.351) and Delta (B.1.617.2)) were significantly greater after second dose than prior to second dose (Supplementary Table 11, $P < 0.001$ for all comparisons; pairwise comparisons using Wilcoxon sign rank test).

Immunogenicity after third dose of ChAdOx1 nCoV-19

The median age of participants who received a third dose of ChAdOx1 nCoV-19 was 37 years (IQR 31-42 years) in the antibody cohort, and 40 years (IQR 32-44 years) in the T-cell cohort.

Antibody responses after a third dose were assessed in 75 participants who had received their first two doses with an interval of 8-16 weeks. Administering a third dose boosted

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antibody response to SARS-CoV-2 Victoria spike (Figure 4A, Supplementary Table 12). Antibody levels after third dose were significantly higher than after a second dose (median tIgG EU at V2+28 and V3+28 were 1792 [IQR 899-4634] and 3746 [IQR 2047-6420] respectively; $P = 0.004$, pairwise comparison using Wilcoxon signed rank test). Binding antibody titres to the Beta variant increased significantly after a third dose and were higher than after the second dose for both Beta (B.1.351) and Victoria variants (Supplementary Table 13). Neutralising antibody titres following a third dose were higher than those after second dose (Figure 4B, Supplementary Table 14) against Alpha (B.1.1.7), Beta (B.1.351) and Delta (B.1.617.2) variants, $P = 0.002$, $P < 0.001$ and $P < 0.001$ respectively, Wilcoxon signed rank test).

Spike specific cellular immune responses were measured after a third dose of ChAdOx1 nCoV-19 in 15 individuals who had received their first two doses with an interval of 8 weeks. Median response increased from 200 SFUx10^6 PBMC (IQR 127, 389) at third dose (V3) to 264 SFUx10^6 PBMC (IQR 131, 452) 14 days after third dose (V3+14), and to 399 SFUx10^6 PBMC by V3+28 [IQR 314, 662] (Figure 5, Supplementary Table 15). Peak responses at day 28 after a third dose was not significantly different to the response after the second dose (Supplementary Table 15).

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DISCUSSION

Antibody levels induced by a single dose of ChAdOx1 nCoV-19 decline gradually remaining elevated above baseline levels after a year. Administration of a second dose induces 4 to 18 fold higher antibody responses by 1 month after the second dose. Furthermore, a long extension of the dose interval (up to 45 weeks) between the first and second dose further enhances the immune response to the second dose, when compared with shorter dose intervals. For the first time, we demonstrate that a third dose of ChAdOx1 nCoV-19 can induce a strong boost to immune responses to the transgene product, SARS-CoV-2 spike protein, and that these responses result in higher neutralising antibody titres and enhanced activity against variants.

The devastating impact of COVID-19 is most apparent in countries with low vaccine coverage and limited healthcare infrastructure including low- and middle-income countries (LMIC). Global vaccine shortages and policy decisions implemented at national levels have curtailed vaccine supplies for some countries where significant numbers of individuals have already received one vaccine dose. We have previously shown that protection against symptomatic COVID-19 is maintained after a single dose for at least 3 months, despite some waning of antibody levels[6] and we now report that the antibody levels remain elevated for at least 1 year after single dose immunisation. These data are important for those countries where administration of a second dose is delayed because of a shortage of supply. We also demonstrate here that a prolonged interval between first and second dose vaccinations results in a significantly higher antibody response after the second dose. This is consistent with previous data demonstrating a longer interval between first and second dose results in an increase in antibody titres[6] , thus providing further reassurance that a delay in second

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dose will not compromise the level of-protection attained after the second dose. This has been reported with other vaccines[10-12]; a delayed two dose regimen, against HPV, given at least 6 months apart results in as good or better antibody response than three doses. A second dose of ChAdOx1 nCoV-19 is well-tolerated in a delayed two dose schedule and third doses are also well tolerated. Reports have emerged of thrombosis and thrombocytopaenia after the first dose of ChAdOx1 nCoV-19[13] but recent information from Public Health England indicates that this very rare event does not occur after a second dose[14].

It is currently unknown if booster vaccinations against SARS-CoV-2 will be required, perhaps to counter waning immunity or to augment protection against emerging variants. Here we show that a third dose of ChAdOx1 nCoV-19 is well tolerated and significantly boosts the antibody titres above those measured after the second dose to achieve titres above the level associated with 80% vaccine efficacy after two vaccine doses (under review, data available on MedRixv[15]). Higher titre neutralising antibodies against Alpha B.1.1.7, Beta B.1.351 and Delta B.1.617.2 viruses were induced after a third dose vaccination when compared with titres induced after second dose. Spike-specific T-cell responses were boosted after a third dose of ChAdOx1 nCoV-19 and were similar in magnitude to the response measured after two doses. While pre-existing immunity to human adenoviral vectors has been shown to dampen vaccine-induced immune responses[16,17], there is no evidence that repeated use of a replication deficient simian adenoviral vector induces anti-vector immunity at a level sufficient to impair responses to further vaccination. The third dose was well tolerated by participants with lower reactogenicity than after the first dose.

Limitations to the study reported here include a paucity of T-cell data after a late second dose, limited tolerability data after the second dose available for those who were recruited

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to receive a third dose, and small number of participants available at a year after single dose (mainly due to being offered a second dose after unblinding, as per protocol). Thus far, data are only available 28 days after the third dose, however follow up at six months is planned. The sample size in this study is not sufficiently large to assess rare vaccine side effects, but there were no tolerability concerns reported in those receiving a late second dose or a third dose booster.

Here, we demonstrate that immunity induced by the viral vectored vaccine ChAdOx1 nCoV-19 is maintained for long periods after a first dose, with greater boosting after the second dose following a longer interval between doses. A single dose of ChAdOx1 nCoV-19, with a second dose given after a prolonged period, may therefore be an effective strategy[6,18] when vaccine supplies are scarce in the short term. A third dose results in a further increase in immune responses, including greater neutralisation of variant SARS-CoV-2 viruses, and could be used to increase vaccine efficacy against variants in vulnerable populations.

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Author Contributions

AJP, TL, MV and DJ contributed to the protocol and design of the study. AJP is chief investigator. AF, JA, PKA, BA, SBR, SB, MB, FC, PC, EAC, SD, WD, CD, KJE, PMF, JF, DJ, AMM, JM, YFM, EP, MNR, HR, HS, ES, ES, HS, MDS, RS, DW contributed to implementation of the study and/or laboratory experimentation. AF, MV and NGM did the statistical analysis. TL, AF, AJP, SG, FC, NGM and MV contributed to the preparation of the report. All authors critically reviewed and approved the final version.

Declaration of interests

Oxford University has entered into a partnership with AstraZeneca for further development of ChAdOx1 nCoV-19. AstraZeneca reviewed the data from the study and the final manuscript before submission, but the authors retained editorial control. SCG and AVSH are cofounders of and shareholders in Vaccitech (collaborators in the early development of this

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vaccine candidate) and named as inventors on a patent covering use of ChAdOx1-vectored vaccines (PCT/GB2012/000467) and a patent application covering this SARS-CoV-2 vaccine (SCG only). TL is named as an inventor on a patent covering use of ChAdOx1-vectored vaccines (PCT/GB2012/000467) and was a consultant to Vaccitech. PMF is a consultant to Vaccitech. AJP is Chair of the UK Department of Health and Social Care's JCVI, but does not participate in policy advice on coronavirus vaccines, and is a member of the WHO Strategic Advisory Group of Experts (SAGE). AJP is a NIHR Senior Investigator.

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FIGURES

Figure 1A: Solicited adverse reactions after second dose vaccination of ChAdOx1 nCoV-19 with differing interval lengths between first and second dose vaccinations. Reactogenicity at second dose with different V1 to V2 intervals: 8-12 weeks interval (n=263 for fever, n=267 for all other symptoms); 15-25 weeks interval (n=23 for fever, n=24 for all other symptoms); 44-45 weeks interval (n=28 for fever, n=30 for all other symptoms). Figure shows maximum severity of respective solicited adverse event recorded for each participant during days 0-7 after V2.

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Figure 1B: Reactogenicity after third dose. Reactogenicity at each dose recorded by participants receiving a third ChAdOx1 nCoV-19 dose: V1 n=80 for all symptoms; V2 n=15; V3 n=77 for fever, n=80 for all other symptoms. Figure shows maximum severity of respective solicited adverse event recorded for each participant during days 0-7 after each vaccination.

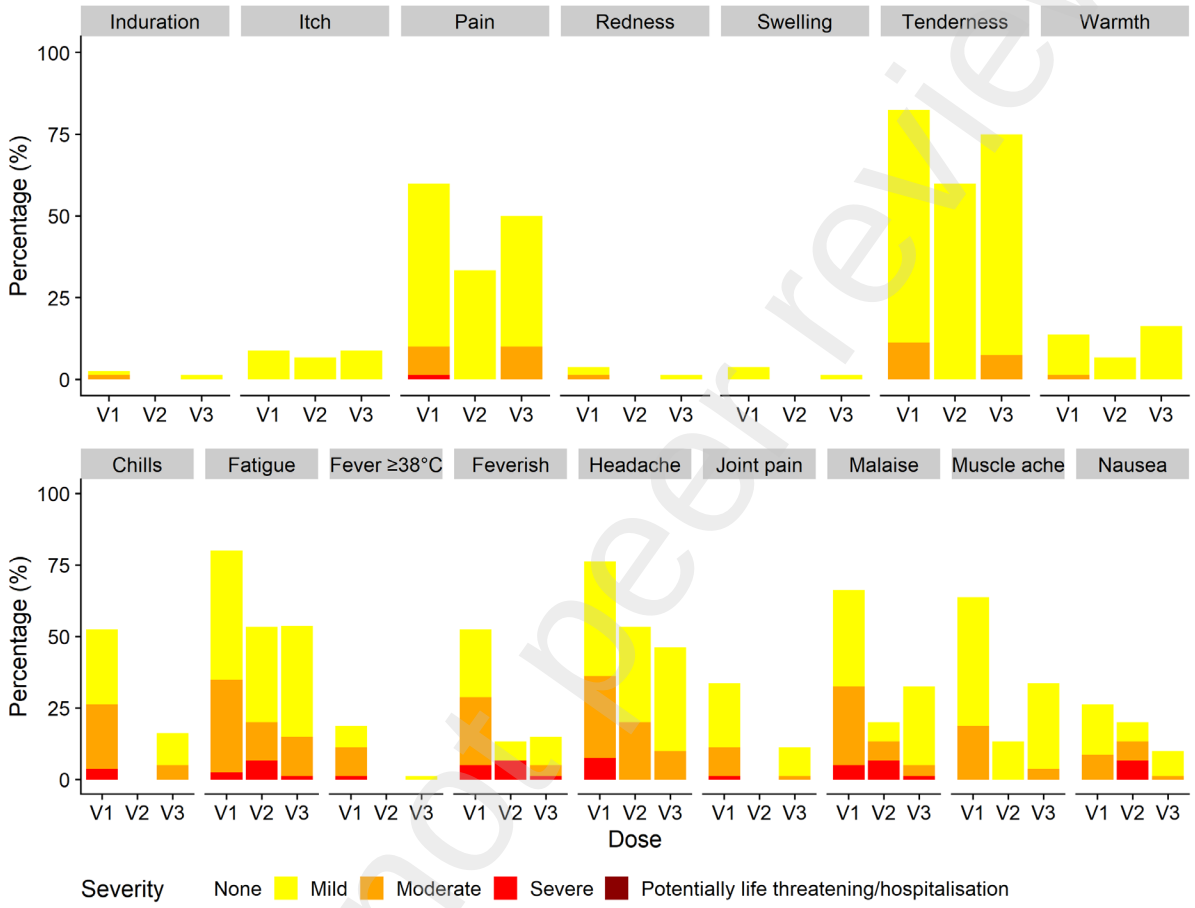

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Figure 2A: Antibody persistence after one dose of ChAdOx1 nCoV-19 vaccine. Antibody levels to SARS-CoV-2 Victoria/01/2020 spike measured by tIgG ELISA over a year post single dose vaccination. Data is included from 261 participants across COV001 and COV002 receiving a standard dose of ChAdOx1 nCoV-19. Participants were censored at the earliest occurrence of PCR +ve result, second dose on trial, or external COVID-19 vaccination. For these participants no ELISA results beyond the date of censoring were used. Individual datapoints are shown. Solid line represents estimates from a linear regression model, with shaded areas showing the confidence interval.

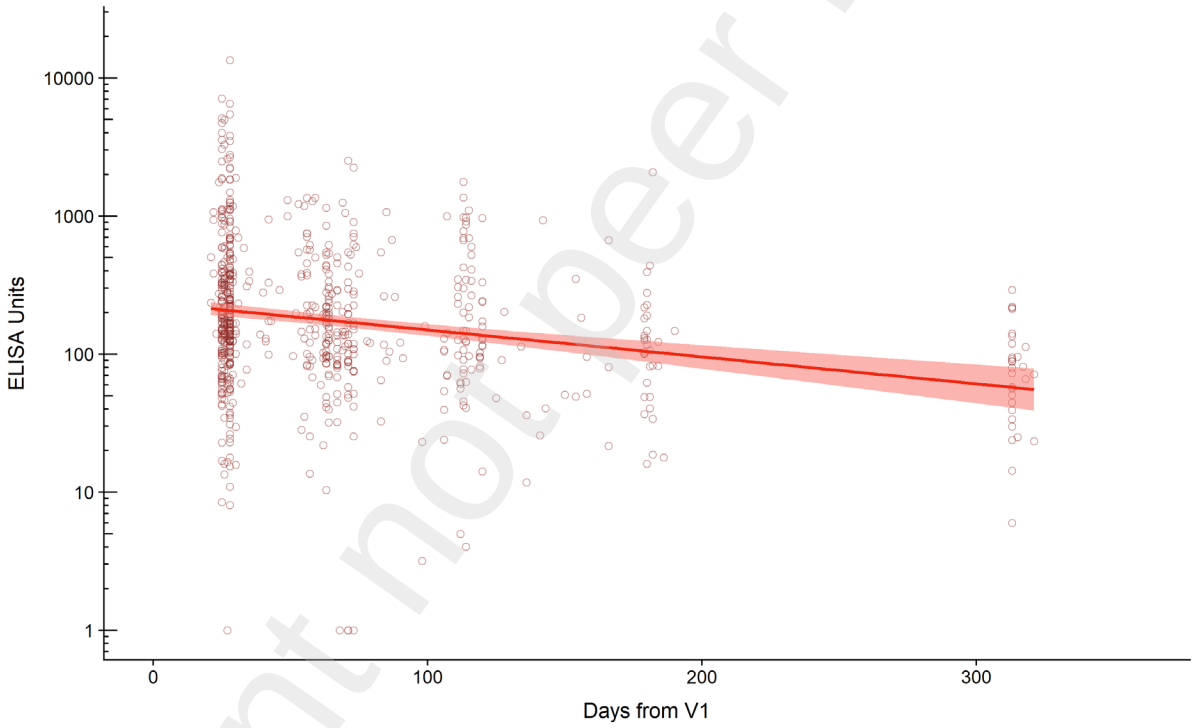

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Figure 2B: T-cell persistence after one dose of ChAdOx1 nCoV-19 vaccine. Vaccine induced T-cell responses against the SARS-CoV-2 spike insert were monitored to day 182 in a cohort of 47 participants receiving a single dose of ChAdOx1 nCoV-19. Isolated PBMCs were stimulated overnight with peptides spanning the SARS-CoV-2 spike insert. Participants were censored at the earliest occurrence of PCR +ve result, second dose on trial, or external COVID-19 vaccination. For these participants no ELISpot results beyond the date of censoring were used. Individual datapoints are shown. Solid line connects median values. SFU=spot-forming unit. PBMC=peripheral blood mononuclear cells.

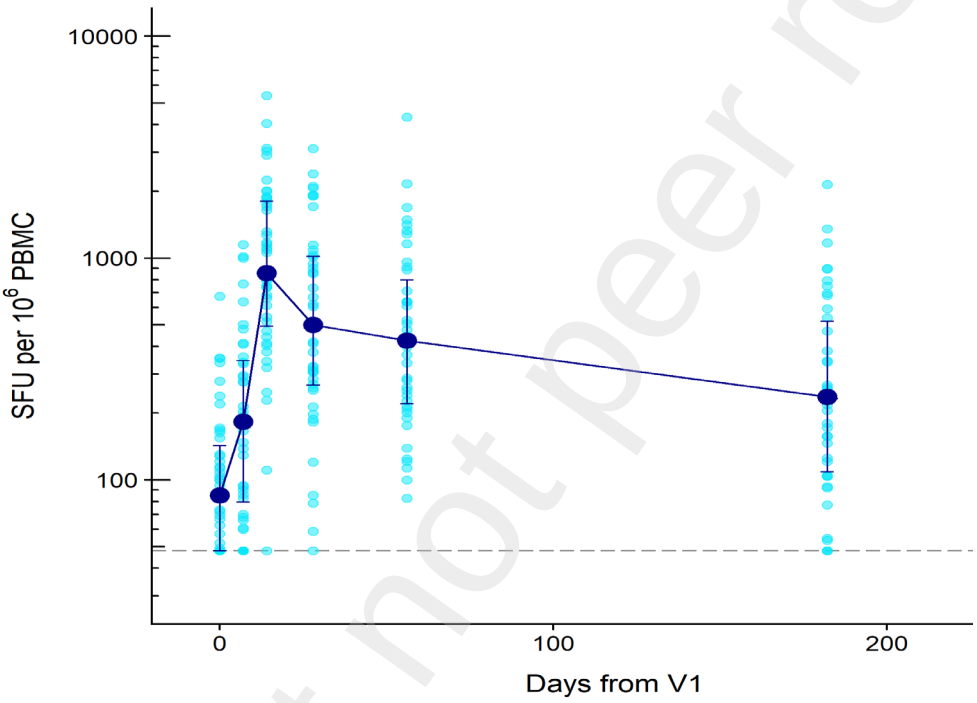

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Figure 3: Antibody response after prolonged interval between first and second vaccination. Antibody levels to SARS-CoV-2 Victoria/01/2020 spike measured by tIgG ELISA. Days after V2 is plotted as the median for each interval group. Median and IQR shown. Dotted line shows the time at which the second dose was given. Number of participants included: 8-12 week interval between V1 and V2 (n=115); 15-25 week interval between V1 and V2 (n=116); 44-45 week interval between V1 and V2 (n=30).

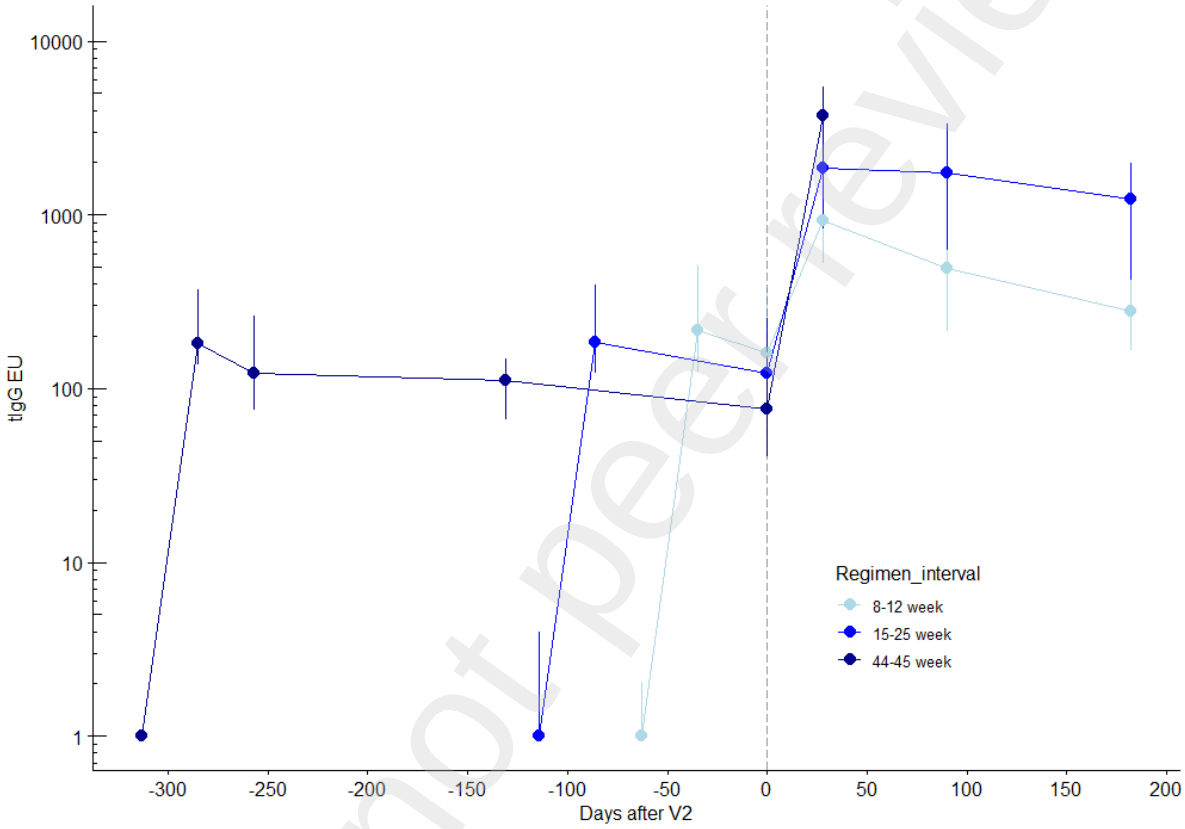

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Figure 4: Antibody responses after third vaccination. (A) Antibody levels to SARS-CoV-2 Victoria/01/2020 spike measured by tIgG ELISA. Individual datapoints are shown in lighter colour. Solid line connects median values. Bars represent inter-quartile ranges (n=75). (B) Neutralisation showing individual datapoints for three VOCs (n=45).

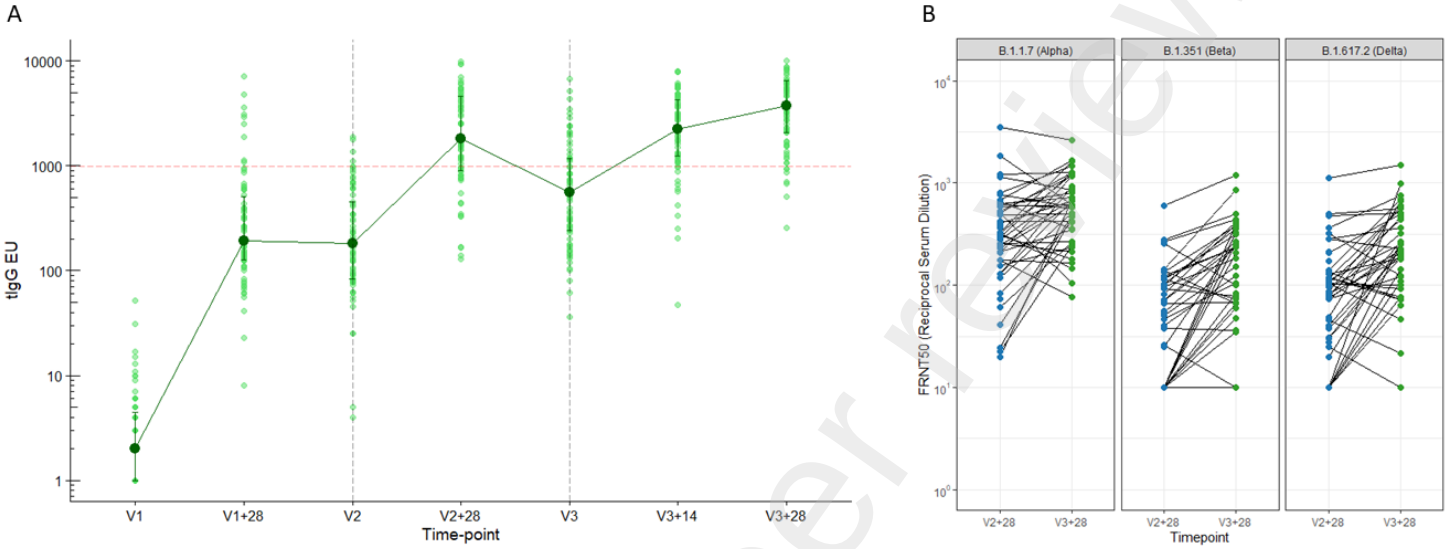

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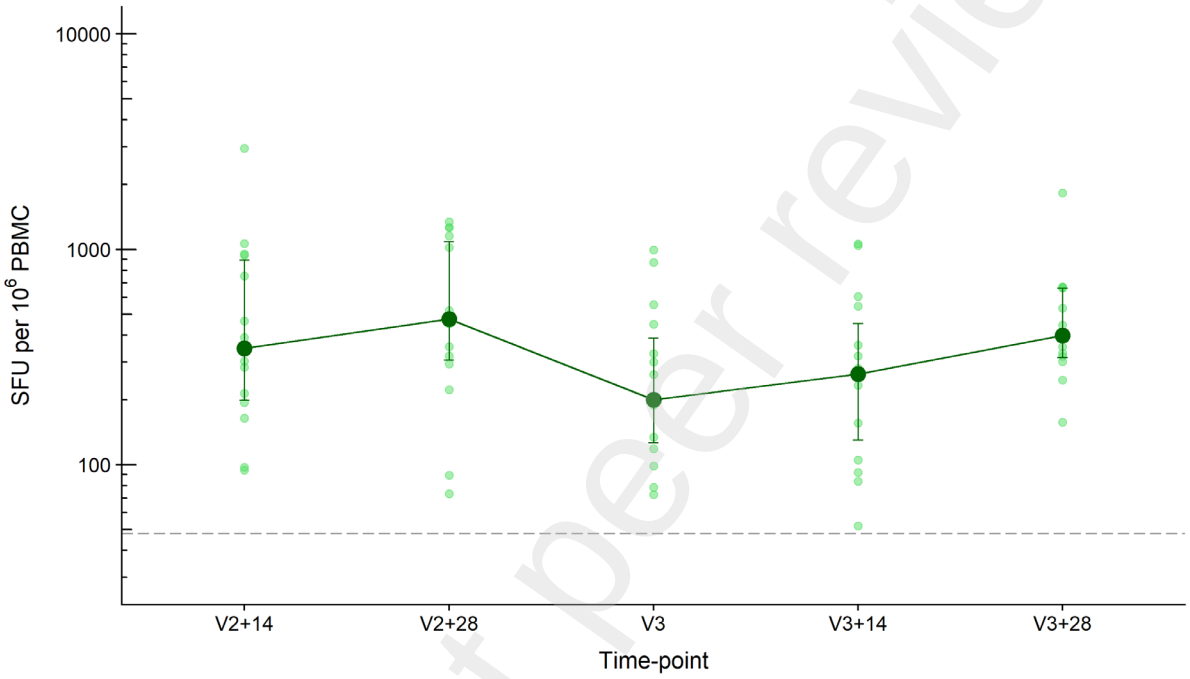
Figure 5: IFNγ ELISpot responses in participants receiving a third dose of ChAdOx1 nCoV-19. Volunteers included in the analysis had previously received two vaccine doses at 8 week interval. Third dose (at V3 time-point) was given 263-266 days after second dose. Individual datapoints are shown in lighter colour. Solid line connects median values. Bars represent inter-quartile ranges. Dotted line represents lower limit of detection of the assay (48 SFU per 10^6 PBMC). SFU=spot-forming unit. PBMC=peripheral blood mononuclear cells.



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