FINAL STUDY REPORT

Trial Title:

Post-approval follow-up for the COV001 and 002 trials, to determine the long-term safety and character of immunological response to the ChAdOx1 nCoV-19 coronavirus vaccine

Short Title:

Safety & immunogenicity extension study for ChAdOx1 nCoV-19

Study Reference: COV009 (OVG2021/03)

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Abbreviations and special terms

Abbreviation or special term	Explantion
Ab	Antibody
AE	Adverse event
AESI	Adverse event of special interest
BMI	Body mass index
BNT162b2	COVID-19 vaccine manufactured by Pfizer
ChAd	ChAdOx1 nCOV-19 vaccine, manufactured by AstraZeneca
CI	Confidence interval
COVID-19	Coronavirus disease 2019
dTaP/IPV	Diphtheria, tetanus, acellular pertussis and inactivated polio vaccine
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immunospot
GMC	Geometric mean concentration
GMR	Geometric mean ratio
IFNγ	Interferon gamma
IgG	Immunoglobulin G
IQR	Interquartile range
LD	Low dose
MedDRA	Medical Dictionary for Regulatory Activities
MenACWY	Quadrivalent capsular group A, C, W and Y meningococcal protein-polysaccharide conjugate vaccine
MHRA	Medicines and Healthcare products Regulatory Agency
mRNA vaccine	Messenger RNA COVID-19 vaccine
mRNA-1273	COVID-19 vaccine manufactured by Moderna
PI	Principal investigator
PT	Preferred term
REC	Research Ethics Committee
SAE	Serious adverse event
SAR	Severe adverse reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard dose
SOC	System organ class
SPEAC	Safety Platform for Emergency Vaccines

Abbreviation or special term	Explantion
SV1	First scheduled study visit
SV2	Second scheduled study visit
UK	United Kingdom
vp	Viral particles

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Study start date

Full approval for study received on 20th August 2021.

Study end date

End of trial notification submitted on 1st February 2025.

Summary

Background and rationale

Safety follow-up of participants in pre-licensure trials may provide the earliest indications of long-term adverse effects. Several effective vaccines against COVID-19 were rapidly developed and rolled out in response to the 2020 pandemic. One of these vaccines, ChAdOx1 nCoV-19, was developed by the University of Oxford and AstraZeneca. This study continued follow-up of participants who had been in two early UK studies of ChAdOx1 nCoV-19 (COV001 and COV002).

Design

This was a prospective safety study extending the follow-up period for participants of the COV001 and COV002 trials for an additional 12 months. It captured serious adverse events (SAEs), adverse events of special interest (AESIs), COVID-19 diagnoses and exposure to other vaccines. Each SAE and AESI was graded for severity, using standard scales, and an assessment was made of the likely causal relationship between the adverse event and ChAdOx1 nCoV-19. Statistical analyses were descriptive.

Results

Between September 2021 and April 2022, 4,468 participants enrolled in the study (37.6% of the 11,889 participants who enrolled in the original parent studies). By study completion, participants had received a wide variety of vaccine schedules. A total of 174 serious adverse events were reported by 159 participants. Twenty-three percent (40/174) were classified as grade 4 severity, and 61% (107/174) were classified as grade 3. There were five deaths, none of which was related to COVID-19 or to COVID-19 vaccination. The causal relationship between ChAdOx1 nCoV-19 and each SAE was assessed to be “no relationship” for 146/174 (84%) events and “unlikely” for 28/174 (16%). A total of 71 AESIs were reported by 68 participants. Thirty-three events were recorded as both an SAE and an AESI. Eleven percent (8/71) of AESIs were classified as grade 4 severity; 45% (32/71) were classified as grade 3. The causal relationship between ChAdOx1 nCoV-19 and AESI was assessed to be “no relationship” for 49/71 (69%) events and “unlikely” for 22/71 (31%). For no AE or AESI was the causal relationship assessed to be possible, probable or definite. Eighteen AESIs were related to COVID-19.

Conclusions

The fall in recruitment between parent and follow-on studies is likely to be because volunteers felt more motivated to participate in COV001 and COV002 (which offered volunteers the notable incentive of potentially receiving a COVID-19 vaccine, when none was available for the general population) than COV009 (which recruited after COVID-19 vaccines became widely available).

Over more than 4,000 participant years, relatively few SAEs and AESIs were recorded, and none was assessed as being likely related to the vaccine. However, long-term follow-up of participants in early clinical trials is not a substitute for careful post-marketing surveillance, which can detect extremely rare adverse events.

Background

The COVID-19 pandemic spread rapidly across the globe in early 2020. By early 2021, several effective vaccines had been developed and were beginning to be rolled out in expedited vaccination campaigns. In the UK, three COVID-19 vaccines, manufactured by AstraZeneca (ChAdOx1 nCoV-19), Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273), were deployed.[1-3] Two other COVID-19 vaccines, manufactured by Janssen and Novavax, were approved for use but not deployed in the UK.[4,5]

With immunisation at scale, it is possible that extremely rare adverse events, undetectable in clinical trials, may emerge. Clinical trials can identify more common adverse events. Safety follow-up of trial participants, who were exposed to the vaccines before the global roll out, may provide the earliest indications of longer-term adverse events.

The COV009 study was developed to follow up volunteers who had previously been enrolled in two clinical trials of ChAdOx2-nCoV19, COV001 and COV002. When the COV009 study began, long-term experience of COVID-19 vaccine safety and efficacy within clinical trials, was limited to about 12 months post-vaccination. Also, the quality and durability of the immune response that vaccination stimulated was yet to be characterised beyond 12 months.

At the time of COV009 recruitment, many of the participants had already been offered a third dose COVID-19 booster vaccine in a national vaccination programme. In the UK, booster vaccination was offered from September 2021, initially for people over 50 years old and other vulnerable groups.[6] From November 2021, adults aged 40 to 49 years who had received their second dose more than six months earlier became eligible for a third dose booster.[7] In December 2021, the booster campaign was extended to include all adults, and the minimum interval from second to third dose was reduced to three months.[8]

The COV009 study continued follow-up of participants who had been in two early UK studies of the ChAdOx1 nCoV-19 vaccine, COV001 and COV002.

COV001 trial

COV001 was a single blind phase I/II trial.[9-11] It was conducted at five sites across the UK. The trial enrolled 1,077 healthy adults, 18-55 years of age, randomly allocating them 1:1 to either an active ChAdOx1 nCoV-19 arm (N=543), or a placebo MenACWY arm (N=534). MenACWY is a licensed, quadrivalent conjugate vaccine to prevent meningitis, chosen to elicit post-injection symptoms, to maintain blinding. The first participants received an initial priming dose and were intensively monitored. Once safety had been ascertained, the next cohorts received a prime dose followed by a booster at 8 weeks or later.

ChAdOx1 nCoV-19 was associated more commonly than MenACWY with local and systemic reactions, including pain, fever, chills, myalgia, headache, and malaise, with highest severity within the first 24 hours. The majority were of mild to moderate severity, and all self-resolved. Prophylactic paracetamol significantly ameliorated reported symptoms. There were no serious adverse events related to ChAdOx1 nCoV-19.

CD8 T-cell responses specific for the SARS-CoV-2 spike protein peaked 14 days after vaccination. Anti-spike IgG antibody levels peaked four weeks after vaccination and remained elevated until eight weeks; they were boosted further by second vaccination. In a sub-analysis, neutralising antibody

responses against SARS-CoV-2 were seen in 91% of participants after a single dose, and in 100% after a booster dose.

It was concluded that ChAdOx1 nCoV-19 was safe, well tolerated, and immunogenic. Observed reactogenicity could be managed with prophylactic paracetamol.

COV002 trial

COV002 was a single blind phase II/III trial.[12-14] It enrolled 10,812 participants across 19 UK sites. Overall, there were 12 groups, recruited according to age. Each group was subdivided according to randomised vaccine (ChAdOx1 nCoV-19 low dose ($2.2x10^{10}$ vp), ChAdOx1 nCoV-19 standard dose ($3.5\text{-}6.5x10^{10}$ vp), or MenACWY control) and dose schedule (single dose, or two doses given 4-6 weeks apart).

For all age groups, vaccination with ChAdOx1 nCoV-19 was frequently associated with local pain and tenderness at injection sites within the first 48 hours. Fatigue, headache, feverishness, and myalgia were commonly reported systemic reactions. Younger age groups were more likely to experience generalised symptoms (86% of 18–55-year-olds, *vs* 77% of 56–69-year-olds, *vs* 65% of those aged 70 years and older).

Priming vaccination with ChAdOx1 nCoV-19 stimulated anti-spike IgG by day 28, with similar levels in both lower and standard dose participants. Advanced age was correlated with reduced anti-spike IgG (median 10k arbitrary units per ml, for 18–55-year-old groups, *vs* 5k AU/ml for 56–69-year-olds, *vs* 4k AU/ml for 70+ year-olds, after a single standard dose). However, participants receiving a booster generated similar IgG titres at 28 days after their second dose, in all age groups, regardless of dose regime.

Study design

COV009 was a prospective safety study designed to extend the follow-up period for participants of the COV001 and COV002 trials for an additional 12 months. It aimed to capture serious adverse events (SAEs), adverse events of special interest (AESIs), COVID-19 diagnoses and exposure to other vaccines.

A subset of participants who received two doses of ChAdOx1 nCoV-19 within the COV002 parent trial, and who received an external third dose of BNT162b2 vaccine, were offered ChAdOx1 nCoV-19 as a fourth dose booster, to assess its impact on immunogenicity (Group 2). Solicited and unsolicited adverse events (AEs) were documented for this subset of participants for 7 and 28 days respectively, and blood samples were taken at baseline and 28 days and 180 days post vaccination to assess immune response.

Inclusion criteria

- Enrolled in COV001 or COV002 trials.
- Able and willing to provide written informed consent to participate in the study.
- Able and willing (in the investigator's opinion) to comply with all study requirements.
- Consent to their general practitioner or responsible physician being notified of their participation in the study.
- Consent to allow investigators to discuss their medical information with their general practitioner or responsible physician and access any medical records where relevant to the study.

- Consent to access NHS SARS-CoV-2 NAAT results including viral sequencing results from NHS Digital and local labs, as well as COVID-19 vaccination records if available.

Additional inclusion criteria for Group 2

- Previous participant in COV002 study.
- Randomised and received 2 doses of ChAdOx1 nCoV-19 in the parent COV002 study.
- Provided blood sample for serology at 28 days post second vaccine in COV002.
- Received external non-study vaccination with BNT162b2 ≥ 4 months before vaccination with 4th dose.
- Willing and able to receive an additional 4th dose vaccination with ChAdOx1 nCoV-19.

Exclusion criteria

- Participants who have enrolled on a COVID-19 vaccine clinical trial of investigational medicinal product (CTIMP), other than COV001 and COV002, will be excluded. Examples include but are not limited to COV-Variant or COV-Boost, where ongoing safety follow up would be duplicated by enrolling in this study.
- Participants must be enrolled within 26 weeks of when the last study visit of their parent study was due.

Additional exclusion criteria for Group 2

- Female participant who is pregnant at time of vaccination.
- Allergy or other contraindication to vaccination with ChAdOx1 nCoV-19.
- History of Guillain-Barré syndrome.
- Any confirmed or suspected immunosuppressive or immunodeficient state, including asplenia; recurrent severe infections and use of immunosuppressant medication within the last 6 months, except topical steroids or short-term oral steroids (course lasting <14 days).
- History of clinically significant thrombocytopenia and/or thrombosis or clinically significant bleeding (*e.g.*, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following intramuscular injections or venepuncture.
- Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder, and neurological illness, as judged by the Investigator (mild/moderate well-controlled comorbidities are allowed.
- Plans to move outside the study area.
- Receipt of additional COVID-19 vaccines other than those listed in the inclusion criteria.
- Receipt of any vaccine (licensed or investigational) other than the study intervention within 30 days before and after the study vaccination (one week for licensed seasonal influenza vaccine or pneumococcal vaccine).

Temporary exclusion criteria for Group 2

If at vaccination visit the volunteer has any of the following, they will not be enrolled that day:

- Acute respiratory illness (moderate or severe illness with or without fever).
- Fever (oral temperature greater than 37.8°C).
- Positive test for COVID-19 within the past 28 days. They may be considered for enrolment later in the trial, if they recover in sufficient time.

Investigational medicinal products

Recombinant Covid-19 vaccine (AstraZeneca) containing chimpanzee adenovirus codifying Spike SARS-CoV-2 glycoprotein was used for the 4th dose booster sub-study (Group 2). It was given at the standard dose of $5x^{10}$vp in 0.5ml, administered intramuscularly.

Objectives and outcome measures

Primary objectives and outcome measures

The primary objective was assessment of long-term safety of ChAdOx1 nCoV-19.

Outcomes were measured using a registry of serious adverse events (SAEs) and adverse events of special interest (AESIs).

Secondary objectives and outcome measures

Secondary objectives were:

1. To investigate the relationship between vaccination, immunological profile, and subsequent SARS-CoV-2 infection, COVID-related hospitalisation, morbidity or mortality.
   Immune responses were measured by anti-SARS-CoV-2 spike protein immunoglobulins and neutralising antibodies against SARS-CoV-2. For a subset of participants, where local lab facilities permitted, further assays were performed: cellular immune response to SARS-CoV-2 spike protein by IFN-ϒ ELISpot, ICS or whole blood assay; anti-vector immunity to ChAdOx1 virus.
2. Evaluation of the safety and immunogenicity of ChAdOx1 nCoV-19 as a fourth dose booster in individuals who had received 2 doses of ChAdOx1 nCoV-19 as a primary schedule in COV002, followed by an external third dose of BNT162b2.
   Outcomes were measured by recording solicited and unsolicited AEs for 7 days post fourth dose booster vaccine using electronic diaries, recording unsolicited AEs for 28 days post fourth dose booster vaccine and recording of COVID-19 diagnoses throughout.

Exploratory objectives and outcome measures

Exploratory objectives were to assess any differences in immunological profile or immunological persistence by age, sex, ethnicity, and reactogenicity. Immune responses were measured using the same assays as noted above in *Secondary objectives (1)*.

SAEs and AESIs

SAEs and AESIs were recorded for the duration of participation in the study.

Definitions

A serious adverse event was defined as any untoward medical occurrence that resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, or consisted of a congenital anomaly or birth defect. Other 'important medical events' were deemed to be a serious adverse event if the evaluating clinician judged that the event might have jeopardised the participant and might have required medical or surgical intervention to prevent one of the above outcomes.

Selection of AESIs for this study was based on the Brighton Collaboration case definitions[15] (SPEAC 2020), clinical experience, and scientific interest. Table A1 lists the AESIs.

Evaluation

SAEs and AESIs were evaluated by PI-delegated clinicians.

An assessment was made of the causal relationship between the adverse event and ChAdOx1 nCoV-19 administered during the parent trial (or, in Group 2 participants, between the adverse event and ChAdOx1 nCoV-19 administered as a fourth dose booster). There were five categories of 'causality': no relationship, unlikely, possible, probable and definite. The guidelines for determining the relevant causality term for an adverse event are shown in Table A2. An adverse event was considered to have a causal relationship to ChAdOx1 nCoV-19 if the attribution was possible, probable, or definite; it was considered to have no causal relationship to ChAdOx1 nCoV-19 if the attribution was 'no relationship' or 'unlikely'.

Each SAE and AESI was graded for severity, using scales based on FDA toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials. Severity was graded as follows:

Grade	Symptoms
Grade 0	No symptoms
Grade 1	Mild: Transient or mild discomfort (< 48 hours); no interference with activity; no medical intervention/therapy required
Grade 2	Moderate: Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required
Grade 3	Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required
Grade 4	Potentially life-threatening: requires assessment in A&E or hospitalisation

Statistical methods

The main analyses are descriptive. Counts and percentages for safety outcomes are presented, with medians and inter-quartile ranges for immunological outcomes.

Sample size

The participants for this study were recruited from the COV001 and COV002 trials. There were 11,889 potentially eligible participants. However, the sample size was determined by the number of eligible individuals who consented to participation.

For the fourth dose sub-study (Group 2), it was calculated that 150 participants would provide 98% power to show non-inferiority of the 4th dose compared with the 2nd dose. The calculation was based on the previously reported standard deviation for the difference between dose 2 and dose 3.[16] Calculation assumed that the standard deviation for the difference between dose 2 and dose 4 is similar to the standard deviation for the difference between dose 2 and dose 3. It also assumed a non-inferiority margin for the lower bound of the GMFR of 2/3 (-0.176 on log10 scale), and alpha of 0.025.

Measurement of antibody responses

Antibody responses were measured in a non-randomised subset of participants using an in-house standardised total IgG ELISA against trimeric SARS-CoV-2 spike protein.

Results

The results presented here are those pertinent to the primary objective of the study, the assessment of the long-term safety of ChAdOx1-nCoV-19, and the antibody responses in a non-randomised subset of participants. The reactogenicty and immunogenicity results from a fourth dose sub-study (Group 2) have been reported previously.[17]

For reasons of pragmatism and clarity, it was decided to present the study results by broadly classifying the participants into one of three groups, based on all available vaccination information recorded for the participant at the time of their exit from the study (by completion, withdrawal or death). These three groups were: “ChAd only” group (who had received only ChAdOx1 nCov-19); “mRNA only” group (who had received only COVID-19 vaccines other than ChAdOx1 nCov-19); “ChAd & mRNA” group (who had received a mixed schedule of both ChAdOx1 nCov-19 and one or more other COVID-19 vaccine).

Participants

A total of 4,470 participants were enrolled in the COV009 study between 3 September 2021 and 11 April 2022. Two were excluded because they had no record of having received a COVID-19 vaccine. Of the remaining 4,468 participants, 469 (10%) were recruited from the 1,077 who enrolled in the original COV001 study, and 3,999 (90%) from the 10,812 who enrolled in the original COV002 study.

The baseline demographic characteristics of enrolled participants are shown in Table 1. Fifty-eight percent (2,594/4,468) were female. Sixty-five percent (2,903/4,468) were aged 18 to 55 years, 17% (751/4,468) were aged 56 to 69 years and 18% (814/4,468) were aged ≥70 years at the time of receiving the first COVID-19 vaccine. Forty-nine percent (2,204/4,468) were health care workers. Ninety-five percent (4,236/4,468), self-identified as being of white ethnicity. Fifteen percent (667/4,468) reported pre-existing cardiovascular disorders, 11% (487/4,468) reported respiratory disorders and 2.2% (98/4,468) were diabetic. Apart from age, the demographic characteristics of the participants enrolled in COV009 were broadly similar to those in COV001 and COV002 (Table A3). However, COV009 participants had a higher baseline median age (49 years, compared with 44 years for all participants enrolled in COV002 and 35 years for all participants enrolled in COV001).

Figure 1 shows a CONSORT diagram for the study. Before the first scheduled study visit (SV1), 6 months after enrolment, 343 participants withdrew and 2 died. Between SV1 and the second scheduled study visit (SV2), 6 months later, a further 270 withdrew and 3 died. None of the five deaths was related to COVID-19 or to COVID-19 vaccination (see Table B1 for further details). A total of 150 individuals were identified for participation in Group 2, the fourth dose sub-study, 126 at SV1 and 24 at SV2. One withdrew before the enrolment/vaccination visit, and so 149 participants were enrolled and vaccinated in Group 2. Five withdrew before their final study visit. Overall, 3,845 (86%) participants completed the study, all of whom attended their final study visit. Further details regarding reasons for not completing the study are shown in Table A4.

Table A5 shows details of when study visits occurred. The median interval between the first COVID-19 vaccination and SV1 was 574 days (IQR: 451, 678). SV1 took place between 17 February 2022 and 31 October 2022. SV2 took place between 22 August 2022 and 28 April 2023. The median interval between SV1 and SV2 was 182 days (IQR: 175, 190).

Table 1. Baseline characteristics of participants

		Female			Male		
	Total* N = 4,468[1]	**ChAd & mRNA† N = 1,741[1]**	**ChAd only† N = 213[1]**	**mRNA only† N = 640[1]**	**ChAd & mRNA† N = 1,328[1]**	**ChAd only† N = 172[1]**	**mRNA only† N = 374[1]**
Study							
COV001	469 (10%)	172 (9.9%)	44 (21%)	37 (5.8%)	137 (10%)	58 (34%)	21 (5.6%)
COV002	3,999 (90%)	1,569 (90%)	169 (79%)	603 (94%)	1,191 (90%)	114 (66%)	353 (94%)
Age (years)**							
N	4,468	1,741	213	640	1,328	172	374
Mean (SD)	51 (15)	50 (14)	42 (13)	47 (13)	55 (16)	44 (14)	51 (16)
Median (IQR)	50 (39, 62)	49 (40, 60)	41 (32, 49)	47 (38, 55)	55 (41, 71)	41 (33, 52)	51 (38, 67)
Range	19, 88	19, 86	20, 78	19, 84	19, 88	21, 81	19, 84
Age group**							
18-55 years	2,903 (65%)	1,194 (69%)	181 (85%)	490 (77%)	667 (50%)	142 (83%)	229 (61%)
56-69 years	751 (17%)	279 (16%)	21 (9.9%)	98 (15%)	273 (21%)	14 (8.1%)	66 (18%)
≥70 years	814 (18%)	268 (15%)	11 (5.2%)	52 (8.1%)	388 (29%)	16 (9.3%)	79 (21%)
Healthcare worker	2,204 (49%)	946 (54%)	108 (51%)	502 (78%)	390 (29%)	51 (30%)	207 (55%)
Ethnicity							
White	4,236 (95%)	1,673 (96%)	198 (93%)	617 (96%)	1,250 (94%)	157 (91%)	341 (91%)
Asian	125 (2.8%)	34 (2.0%)	8 (3.8%)	12 (1.9%)	41 (3.1%)	6 (3.5%)	24 (6.4%)
Black	17 (0.4%)	5 (0.3%)	0 (0%)	0 (0%)	7 (0.5%)	4 (2.3%)	1 (0.3%)
Other	86 (1.9%)	28 (1.6%)	7 (3.3%)	11 (1.7%)	28 (2.1%)	5 (2.9%)	7 (1.9%)
Missing	4 (<0.1%)	1 (<0.1%)	0 (0%)	0 (0%)	2 (0.2%)	0 (0%)	1 (0.3%)

		Female			Male		
	Total* N = 4,468[1]	**ChAd & mRNA† N = 1,741[1]**	**ChAd only† N = 213[1]**	**mRNA only† N = 640[1]**	**ChAd & mRNA† N = 1,328[1]**	**ChAd only† N = 172[1]**	**mRNA only† N = 374[1]**
BMI							
N	4,462	1,740	213	639	1,325	172	373
Mean (SD)	26.3 (4.9)	26.3 (5.4)	26.9 (5.6)	26.1 (5.2)	26.3 (4.0)	26.0 (4.0)	26.4 (4.2)
Median (IQR)	25.5 (23.0, 28.7)	25.2 (22.5, 29.0)	25.5 (22.9, 30.0)	25.2 (22.3, 28.5)	25.9 (23.7, 28.4)	25.2 (23.5, 28.1)	26.0 (23.3, 28.7)
Range	13.8, 68.5	13.8, 64.1	17.8, 49.2	15.4, 57.3	15.3, 68.5	18.9, 41.7	17.9, 45.8
Cardiovascular disorders	667 (15%)	207 (12%)	11 (5.2%)	62 (9.7%)	295 (22%)	12 (7.0%)	80 (21%)
Respiratory disorders	487 (11%)	198 (11%)	17 (8.0%)	72 (11%)	135 (10%)	17 (9.9%)	48 (13%)
Diabetes	98 (2.2%)	28 (1.6%)	2 (0.9%)	12 (1.9%)	41 (3.1%)	0	15 (4.0%)

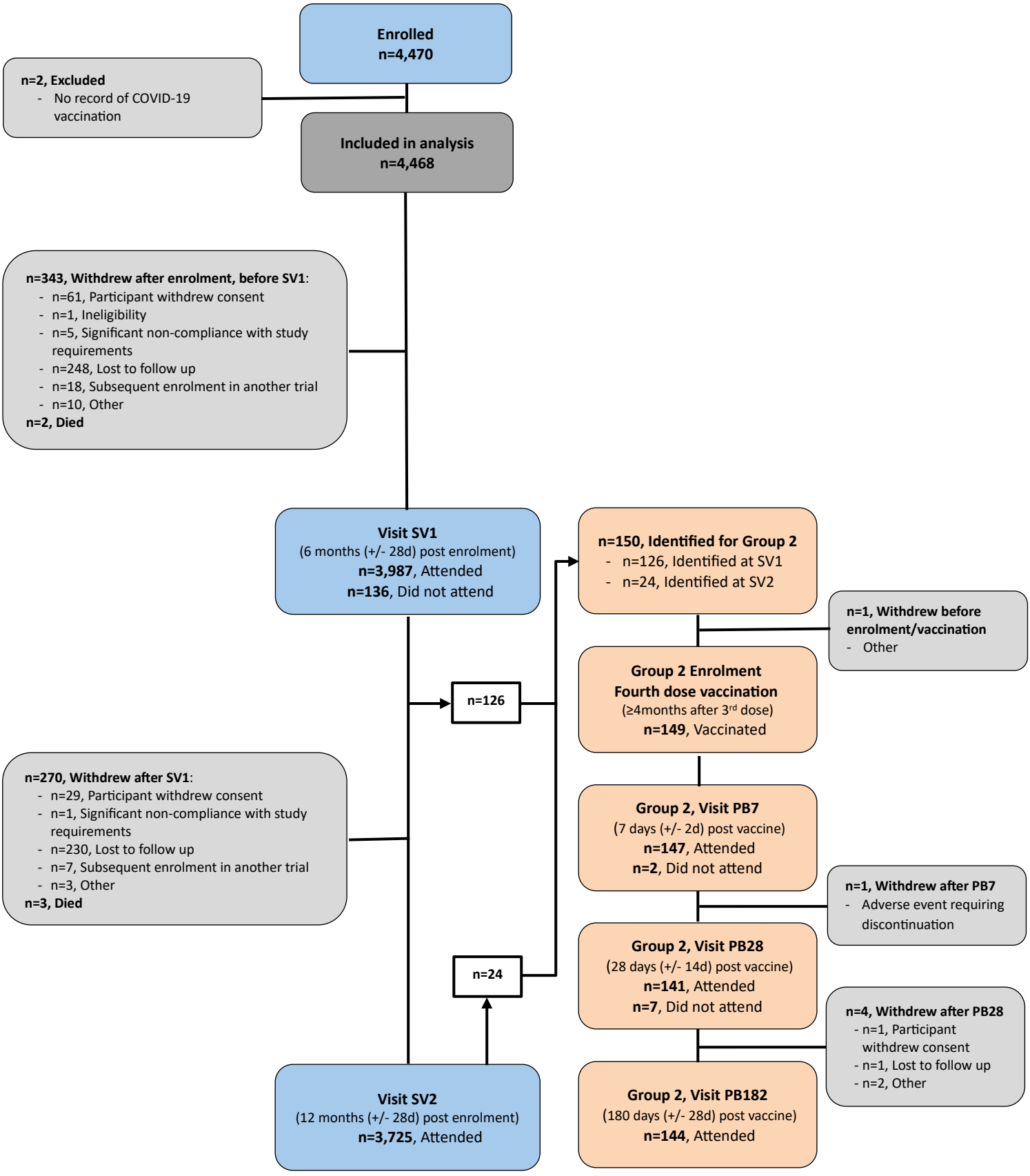
[1] n (%)

* Two enrolled participants with no record of receiving a COVID-19 vaccine were excluded from the analysis.

** Age at the time of receiving the first COVID-19 vaccine.

† COVID-19 vaccines received at time of exit from study: **ChAd & mRNA**: Both ChAdOx1 nCoV-19 and mRNA/other vaccine (Pfizer, Moderna, or other COVID-19 vaccine); **ChAd only**: Only ChAdOx1 nCoV-19; **mRNA only**: Only mRNA/other vaccine (Pfizer, Moderna, or other COVID-19 vaccine).

Figure 1. CONSORT diagram.



Vaccinations

Table A6 shows the vaccinations received by COV009 participants in the parent studies, COV001 and COV002. Fifty-nine percent (2,623/4,468) received at least one dose of ChAdOx1 nCoV-19 in COV001/COV002; the remaining 41% (1,845/4,468) received only the control MenACWY vaccine. Various combinations of standard dose ChAdOx1 nCov-19 (3.5-6.5x10^{10} vp), low dose ChAdOx1 nCov-19 (2.2x10^{10} vp) and control MenACWY vaccine were given. The combinations most frequently given were two doses of MenACWY (1,773/4.468; 40%), two standard doses of ChAdOx1 nCov-19 (1,651/4,468; 37%) and low dose followed by standard dose ChAdOx1 nCov-19 (666/4,468; 15%). Six percent (272/4,468) received only one dose of vaccine in the parent study; for 7/4,468 participants vaccination records were missing; all other participants (4,189/4,468) received two doses.

Table 2 shows the total number of COVID-19 vaccine doses received by COV009 participants, both in studies and in the community, at the point of completing the study, or at the time of the last study visit before withdrawal or death. The range was from one to seven doses; 48% (2,149/4,468) received three doses and 33% (1,458/4,468) received four doses of a COVID-19 vaccine. Table 2 also indicates how many doses of ChAdOx1 nCoV-19 and how many doses of other COVID-19 vaccines (predominantly mRNA vaccines) participants had received at the time they exited the study. Sixty eight percent (3,030/4,468) received two doses of ChAdOx1 nCoV-19; 23% (1,014/4,468) received no ChAdOx1 nCoV-19. Further details of the COVID-19 vaccines received by study participants are provided in Table A7 and Figure A1, which show the order in which vaccinations were received. The most frequent combinations received were two doses of ChAdOx1 nCoV-19, followed by one dose of mRNA/other vaccine (1,601/4,468; 36%) and two doses of ChAdOx1 nCoV-19, followed by two doses of mRNA/other vaccine (915/4,468; 20%). Three doses of mRNA/other vaccine were received by 9.9% (442/4,468) and four doses of mRNA/other vaccine were received by 7.7% (343/4,468).

Table A8 shows which mRNA vaccines had been received by participants at the time they exited the study. Eighty-two percent (3,667/4,468) received at least one dose of Pfizer vaccine, 35% (1,576/4,468) received at least one dose of Moderna vaccine, and 26% (1,162/4,468) received at least one dose of Pfizer and at least one dose of Moderna vaccine.

Table A9 shows the intervals between successive COVID-19 vaccinations. The median interval between first and second doses was 76 days (IQR: 57-91). Overall, the median interval between second and third doses was 339 days (IQR: 198-401). This interval was longer in participants who received a combination of ChAdOx1 nCoV-19 and another COVID-19 vaccine than those who only received ChAdOx1 nCoV-19 or who only received other COVID-19 vaccines. The median interval between third and fourth doses was 341 days (IQR: 265-358) and was similar whether participants had received a combination of ChAdOx1 nCoV-19 and another COVID-19 vaccine or had only received other COVID-19 vaccines.

Table 2. COVID-19 vaccinations received by participants before exit from COV009.

		Female			Male		
	Total N = 4,468[1]	**ChAd & mRNA N = 1,741[1]**	**ChAd only N = 213[1]**	**mRNA only N = 640[1]**	**ChAd & mRNA N = 1,328[1]**	**ChAd only N = 172[1]**	**mRNA only N = 374[1]**
Total number of COVID-19 vaccine doses received*							
1	43 (1.0%)	0 (0%)	7 (3.3%)	23 (3.6%)	0 (0%)	7 (4.1%)	6 (1.6%)
2	534 (12%)	34 (2.0%)	177 (83%)	108 (17%)	23 (1.7%)	133 (77%)	59 (16%)
3	2,149 (48%)	954 (55%)	28 (13%)	281 (44%)	693 (52%)	32 (19%)	161 (43%)
4	1,458 (33%)	657 (38%)	1 (0.5%)	214 (33%)	457 (34%)	0 (0%)	129 (34%)
5	243 (5.4%)	80 (4.6%)	0 (0%)	13 (2.0%)	131 (9.9%)	0 (0%)	19 (5.1%)
6	39 (0.9%)	15 (0.9%)	0 (0%)	1 (0.2%)	23 (1.7%)	0 (0%)	0 (0%)
7	2 (<0.1%)	1 (<0.1%)	0 (0%)	0 (0%)	1 (<0.1%)	0 (0%)	0 (0%)
Number of ChAdOx1 nCoV-19 vaccine doses							
0	1,014 (23%)	0 (0%)	0 (0%)	640 (100%)	0 (0%)	0 (0%)	374 (100%)
1	138 (3.1%)	76 (4.4%)	7 (3.3%)	0 (0%)	48 (3.6%)	7 (4.1%)	0 (0%)
2	3,030 (68%)	1,544 (89%)	177 (83%)	0 (0%)	1,176 (89%)	133 (77%)	0 (0%)
3	275 (6.2%)	116 (6.7%)	28 (13%)	0 (0%)	99 (7.5%)	32 (19%)	0 (0%)
4	11 (0.2%)	5 (0.3%)	1 (0.5%)	0 (0%)	5 (0.4%)	0 (0%)	0 (0%)
Number of mRNA/other COVID-19 vaccine doses							
0	385 (8.6%)	0 (0%)	213 (100%)	0 (0%)	0 (0%)	172 (100%)	0 (0%)
1	1,880 (42%)	1,075 (62%)	0 (0%)	23 (3.6%)	776 (58%)	0 (0%)	6 (1.6%)
2	1,156 (26%)	572 (33%)	0 (0%)	108 (17%)	417 (31%)	0 (0%)	59 (16%)
3	632 (14%)	74 (4.3%)	0 (0%)	281 (44%)	116 (8.7%)	0 (0%)	161 (43%)
4	378 (8.5%)	18 (1.0%)	0 (0%)	214 (33%)	17 (1.3%)	0 (0%)	129 (34%)
5	36 (0.8%)	2 (0.1%)	0 (0%)	13 (2.0%)	2 (0.2%)	0 (0%)	19 (5.1%)
6	1 (<0.1%)	0 (0%)	0 (0%)	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)

[1]n (%)

* Includes all COVID-19 vaccines recorded as received by participant, regardless of whether given as part of study, up to time of exit from COV009 (either by completion of study or withdrawal/death).

Serious adverse events (SAEs)

A total 174 serious adverse events were reported by 159 participants; 13 participants reported two SAEs, and one participant reported three. Table 3 summarises the data for SAEs. Overall, 23% (40/174) were classified as grade 4 severity, and 61% (107/174) were classified as grade 3 severity. There were five deaths (caused by pancreatic cancer, motor neurone disease, cerebral vascular accident, peritonitis with neutropenic sepsis, and metastatic cholangiocarcinoma).

The most recent vaccination before the occurrence of 145 (83%) SAEs included a COVID-19 vaccine; in 122 (70%) SAEs this was a COVID-19 vaccine given alone, and in 23 SAEs (13%) the COVID-19 vaccine was given at the same time as another vaccine. In the remaining 29 (17%) SAEs, the most recent vaccination before the event was a non-COVID-19 vaccine. The most recent COVID-19 vaccine received before an SAE was Pfizer (125/174; 72%), Moderna (22/174; 13%), and ChAdOx1 nCoV-19 (27/174; 16%). Other vaccines received after COVID-19 vaccines but before the SAE included influenza, shingles, and dTaP/IPV. The median interval between the most recent COVID-19 vaccination and an SAE was 159 days (IQR: 66, 262). The causal relationship between ChAdOx1 nCoV-19 and an SAE was assessed to be “no relationship” for 146/174 (86%) events and “unlikely” for 28/174 (14%). In no case was the causal relationship assessed to be possible, probable or definite.

Eight SAEs were classified as being related to SARS-CoV-2 infection. Details are shown in Table B2. The most recent COVID-19 vaccine received before the event was Pfizer in 5/8 cases; it was ChAdOx1 nCoV-19 in two cases and Moderna in one. There were two cases of pulmonary embolism; in both, Pfizer was the most recent COVID-19 vaccine to have been received before the event.

Classification of SAEs by MedDRA system organ class (SOC) and preferred term (PT) is shown in Table B3. The most common MedDRA SOC assignations were “Neoplasms benign, malignant and unspecified” (36/174, 20.7%), “General disorders and administration site conditions” (34/174, 19.5%) and “Infections and infestations” (20/174, 11.5%).

Table 3. Summary of SAEs.

	Total N = 4,468[1]	ChAd & mRNA N = 3,069[1]	ChAd only N = 385[1]	mRNA only N = 1,014[1]
Number of participants experiencing at least one SAE	159 (3.6%)	118 (3.8%)	9 (2.3%)	32 (3.2%)
Number of SAEs	174	128	9	37
Category of SAE				
An important medical event	54 (31%)	39 (30%)	4 (44%)	11 (30%)
Death	5 (2.9%)	4 (3.1%)	1 (11%)	0
Hospitalisation	101 (58%)	72 (56%)	4 (44%)	25 (68%)
Life threatening	3 (1.7%)	3 (2.3%)	0	0
Significant disability/incapacity	11 (6.3%)	10 (7.8%)	0	1 (2.7%)
Severity				
Grade 1	5 (2.9%)	4 (3.1%)	0	1 (2.7%)
Grade 2	22 (13%)	15 (12%)	2 (22%)	5 (14%)
Grade 3	107 (61%)	78 (61%)	3 (33%)	26 (70%)
Grade 4	40 (23%)	31 (24%)	4 (44%)	5 (14%)
Causality				
No relationship	146 (84%)	106 (83%)	8 (89%)	32 (86%)
Unlikely	28 (16%)	22 (17%)	1 (11%)	5 (14%)
Relationship to ChAdOx1 nCoV-19				
Not related	174 (100%)	128 (100%)	9 (100%)	37 (100%)
SARS-CoV2 infection related SAE	8 (4.6%)	5 (3.9%)	1 (11%)	2 (5.4%)
Outcome				
Fatal	5 (2.9%)	4 (3.1%)	1 (11%)	0
Not recovered or resolved	35 (20%)	27 (21%)	1 (11%)	7 (19%)
Recovered/resolved	98 (56%)	67 (52%)	6 (67%)	25 (68%)
Recovered/resolved with sequelae	22 (13%)	20 (16%)	0	2 (5.4%)
Recovering/resolving	14 (8.0%)	10 (7.8%)	1 (11%)	3 (8.1%)
Last COVID-19 vaccine before SAE				
ChAdOx1	27 (16%)	18 (14%)	9 (100%)	-
Moderna	22 (13%)	18 (14%)	-	4 (11%)
Pfizer	125 (72%)	92 (72%)	-	33 (89%)
Days since last COVID-19 vaccine				
Median (IQR)	159 (66, 262)	149 (65, 264)	472 (232, 488)	131 (59, 235)
Min, Max	1, 789	9, 473	11, 789	1, 561
Duration of SAE until recovered/resolved (days)				
Median (IQR)	4 (1, 31)	4 (1, 35)	5 (2, 171)	4 (1, 25)
Min, Max	0, 624	0, 408	1, 624	1, 301

[1]n (%)

Adverse events of special interest (AESIs)

Sixty-eight participants reported a total of 71 AESIs. One participant experienced two AESIs and one participant reported three. Thirty-three events were recorded as both an SAE and an AESI. Table 4 summarises the data for AESIs. Overall, 11% (8/71) were classified as grade 4 severity, and 45% (32/71) were classified as grade 3 severity. There was one death (caused by motor neurone disease).

The most recent vaccination before the occurrence of 61 (86%) AESIs included a COVID-19 vaccine; in 51 (72%) AESIs this was a COVID-19 vaccine given alone, and in 10 AESIs (14%) the COVID-19 vaccine was given at the same time as another vaccine. In the remaining 10 (14%) AESIs, the most recent vaccination before the event was a non-COVID-19 vaccine. The most recent COVID-19 vaccine received before the AESI was Pfizer (49/71; 69%), Moderna (9/71; 13%), ChAdOx1 nCoV-19 (12/71; 17%) and other (1/71; 1.4%). Other vaccines received after COVID-19 vaccines but before the AESI included influenza and dTaP/IPV. The median interval between most recent COVID-19 vaccination and AESI was 134 days (IQR: 43, 238). The causal relationship between ChAdOx1 nCoV-19 and AESI was assessed to be “no relationship” for 49/71 (69%) events and “unlikely” for 22/71 (31%). In no case was the causal relationship assessed to be possible, probable or definite.

Eighteen AESIs were classified as being related to SARS-CoV-2 infections. Details are shown in Table B4. The most recent COVID-19 vaccine received before the event was Pfizer in 13/18 cases; it was ChAdOx1 nCoV-19 in 3/18 cases, Moderna in 1/18 case and other vaccine in 1/18 case.

Classification of AESIs by MedDRA system organ class (SOC) and preferred term (PT) is shown in Table B5. The most common MedDRA SOC assignations were “Nervous system disorders” (18/71; 25%), “Infections and infestations” (18/71; 25%), “Gastrointestinal disorders (6/71; 8.5%) and “Neoplasms benign, malignant and unspecified” (6/71; 8.5%).

Table 4. Summary of AESIs

	Overall N = 4,468[1]	ChAd & mRNA N = 3,069[1]	ChAd only N = 385[1]	mRNA only N = 1,014[1]
Number of participants experiencing at least one AESI	68 (1.5%)	51 (1.7%)	7 (1.8%)	10 (1.0%)
Number of AESIs	71	54	7	10
Severity				
Grade 1	10 (14%)	9 (17%)	0	1 (10%)
Grade 2	21 (30%)	17 (31%)	3 (43%)	1 (10%)
Grade 3	32 (45%)	24 (44%)	1 (14%)	7 (70%)
Grade 4	8 (11%)	4 (7.4%)	3 (43%)	1 (10%)
Causality				
No relationship	49 (69%)	35 (65%)	5 (71%)	9 (90%)
Unlikely	22 (31%)	19 (35%)	2 (29%)	1 (10%)
Relationship to ChAdOx1 nCoV-19				
Not related	71 (100%)	54 (100%)	7 (100%)	10 (100%)
SARS-CoV-2 infection related AESI	18 (25%)	14 (26%)	2 (29%)	2 (20%)
Outcome				
Fatal	1 (1.4%)	0	1 (14%)	0
Not recovered or resolved	16 (23%)	14 (26%)	1 (14%)	1 (10%)
Recovered/resolved	42 (59%)	31 (57%)	4 (57%)	7 (70%)
Recovered resolved with sequelae	6 (8.5%)	6 (11%)	0	0
Recovering/resolving	6 (8.5%)	3 (5.6%)	1 (14%)	2 (20%)
Last COVID-19 vaccine before AESI				
ChAdOx1	12 (17%)	5 (9.3%)	7 (100%)	-
Moderna	9 (13%)	8 (15%)	-	1 (10%)
Other	1 (1.4%)	1 (1.9%)	-	0
Pfizer	49 (69%)	40 (74%)	-	9 (90%)
Days since last COVID-19 vaccine				
Median (IQR)	134 (43, 238)	126 (41, 230)	233 (187, 473)	81 (50, 225)
Min, Max	3, 801	3, 348	11, 801	31, 500
Duration of AESI until recovered/resolved (days)				
Median (IQR)	7 (2, 35)	6 (3, 35)	171 (7, 292)	7 (1, 18)
Min, Max	0, 624	0, 237	2, 624	0, 34

[1]n (%)

Antibody responses

Humoral immune responses were measured in a small non-randomised subset of participants, at timepoints from the commencement of COV001/COV002 until completion of COV009, a period of approximately two years. Results are reported here according to the interval between first and second doses of ChAdOx1 nCoV-19 given in COV001/COV002 (28 days, 2 to <6 months, and 6 to 11 months). Results are also reported for a few participants who received a third dose of ChAdOx1 nCoV-19 in COV001.

Figure 2 and Table 5 show antibody responses in 46 participants who received a second dose of ChAdOx1 nCoV-19 at 28 days after the first dose in COV001/COV002. Figure C1 shows a subgroup analysis of these 46 participants according to age group, sex, and ChAdOx1 n-Cov-19 dosage in COV001/COV002.

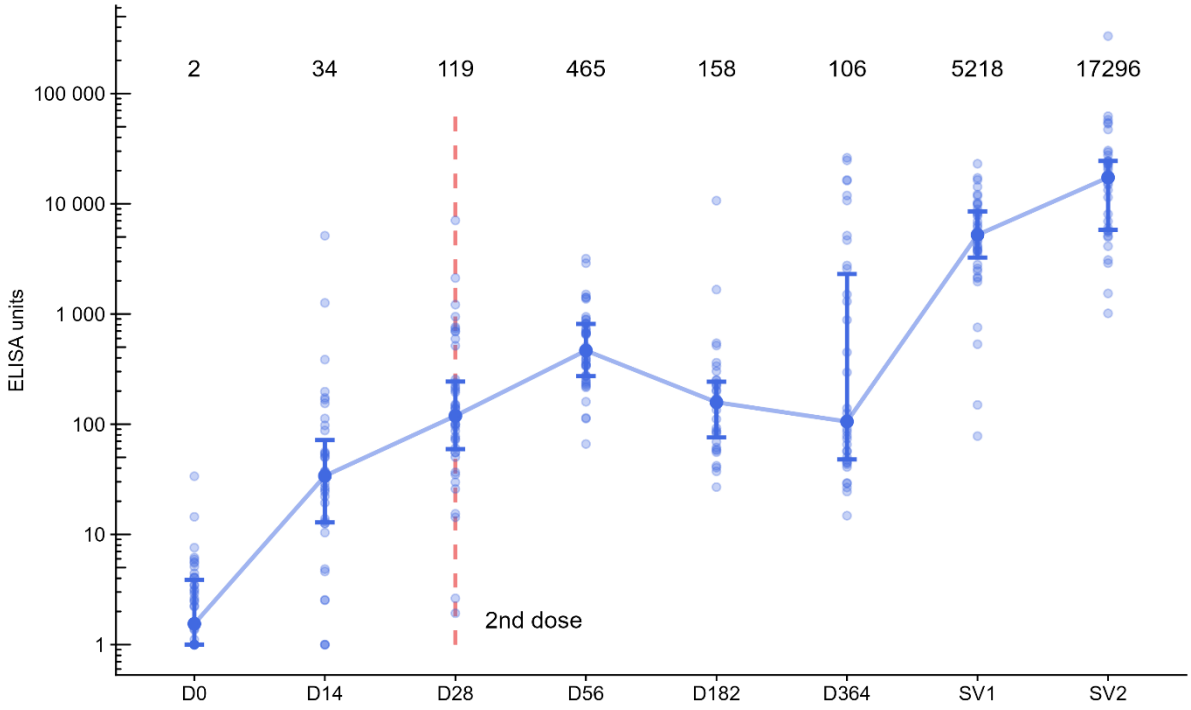
Figure 3 and Table 6 show antibody responses in 27 participants who received a second dose of ChAdOx1 nCoV-19 at 2 to <6 months after receiving the first dose in COV001/COV002. Figure C2 shows a subgroup analysis of these 27 participants according to interval between first and second dose, vaccine platform across the follow-up period, and ChAdOx1 n-Cov-19 dosage in COV001/COV002.

Figure 4 and Table 7 show antibody responses in 19 participants who received a late standard second dose of ChAdOx1 nCoV-19 at 6 to 11 months after receiving a standard first dose in COV001/COV002. Figure C3 shows a subgroup analysis of these 19 participants according to original study (COV001 or COV002) and age group.

Figure 5 and Table 8 show antibody responses in 9 participants who received a third dose of ChAdOx1 nCoV-19 after two doses standard doses in COV001.

Figure 6 and Table 9 show antibody responses in 10 participants who initially received one or two doses of control vaccine (MenACWY) and who were then given a late first dose of ChAdOx1 nCoV-19 in COV001/COV002.

Figure 1. Antibody responses in 46 participants who received a second dose of ChAdOx1 nCoV-19 at 28 days after the first dose in COV001/COV002.



Antibody responses measured using total IgG ELISA against trimeric SARS-CoV-2 spike protein.

Numbers at the top of the figure show the median antibody response at each time point. Bars show IQR.

D0, D14, D28, D56, D182, D364: Timepoints in COV001/COV002. D0 was when the first dose of ChAdOx1 nCov-19 was given. Numbers in subsequent D timepoints indicate number of days after first dose.

SV1, SV2: Timepoints in COV009. First (SV1) and second (SV2) study visits.

Timepoint	D0	D14	D28	D56	D182	D364	SV1	SV2
Number of participants with data for analysis	46/46	39/46	44/46	44/46	35/46	38/46	40/46	38/46

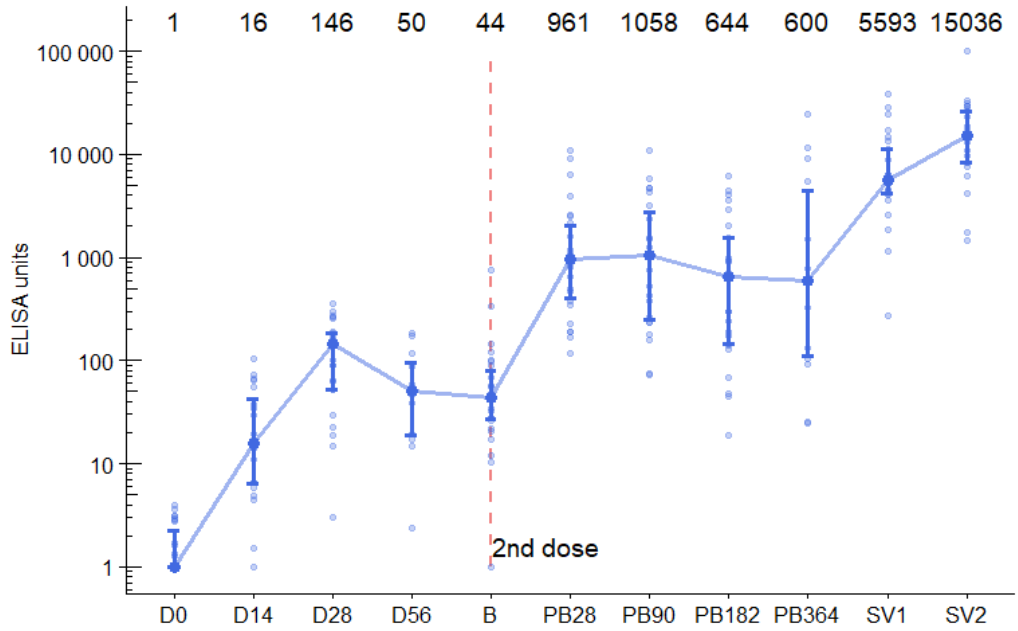
Table 5. Antibody responses for participants who received a second dose of ChAdOx1 nCoV-19 at 28 days after their first dose in COV001/COV002.

Geometric mean concentration (GMC) at 28 days post second dose (D56), and at COV009 first and second visits (SV1 and SV2).

Geometric mean ratio (GMR), comparing GMC at SV1 and SV2 with D56.

Visit	GMC	GMR
D56	481 (375-617) [n=44]	Reference
SV1	4301 (2970-6229) [n=40]	9.34 (5.74-15.18) [n=38]
SV2	14342 (9890-20800) [n=38]	32.90 (21.64-50.00) [n=36]

Figure 3. Antibody responses in 27 participants who received a second dose of ChAdOx1 nCoV-19 at 2 to 6 months after receiving the first dose in COV001/COV002.



Antibody responses measured using total IgG ELISA against trimeric SARS-CoV-2 spike protein.

Numbers at the top of the figure show the median antibody response at each time point. Bars show IQR.

D0, D14, D28, D56: Timepoints in COV001/COV002. D0 was when the first dose of ChAdOx1 nCov-19 was given. Numbers in subsequent D timepoints indicate number of days after first dose.

B, PB28, PB90, PB182, PB364: Timepoints in COV001/COV002. B was when the second dose of ChAdOx1 nCov-19 was given. Numbers in subsequent PB timepoints indicate number of days after second dose.

SV1, SV2: Timepoints in COV009. First (SV1) and second (SV2) study visits.

Timepoint	D0	D14	D28	D56	B	PB28	PB90	PB182	PB364	SV1	SV2
Number of participants with data for analysis	27/27	20/27	25/27	12/27	27/27	26/27	23/27	25/27	14/27	25/27	24/27

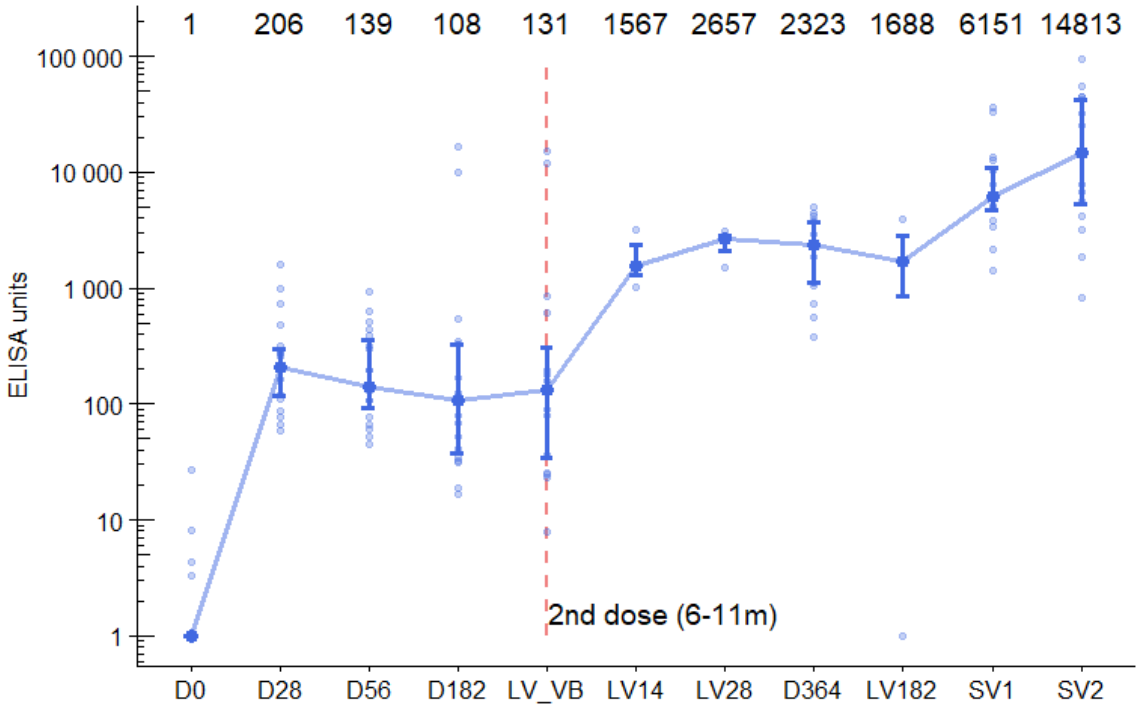
Table 2. Antibody responses for participants who received a second dose of ChAdOx1 nCoV-19 at 2 to 6 months after receiving the first dose in COV001/COV002.

Geometric mean concentration (GMC) at 28 days post second dose (PB28), and at COV009 first and second visits (SV1 and SV2).

Geometric mean ratio (GMR), comparing GMC at SV1 and SV2 with PB28.

Visit	GMC	GMR
PB28	928 (567-1519) [n=26]	Reference
SV1	5905 (3841-9076) [n=25]	5.51 (3.06-9.92) [n=24]
SV2	13396 (9016-19902) [n=24]	12.32 (7.52-20.17) [n=24]

Figure 2. Antibody responses in 19 participants who received a late standard second dose of ChAdOx1 nCoV-19 at 6 to 11 months after a standard first dose in COV001/COV002.



Antibody responses measured using total IgG ELISA against trimeric SARS-CoV-2 spike protein.

Numbers at the top of the figure show the median antibody responses at each time point. Bars show IQR.

D0, D28, D56, D182, D364: Timepoints in COV001/COV002. D0 was when the first dose of ChAdOx1 nCov-19 was given. Numbers in subsequent timepoints indicate number of days after first dose.

LV_VB, LV14, LV28, LV182: Timepoints in COV001/COV002. LV_VB was when the second dose of ChAdOx1 nCov-19 was given. Numbers in subsequent timepoints indicate number of days after second dose.

SV1, SV2: Timepoints in COV009. First (SV1) and second (SV2) study visits.

Timepoint	D0	D28	D56	D182	LV_VB	LV14	LV28	D364	LV182	SV1	SV2
Number of participants with data for analysis	19/19	19/19	19/19	19/19	16/19	3/19	3/19	16/19	3/19	16/19	16/19

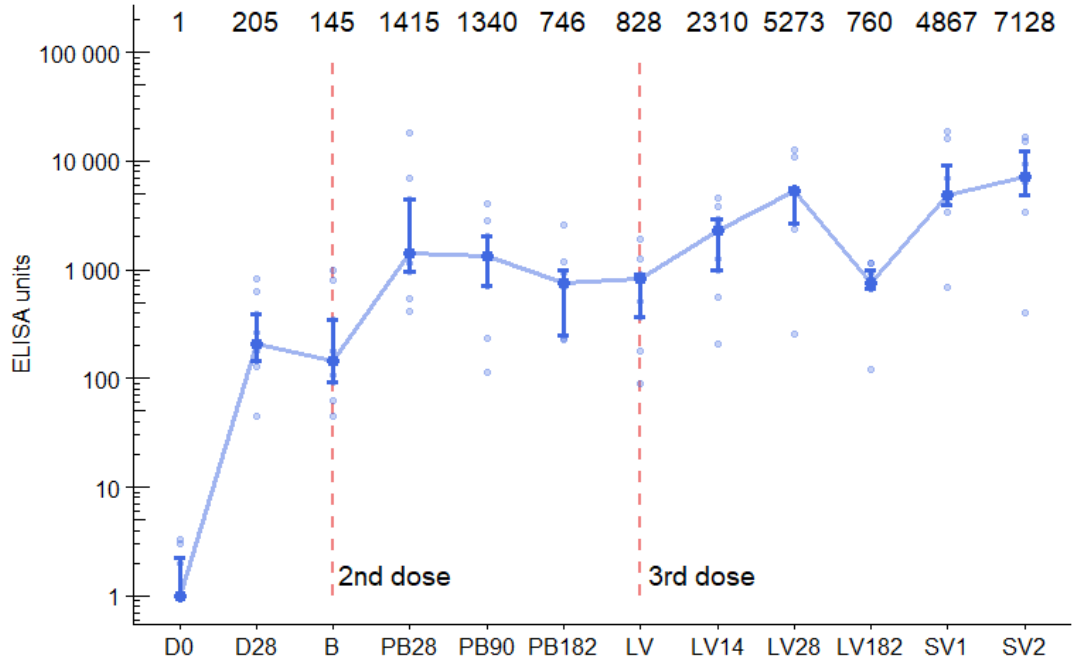
Table 7. Antibody responses for participants who received a second dose of ChAdOx1 nCoV-19 at 6 to 11 months after receiving a standard first dose in COV001/COV002.

Geometric mean concentration (GMC) at 28 days post first dose (D28), 28 days post second dose (LV28), and at COV009 first and second visits (SV1 and SV2).

Geometric mean ratio (GMR), comparing GMC at SV1 and SV2 with D28.

Visit	GMC	GMR (compared with D28)
D28	221 (143-341) [n=19]	Reference
LV28	2307 (922-5773) [n=3]	
SV1	6847 (4318-10858) [n=16]	30.94 (16.43-58.24) [n=16]
SV2	12701 (6140-26272) [n=16]	60.00 (31.50-114.27) [n=16]

Figure 5. Antibody responses in 9 participants who received a third standard dose of ChAdOx1 nCoV-19 after two standard doses in COV001.



Antibody responses measured using total IgG ELISA against trimeric SARS-CoV-2 spike protein.

Numbers at the top of the figure show the median antibody response at each time point. Bars show IQR.

D0, D28: Timepoints in COV001/COV002. D0 was when the first dose of ChAdOx1 nCov-19 was given. D28 was 28 timepoints days after first dose.

B, PB28, PB90, PB182: Timepoints in COV001/COV002. B was when the second dose of ChAdOx1 nCov-19 was given. Numbers in subsequent PB timepoints indicate number of days after second dose.

LV, LV14, LV28, LV182: Timepoints in COV001/COV002. LV was when the third dose of ChAdOx1 nCov-19 was given. Numbers in subsequent LV timepoints indicate number of days after second dose.

SV1, SV2: Timepoints in COV009. First (SV1) and second (SV2) study visits.

Timepoint	D0	D28	B	PB28	PB90	PB182	LV	LV14	LV28	LV182	SV1	SV2
Number of participants with data for analysis	8/9	9/9	9/9	9/9	9/9	8/9	9/9	9/9	9/9	8/9	8/9	7/9

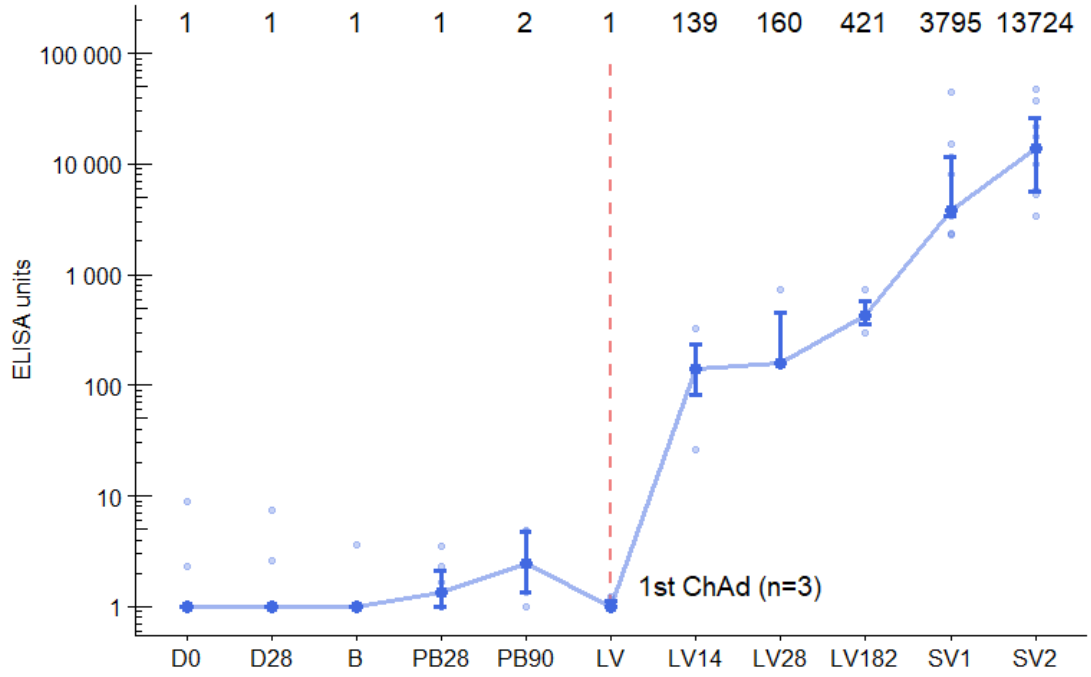
Table 8. Antibody responses for participants who received a third standard dose of ChAdOx1 nCoV-19 after two doses standard doses in COV001.

Geometric mean concentration (GMC) at 28 days post second dose (PB28), 28 days post third dose (LV28), and at COV009 first and second visits (SV1 and SV2).

Geometric mean ratio (GMR), comparing GMC at SV1 and SV2 with PB28 and with LV28.

Visit	GMC	GMR (compared with PB28)	GMR (compared with LV28)
PB28	1867 (718-4857) [n=9]	Reference	
LV28	3871 (1590-9426) [n=9]		Reference
SV1	5124 (2173-12081) [n=8]	2.65 (0.50-14.19) [n=8]	1.53 (0.42-5.55) [n=8]
SV2	5495 (1698-17783) [n=7]	3.28 (0.94-11.48) [n=7]	1.57 (0.23-10.67) [n=7]

Figure 6. Antibody responses in 10 participants who initially received one or two doses of MenACWY in COV001/COV002, who then received a late first dose of ChAdOx nCoV-19.



Antibody responses measured using total IgG ELISA against trimeric SARS-CoV-2 spike protein.

Numbers at the top of the figure show the median antibody responses at each time point. Bars show IQR.

D0, D28: Timepoints in COV001/COV002. D0 was when the first dose of MenACWY was given. D28 was 28 days after D0.

B, PB28, PB90: Timepoints in COV001/COV002. B was when the second dose of MenACWY was given. Numbers in subsequent PB timepoints indicate number of days after second dose.

LV, LV14, LV28, LV182: Timepoints in COV001/COV002. LV was when the late first dose of ChAdOx1 nCov-19 was given. Numbers in subsequent LV timepoints indicate number of days after this dose. All 10 participants received the late first dose, but data were only available for three participants at the LV timepoints.

SV1, SV2: Timepoints in COV009. First (SV1) and second (SV2) study visits.

Timepoint	D0	D28	B	PB28	PB90	LV	LV14	LV28	LV182	SV1	SV2
Number of participants with data for analysis	10/10	9/10	6/10	6/10	5/10	3/3	3/3	3/3	3/3	9/10	8/10

Table 9. Antibody responses for participants who initially received one or two doses of MenACWY in COV001 or COV002, who then received a late first dose of ChAdOx nCoV-19.

Geometric mean concentration (GMC) at 28 days post late first dose (LV28), and at COV009 first and second visits (SV1 and SV2).

Visit	GMC
LV28	264 (29-2435) [n=3]
SV1	6280 (2903-13586) [n=9]
SV2	12814 (5733-28645) [n=8]

Discussion and conclusions

In this study, 4,468 participants from two early clinical trials of the ChAdOx1 nCoV-19 vaccine were followed up for a further one year after completion of the original trials. Eighty-six percent (3,845/4,468) of participants completed the study. A total 174 serious adverse events were reported by 159 participants, and a total of 71 adverse events of special interest were reported by 68 participants. Of these, 33 events were recorded as both SAE and AESI. None of these events was assessed as being likely to have been related to the ChAdOx1 nCoV-19 vaccine.

Of the 11,889 participants who enrolled in the parent studies, 4,468 (37.6%) took part in the follow-up study. The fall in recruitment is likely to be the result of volunteers perceiving less incentive to participate in the follow-up study than the parent studies. Participation in the COV001 and COV002 studies offered volunteers the notable incentive of potentially being randomised to receive a COVID-19 vaccine, at a time when no such vaccine was available for the general population; by the time COV009 recruited, COVID-19 vaccines were being routinely used. Also, the COV001 and COV002 studies recruited at a time when there was an urgent global imperative to develop an effective COVID-19 vaccine, and many individuals felt strongly motivated to participate in these clinical trials. Volunteers may have viewed COV009 as being less likely to "make a difference" than the earlier trials.

The age demographic of participants in the COV009 study was a little higher than would have been expected from the ages of participants in the parent studies. At the time of enrolment in the parent studies, COV009 participants had a higher median age (49 years) than COV002 participants (44 years) or COV001 participants (35 years). About 18 months can be accounted for by the later date of enrolment in COV009 (September 2021 to April 2022) than in COV002 (May 2020 to December 2020) and COV001 (April to May 2020). The additional difference is possibly partly because older people felt more motivated than younger people to remain involved with COVID-19 research, as they were more likely to suffer serious COVID-19 disease, and possibly partly because older people find it easier to give time to take part in research than younger individuals, who are more likely to have the commitments of full-time jobs or dependent children.

The COVID-19 vaccinations received by study participants varied widely, both in number and type. This reflects the routine use of three different vaccines in the UK, whose availability varied by region; it also reflects changing national recommendations over the period of follow-up.[18] The majority of participants (3,069/4,468; 68.7%) received a combination of both ChAdOx1 nCoV-19 and one or more mRNA COVID-19 vaccines. Heterologous schedules had been shown to be safe and immunogenic in previous studies.[19,20]

Serious adverse events were reported by a slightly smaller proportion of participants in the "ChAd only" group (9/385; 2.3%) than in the "ChAd & mRNA" group (118/3,069; 3.8%) or in the "mRNA only" group (32/1,014; 3.2%). Adverse events of special interest were reported by a slightly smaller proportion of participants in the "mRNA only" group (10/1,014; 1.0%) than in the "ChAd only" group (7/385; 1.8%) or the "ChAd & mRNA" group (51/3,069; 1.7%). However, caution is required in making direct comparisons between the three groups. The groups were not randomised, and each group contains an assortment of vaccine schedules. The "ChAd only" group is relatively small compared to the other two groups. Also, it is possible that for some participants allocated to the "ChAd & mRNA" group, the adverse event might have occurred at a point when they had either only received

ChAdOx1 nCoV-1, or only received another COVID-19 vaccine (*i.e*, before they had received the vaccination which caused them to be assigned to the "ChAd & mRNA" group).

Immunology data were only available for a small, non-randomised subset of study participants. However, some consistent patterns emerged. Levels of total IgG against trimeric SARS-CoV-2 spike protein were notably greater during the COV009 phase of the study than after two doses of ChAdOx1 nCoV-1 vaccine in COV001/002. These levels were also higher at the end of COV009 (at SV2) than they were six months earlier (at SV1). These findings are likely to be due to a combination of the effects of additional COVID-19 vaccination doses and natural boosting from encounters with the SARS-CoV2 virus.[21] In the fourth dose sub-study (Group 2), 37.9% (33/87) of participants were anti-nucleocapsid seropositive immediately before they received their fourth dose in September 2022; 39.6% (59/149) self-reported SARS-CoV2 infection in the six months before their fourth dose and 15.4% (23/149) self-reported infection 14-180 days after the fourth dose.[17]

One limitation of the study was that nearly all participants were of white ethnicity, limiting the generalisability of the results. Another limitation was the inherent subjectivity of clinicians when assigning the likelihood of an event being related to a previous vaccination. A particular problem is that adverse events caused by vaccines generally occur soon after vaccination. An event occurring many months after vaccination is unlikely to be assessed as possibly or probably related to the vaccine. This makes it harder for a follow-up study such as this to detect late-onset adverse effects of vaccination. Also, in a large study, many coincidental events are likely to occur after vaccination. Without good data on the expected rates of a plethora of diagnoses in the study population, it can be difficult to make an objective assessment of likely causality. Despite these limitations, the relatively small number of SAEs and AESIs recorded in our study over a period of more than 4,000 participant years, and the fact that no event occurred unduly often, provided some reassurance regarding long-term safety.

Reports began to appear from April 2021 linking ChAdOx1 nCoV-19 vaccination with thrombotic thrombocytopaenia, a very unusual but potentially life-threatening condition.[22,23] Although long-term follow-up of participants in early clinical trials of a vaccine offers the potential for early identification of late-onset hazards, the strategy is not a replacement for careful post-marketing surveillance, which enables detection of extremely rare adverse events. Nevertheless, the prospective nature of our study, with its prolonged and detailed follow-up of participants, does provide a unique dataset.

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APPENDIX A. Study design, participants and vaccinations

Table A1. Adverse events of special interest (AESIs).

AESI	Medical concept
Neuroinflammatory disorders	• Cranial nerve neuropathy including palsy and paresis (eg, Bell's palsy) • Optic neuritis • Multiple sclerosis • Transverse myelitis • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants • Acute disseminated encephalomyelitis, including site-specific variants, *e.g.,* non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome • Peripheral demyelinating neuropathies, including: ▪ Chronic inflammatory demyelinating polyneuropathy ▪ Multifocal motor neuropathy • Polyneuropathies associated with monoclonal gammopathy • Narcolepsy • Generalised convulsions
Musculoskeletal disorders	• Systemic lupus erythematosus and associated conditions • Systemic scleroderma (systemic sclerosis) including: ▪ Diffuse scleroderma ▪ Calcinosis, Raynaud's phenomenon, Oesophageal dysmotility, Sclerodactyly and telangiectasia syndrome (CREST) • Idiopathic inflammatory myopathies including: ▪ Dermatomyositis ▪ Polymyositis ▪ Anti-synthetase syndrome • Rheumatoid arthritis and associated conditions including: ▪ Still's disease • Polymyalgia rheumatica • Spondyloarthropathies including: ▪ Ankylosing spondylitis ▪ Reactive arthritis (Reiter's syndrome) ▪ Undifferentiated spondyloarthritis
Skin disorders	• Psoriasis • Vitiligo • Erythema Nodosum • Autoimmune bullous skin diseases (including pemphigus, pemphigoid, and dermatitis herpetiformis) • Lichen planus • Sweet's syndrome • Localized scleroderma (morphea)

AESI	Medical concept
Vasculitis	• Large vessel vasculitis including: ▪ Giant cell arteritis (temporal arteritis) ▪ Takayasu's arteritis • Vasculitis of medium and/or small vessels including: ▪ Polyarteritis nodosa ▪ Kawasaki disease ▪ Microscopic polyangiitis ▪ Wegener's granulomatosis (granulomatosis with polyangiitis) ▪ Churg-Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis) ▪ Buerger's disease (thromboangiitis obliterans) ▪ Necrotizing vasculitis (cutaneous or systemic) ▪ Vasculitis positive for anti-neutrophil cytoplasmic antibody (type unspecified) ▪ Henoch-Schonlein purpura (immunoglobulin A vasculitis) ▪ Behcet's syndrome ▪ Leukocytoclastic vasculitis
Blood disorders	• Autoimmune haemolytic anaemia • Autoimmune thrombocytopenia • Antiphospholipid syndrome • Pernicious anaemia • Autoimmune aplastic anaemia • Autoimmune neutropenia • Autoimmune pancytopenia • Anti-platelet antibodies • Vascular thrombosis • Stroke
Liver disorders	• Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis • Autoimmune cholangitis
Gastrointestinal disorders	• Inflammatory bowel disease including: ▪ Crohn's disease ▪ Ulcerative colitis ▪ Microscopic colitis ▪ Ulcerative proctitis ▪ Celiac disease ▪ Autoimmune pancreatitis
Endocrine disorders	• Autoimmune thyroiditis (Hashimoto's thyroiditis) • Grave's or Basedow's disease • Type 1 diabetes mellitus • Addison's disease • Polyglandular autoimmune syndrome • Autoimmune hypophysis

AESI	Medical concept
Others	• Autoimmune glomerulonephritis including: ▪ Immunoglobulin A nephropathy ▪ Rapidly progressive glomerulonephritis ▪ Membranous glomerulonephritis ▪ Membranoproliferative glomerulonephritis ▪ Mesangioproliferative glomerulonephritis ▪ Tubulointerstitial nephritis and uveitis syndrome • Autoimmune eye diseases including: ▪ Autoimmune uveitis ▪ Autoimmune retinitis

Table A2. Guidelines for assessing the relationship of vaccine administration to an AE.

Causality term	Assessment criteria
No relationship	No temporal relationship to study product; **and** Alternate aetiology (clinical state, environmental or other interventions); **and** Does not follow known pattern of response to study product
Unlikely	Unlikely temporal relationship to study product; **and** Alternate aetiology likely (clinical state, environmental or other interventions); **and** Does not follow known typical or plausible pattern of response to study product.
Possible	Reasonable temporal relationship to study product; **or** Event not readily produced by clinical state, environmental or other interventions; **or** Similar pattern of response to that seen with other vaccines
Probable	Reasonable temporal relationship to study product; **and** Event not readily produced by clinical state, environment, or other interventions; **or** Known pattern of response seen with other vaccines
Definite	Reasonable temporal relationship to study product; **and** Event not readily produced by clinical state, environment, or other interventions; **and** Known pattern of response seen with other vaccines

Table A3. Baseline characteristics of participants in COV009, COV001 and COV002.

	COV009	COV001		COV002	
	Total N = 4,468	Enrolled in COV009 N=469	Total* N=1,077	Enrolled in COV009 N=3,999	Total** N=10,717
Age (years)* **					
N	4,468	469	1,077	3,999	10,717
Mean (SD)	50 (15)	38 (10)		52 (15)	46 (15)
Median (IQR)	49 (39, 62)	38 (30, 47)	35 (28,44)	51 (40, 64)	44
Range	18, 88	19, 55		18, 88	18, 88
Age group					
18-55 years	2,929 (66%)	469 (100%)	1,077 (100%)	2,460 (62%)	8,270 (77%)
56-69 years	732 (16%)	0	0	732 (18%)	1,188 (11%)
≥70 years	807 (18%)	0	0	807 (20%)	1,259 (12%)
Sex					
Female	2,594 (58%)	253 (54%)	536 (50%)	2,341 (59%)	6,423 (60%)
Male	1,874 (42%)	216 (46%)	541 (50%)	1,658 (41%)	4,294 (40%)
Healthcare worker	2,204 (49%)	63 (13%)	197 (18%)	2,141 (54%)	5,381 (50%)
Ethnicity					
White	4,236 (95%)	434 (93%)	979 (90.9%)	3,802 (95%)	9,886 (92.2%)
Asian	125 (2.8%)	8 (1.7%)	48 (4.5%)	117 (2.9%)	548 (5.1%)
Black	17 (0.4%)	10 (2.1%)	6 (0.6%)	7 (0.2%)	49 (0.5%)
Other	86 (1.9%)	17 (3.6%)	21 (1.9%)	69 (1.7%)	55 (0.5%)
Mixed			21 (1.9%)		175 (1.6%)
Missing	4 (<0.1%)	0 (0%)	2 (0.2%)	4 (0.1%)	4 (<0.1%)
BMI					
N	4,462	469	1,077	3,993	10,712
Mean (SD)	26.3 (4.9)	25.1 (4.0)		26.5 (4.9)	26.43 (5.1)
Median (IQR)	25.5 (23.0, 28.7)	24.5 (22.2, 27.3)	24 (22, 27)	25.6 (23.1, 28.9)	25.40
Range	13.8, 68.5	18.2, 37.7		13.8, 68.5	13.3, 68.5
Cardiovascular disorders****	667 (15%)	0	0	667 (17%)	1,342 (12.5%)
Respiratory disorders****	487 (11%)	0	0	487 (12%)	1,319 (12.3%)
Diabetes****	98 (2.2%)	0	0	98 (2.5%)	214 (2.0%)

*Data from Folegatti *et al., Lancet* 2020: **396**: 467-478 (main paper and Supplementary Appendix Table S1).

** Data from the Any Dose Safety Analysis Set in the Final Clinical Study Report AZD1222-COV002 (AstraZeneca), with a data cut-off of 31 December 2021 (Tables 21 and 7.1.3.1.1).

*** Age at the time of screening in the parent studies.

****For the COV001 study, chronic respiratory diseases, cardiovascular disease, and diabetes were exclusion criteria.

Table A4. Reasons participants did not complete study.

	Total N = 4,468[1]	**ChAd & mRNA** N = 3,069[1]	**ChAd only** N = 385[1]	**mRNA only** N = 1,014[1]
Number of participants not completing study	623 (14%)	256 (8.3%)	204 (53%)	163 (16%)
Last visit conducted				
Consent and Enrolment	345 (55%)	78 (30%)	178 (87%)	89 (55%)
Study Visit 1	272 (44%)	172 (67%)	26 (13%)	74 (45%)
Pre-Vaccination	1 (0.2%)	1 (0.4%)	0 (0%)	0 (0%)
Visit PB7	1 (0.2%)	1 (0.4%)	0 (0%)	0 (0%)
Visit PB28	4 (0.6%)	4 (1.6%)	0 (0%)	0 (0%)
Reason for not completing study				
Death	5 (0.8%)	4 (1.6%)	0	1 (0.6%)
Withdrawal	618 (99%)	252 (98%)	204 (100%)	162 (99%)
Reason for withdrawal				
- Adverse event which requires discontinuation of the study procedures or results in an inability to continue to comply with study procedure	1 (0.2%)	1 (0.4%)	0	0
- Ineligibility (either arising during the study or in the form of new information not declared or detected during the eligibility assessment)	1 (0.2%)	1 (0.4%)	0	0
- Lost to follow up	479 (78%)	192 (76%)	163 (80%)	124 (77%)
- Participant withdrew consent	91 (15%)	36 (14%)	30 (15%)	25 (15%)
- Significant non-compliance with study requirements	6 (1.0%)	4 (1.6%)	1 (0.5%)	1 (0.6%)
- Subsequent enrolment in another trial which may duplicate COV009 study procedures including safety monitoring *e.g.*, trials that involve further doses of COVID-19 vaccines	25 (4.0%)	12 (4.8%)	3 (1.5%)	10 (6.2%)
- Other	15 (2.4%)	6 (2.4%)	7 (3.4%)	2 (1.2%)

[1]n=%

Table A5. Timing of study visits.

		Female			Male		
	Total N = 4,468[1]	**ChAd & mRNA N = 1,741[1]**	**ChAd only N = 213[1]**	**mRNA only N = 640[1]**	**ChAd & mRNA N = 1,328[1]**	**ChAd only N = 172[1]**	**mRNA only N = 374[1]**
Interval between first COVID-19 vaccine and first visit (Days)							
N	3,986*	1,643	103	568	1,257	86	329
Mean (SD)	566 (125)	607 (118)	611 (131)	455 (58)	587 (121)	592 (134)	450 (60)
Median (IQR)	574 (451, 678)	646 (552, 688)	668 (571, 698)	458 (427, 482)	618 (494, 684)	668 (441, 688)	455 (425, 482)
Range	192, 874	277, 874	305, 783	192, 638	305, 863	308, 853	232, 631
First Visit (SV1)							
N	3,987	1,643	103	569	1,257	86	329
Min.	2022-02-17	2022-02-17	2022-02-17	2022-02-17	2022-02-17	2022-02-17	2022-02-17
1st Qu.	2022-03-23	2022-03-23	2022-03-23	2022-03-23	2022-03-23	2022-03-23	2022-03-23
Median	2022-04-20	2022-04-20	2022-04-20	2022-04-20	2022-04-20	2022-04-20	2022-04-20
Mean	2022-04-24	2022-04-24	2022-04-24	2022-04-24	2022-04-24	2022-04-24	2022-04-24
3rd Qu.	2022-05-14	2022-05-14	2022-05-14	2022-05-14	2022-05-14	2022-05-14	2022-05-14
Max.	2022-10-31	2022-10-31	2022-10-31	2022-10-31	2022-10-31	2022-10-31	2022-10-31
Second Visit (SV2)							
N	3,725	1,519	96	537	1,174	85	314
Min.	2022-08-22	2022-08-22	2022-08-22	2022-08-22	2022-08-22	2022-08-22	2022-08-22
1st Qu.	2022-09-27	2022-09-27	2022-09-27	2022-09-27	2022-09-27	2022-09-27	2022-09-27
Median	2022-10-16	2022-10-16	2022-10-16	2022-10-16	2022-10-16	2022-10-16	2022-10-16
Mean	2022-10-23	2022-10-23	2022-10-23	2022-10-23	2022-10-23	2022-10-23	2022-10-23
3rd Qu.	2022-11-11	2022-11-11	2022-11-11	2022-11-11	2022-11-11	2022-11-11	2022-11-11
Max.	2023-04-28	2023-04-28	2023-04-28	2023-04-28	2023-04-28	2023-04-28	2023-04-28

		Female			Male		
	Total N = 4,468[1]	**ChAd & mRNA N = 1,741[1]**	**ChAd only N = 213[1]**	**mRNA only N = 640[1]**	**ChAd & mRNA N = 1,328[1]**	**ChAd only N = 172[1]**	**mRNA only N = 374[1]**
Interval between first visit and second visit (Days)							
N	3,596	1,471	91	523	1,138	72	301
Mean (SD)	183 (20)	183 (21)	176 (23)	184 (20)	182 (19)	185 (24)	184 (17)
Median (IQR)	182 (175, 190)	182 (175, 190)	175 (166, 189)	182 (176, 194)	182 (175, 189)	183 (175, 196)	182 (176, 190)
Range	39, 316	68, 316	108, 238	39, 269	69, 315	118, 293	144, 287

[1]n (%)

*One participant recorded as receiving the first Covid -19 vaccine after the first study visit not included.

Table A6. Vaccinations received by COV009 participants whilst in COV001 and COV002

		Female			Male		
	Total N = 4,468[1]	**ChAd & mRNA N = 1,741[1]**	**ChAd only N = 213[1]**	**mRNA only N = 640[1]**	**ChAd & mRNA N = 1,328[1]**	**ChAd only N = 172[1]**	**mRNA only N = 374[1]**
Vaccination in COV001/COV002							
ChAdOx1	2,623 (59%)	1,357 (78%)	173 (81%)	0 (0%)	972 (73%)	121 (70%)	0 (0%)
MenACWY	1,845 (41%)	384 (22%)	40 (19%)	640 (100%)	356 (27%)	51 (30%)	374 (100%)
Vaccination details							
Control	71 (1.6%)	14 (0.8%)	4 (1.9%)	18 (2.8%)	23 (1.7%)	2 (1.2%)	10 (2.7%)
Control/Control	1,773 (40%)	370 (21%)	36 (17%)	622 (97%)	333 (25%)	49 (28%)	363 (97%)
LD	32 (0.7%)	22 (1.3%)	2 (0.9%)	0 (0%)	8 (0.6%)	0 (0%)	0 (0%)
LD/Control	1 (<0.1%)	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
LD/LD	78 (1.7%)	36 (2.1%)	1 (0.5%)	0 (0%)	40 (3.0%)	1 (0.6%)	0 (0%)
LD/SD	666 (15%)	397 (23%)	48 (23%)	0 (0%)	193 (15%)	28 (16%)	0 (0%)
SD	169 (3.8%)	94 (5.4%)	8 (3.8%)	0 (0%)	61 (4.6%)	6 (3.5%)	0 (0%)
SD/Control	1 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1%)	0 (0%)	0 (0%)
SD/LD	19 (0.4%)	12 (0.7%)	1 (0.5%)	0 (0%)	6 (0.5%)	0 (0%)	0 (0%)
SD/SD	1,651 (37%)	793 (46%)	113 (53%)	0 (0%)	660 (50%)	85 (49%)	0 (0%)
Missing	7 (0.2%)	2 (0.1%)	0 (0%)	0 (0%)	3 (0.2%)	1 (0.6%)	1 (0.3%)

[1]n (%)

ChAdOX1: Received at least one dose of ChAdOx1 nCoV-19 vaccine as part of COV001/COV002, other vaccines were received outside the study.

MenACWY: Received only MenACWY vaccine (one or two doses) as part of COV001/COV002, other vaccines were received outside the study.

Control: One dose of MenACWY vaccine

LD: One low dose ChAdOx nCoV-19 vaccine ($2.2x10^{10}$ vp)

SD: One standard dose ChAdOx nCoV-19 vaccine ($3.5\text{-}6.5x10^{10}$ vp)

Table A7. COVID-19 vaccine combinations received by participants.

		Female			Male		
	Total N = 4,468[1]	**ChAd & mRNA N = 1,741[1]**	**ChAd only N = 213[1]**	**mRNA only N = 640[1]**	**ChAd & mRNA N = 1,328[1]**	**ChAd only N = 172[1]**	**mRNA only N = 374[1]**
COVID-19 vaccine doses received*							
2ChAd/mRNA	1,601 (36%)	926 (53%)	-	-	675 (51%)	-	-
2ChAd/2mRNA	915 (20%)	538 (31%)	-	-	377 (28%)	-	-
3mRNA	442 (9.9%)	-	-	281 (44%)	-	-	161 (43%)
4mRNA	343 (7.7%)	-	-	214 (33%)	-	-	129 (34%)
2ChAd	310 (6.9%)	-	177 (83%)	-	-	133 (77%)	-
2ChAd/3mRNA	172 (3.8%)	65 (3.7%)	-	-	107 (8.1%)	-	-
2mRNA	167 (3.7%)	-	-	108 (17%)	-	-	59 (16%)
2ChAd/mRNA/ChAd	143 (3.2%)	89 (5.1%)	-	-	54 (4.1%)	-	-
3ChAd	60 (1.3%)	-	28 (13%)	-	-	32 (19%)	-
ChAd/mRNA	57 (1.3%)	34 (2.0%)	-	-	23 (1.7%)	-	-
3ChAd/mRNA	42 (0.9%)	21 (1.2%)	-	-	21 (1.6%)	-	-
ChAd/2mRNA	39 (0.9%)	23 (1.3%)	-	-	16 (1.2%)	-	-
5mRNA	32 (0.7%)	-	-	13 (2.0%)	-	-	19 (5.1%)
mRNA	29 (0.6%)	-	-	23 (3.6%)	-	-	6 (1.6%)
2ChAd/4mRNA	27 (0.6%)	12 (0.7%)	-	-	15 (1.1%)	-	-
3ChAd/2mRNA	15 (0.3%)	4 (0.2%)	-	-	11 (0.8%)	-	-
ChAd	14 (0.3%)	-	7 (3.3%)	-	-	7 (4.1%)	-
ChAd/3mRNA	12 (0.3%)	7 (0.4%)	-	-	5 (0.4%)	-	-
2ChAd/mRNA/ChAd/mRNA	11 (0.2%)	2 (0.1%)	-	-	9 (0.7%)	-	-
Other	37 (0.8%)	20 (1.1%)	1 (0.5%)	1 (0.2%)	15 (1.1%)	-	-

* Includes all COVID-19 vaccines recorded as received by participant, regardless of whether given as part of study, up to time of exit from COV009 (either by completion of study or withdrawal/death). Number of doses of vaccines and order of vaccination shown.

ChAd: ChAdOx1 nCoV-19 vaccine dose.

mRNA: mRNA/other COVID-19 vaccine dose.

Figure A1. COVID-19 vaccine combinations in COV009.

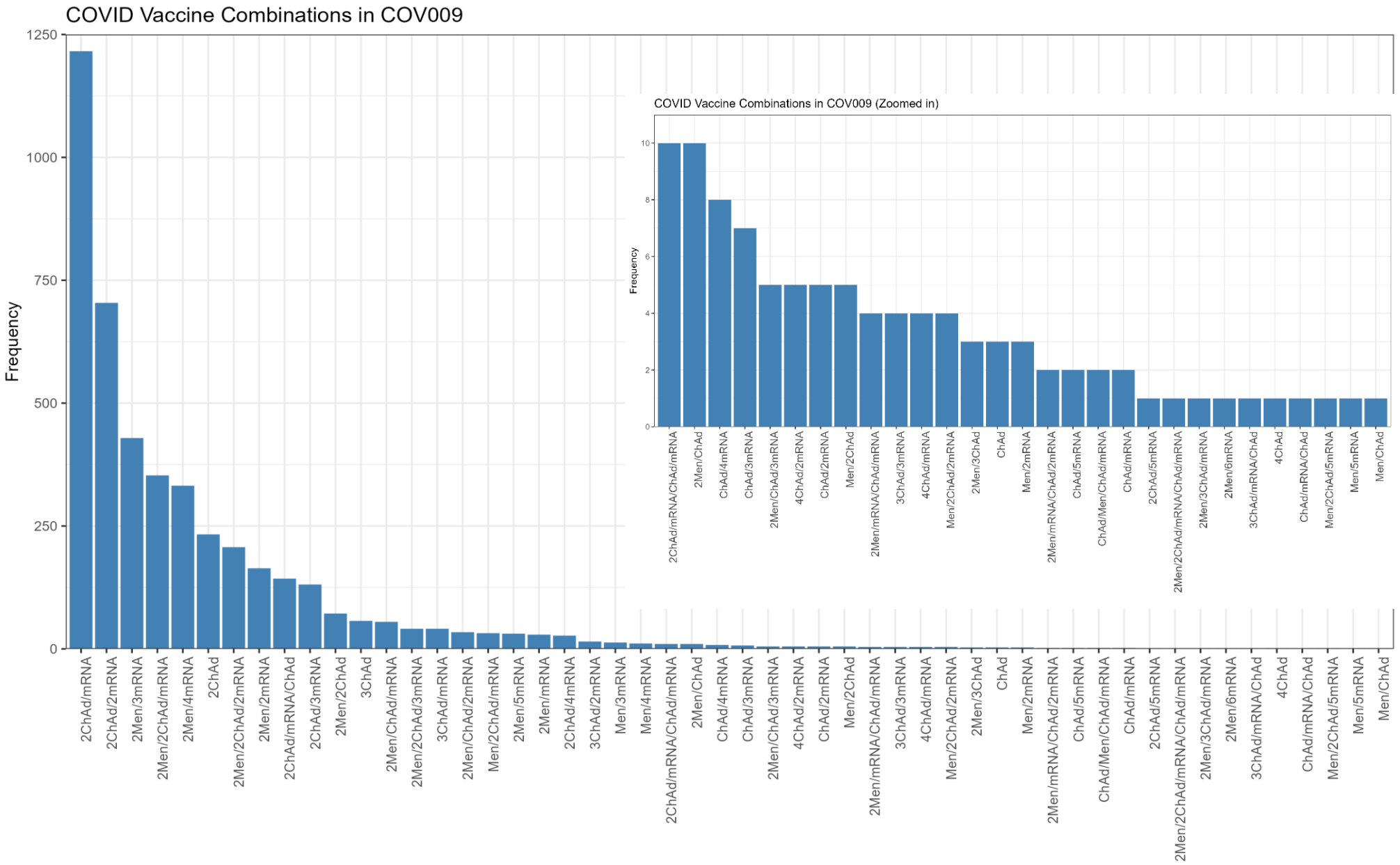


Table A8. Pfizer and Moderna mRNA vaccines received by participants.

		Female			Male		
mRNA vaccinations received	**Total N = 4,468[1]**	**ChAd & mRNA N = 1,741[1]**	**ChAd only N = 213[1]**	**mRNA only N = 640[1]**	**ChAd & mRNA N = 1,328[1]**	**ChAd only N = 172[1]**	**mRNA only N = 374[1]**
At least one Pfizer vaccine	3,667 (82%)	1,534 (88%)	0	638 (100%)	1,124 (85%)	0	371 (99%)
At least one Moderna vaccine	1,576 (35%)	639 (37%)	0	234 (37%)	551 (41%)	0	152 (41%)
At least one Pfizer and at least one Moderna vaccine	1,162 (26%)	433 (25%)	0	232 (36%)	348 (26%)	0	149 (40%)

[1] n (%)

Table A9. Intervals between successive COVID-19 vaccinations.

		Female			Male		
Interval between vaccinations	**Total N = 4,468[1]**	**ChAd & mRNA N = 1,741[1]**	**ChAd only N = 213[1]**	**mRNA only N = 640[1]**	**ChAd & mRNA N = 1,328[1]**	**ChAd only N = 172[1]**	**mRNA only N = 374[1]**
Interval between first and second COVID-19 vaccination (Days)							
N	4,423	1,740	206	617	1,327	165	368
Mean (SD)	90 (68)	93 (66)	90 (53)	91 (74)	83 (67)	91 (46)	93 (78)
Median (IQR)	76 (57, 91)	80 (59, 98)	84 (70, 95)	70 (62, 77)	73 (35, 92)	84 (67, 113)	72 (63, 78)
Range	17, 623	26, 622	25, 496	19, 609	17, 596	26, 313	20, 623
Interval between second and third COVID-19 vaccination (Days)							
N	3,887	1,705	29	509	1,303	32	309
Mean (SD)	315 (123)	347 (115)	239 (81)	227 (83)	335 (129)	225 (45)	219 (72)
Median (IQR)	339 (198, 401)	377 (266, 411)	211 (208, 264)	203 (191, 225)	362 (203, 414)	211 (210, 213)	201 (185, 226)
Range	20, 835	20, 824	77, 505	58, 657	28, 835	154, 396	76, 566
Interval between third and fourth COVID-19 vaccination (Days)							
N	1,738	753	1	227	611	0	146
Mean (SD)	301 (91)	308 (91)	70	335 (68)	279 (95)	-	307 (83)
Median (IQR)	341 (265, 358)	344 (300, 360)	70	351 (338, 367)	323 (192, 351)	-	341 (315, 357)
Range	3, 558	14, 558	70	11, 427	3, 438	-	20, 435
Interval between fourth and fifth COVID-19 vaccination (Days)							
N	282	96	0	14	153	0	19
Mean (SD)	194 (74)	204 (82)	-	207 (73)	190 (73)	-	172 (38)
Median (IQR)	176 (156, 208)	177 (157, 231)	-	185 (163, 195)	177 (154, 203)	-	164 (158, 178)
Range	18, 513	21, 410	-	114, 345	18, 513	-	126, 305

[1] n (%)

APPENDIX B. Safety analysis results: Deaths, SAEs and AESIs

Table B1. Details of participant deaths.

Group	Diagnosis	Causality	Relationship to ChAdOx1 nCoV-19	COVID-19 related?	SOC	PT	Last COVID-19 vaccine before death	Days since last COVID-19 vaccine	Last visit before death
ChAd & mRNA	Metastatic cholangiocarcinoma	No relationship	Not related	No	Neoplasms benign, malignant and unspecified (including cysts and polyps)	Cholangiocarcinoma	Pfizer	232	Study Visit 1
ChAd & mRNA	Peritonitis and neutropenic sepsis	No relationship	Not related	No	Infections and infestations	Peritonitis	Pfizer	155	Consent and enrolment
ChAd & mRNA	Cerebral vascular accident	No relationship	Not related	No	Nervous system disorders	Cerebrovascular accident	Pfizer	296	Study Visit 1
ChAd only	Motor neurone disease	No relationship	Not related	No	Nervous system disorders	Motor neurone disease	ChAdOx1	11	Consent and enrolment
ChAd & mRNA	Pancreatic cancer	No relationship	Not related	No	Neoplasms benign, malignant and unspecified (including cysts and polyps)	Pancreatic carcinoma	Pfizer	169	Study Visit 1

Table B2. SAEs related to SARS-CoV-2 infection.

Sex	Age	Ethnicity	Group	Category	Diagnosis	Causality	Relationship to ChAdOx1 nCoV-19	Severity	SOC	PT	Duration of SAE (days)	Last COVID-19 vaccine before SAE	Days since last COVID-19 vaccine
Male	33	White	ChAd only	Hospitalisation	COVID-19	No relationship	Not related	Grade 4	Infections and infestations	COVID-19	2	ChAdOx1	473
Female	30	Other	mRNA only	Hospitalisation	COVID-19	No relationship	Not related	Grade 2	Infections and infestations	COVID-19	1	Pfizer	49
Female	70	White	ChAd & mRNA	Hospitalisation	Pulmonary embolus	Unlikely	Not related	Grade 4	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	104	Pfizer	134
Female	40	White	ChAd & mRNA	Hospitalisation	Pulmonary embolism	Unlikely	Not related	Grade 4	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	3	Pfizer	19
Female	76	White	ChAd & mRNA	Hospitalisation	Hypokalaemia and chest pain	No relationship	Not related	Grade 3	General disorders and administration site conditions	Unevaluable event	1	Pfizer	182
Female	44	White	ChAd & mRNA	Significant disability/ incapacity	Long COVID	No relationship	Not related	Grade 3	Infections and infestations	COVID-19	Ongoing	ChAdOx1	413
Male	74	White	ChAd & mRNA	Hospitalisation	Covid-19 positive, on chemo for mesothelioma, admitted with spikes of fever and shortness of breath	No relationship	Not related	Grade 3	General disorders and administration site conditions	Unevaluable event	10	Moderna	21
Female	56	White	mRNA only	Significant disability/ incapacity	Long COVID	Unlikely	Not related	Grade 3	Infections and infestations	COVID-19	301	Pfizer	95

Table B3. SAEs by system organ class and preferred term.

System Organ Class Preferred Term	Total N = 174	ChAd & mRNA N = 128	ChAd only N = 9	mRNA only N = 37
Cardiac disorders	**11 (6.3%)**	**9 (7.0%)**	**0**	**2 (5.4%)**
Acute myocardial infarction	1 (0.6%)	0	0	1 (2.7%)
Angina pectoris	1 (0.6%)	1 (0.8%)	0	0
Atrial fibrillation	2 (1.1%)	2 (1.6%)	0	0
Coronary artery disease	1 (0.6%)	1 (0.8%)	0	0
Myocardial infarction	3 (1.7%)	3 (2.3%)	0	0
Sinus tachycardia	1 (0.6%)	1 (0.8%)	0	0
Supraventricular tachycardia	1 (0.6%)	0	0	1 (2.7%)
Trifascicular block	1 (0.6%)	1 (0.8%)	0	0
Congenital, familial and genetic disorders	**1 (0.6%)**	**0**	**1 (11%)**	**0**
Accessory navicular syndrome	1 (0.6%)	0	1 (11%)	0
Ear and labyrinth disorders	**1 (0.6%)**	**1 (0.8%)**	**0**	**0**
Conductive deafness	1 (0.6%)	1 (0.8%)	0	0
Eye disorders	**1 (0.6%)**	**1 (0.8%)**	**0**	**0**
Retinal detachment	1 (0.6%)	1 (0.8%)	0	0
Gastrointestinal disorders	**9 (5.2%)**	**6 (4.7%)**	**1 (11%)**	**2 (5.4%)**
Abdominal pain	1 (0.6%)	1 (0.8%)	0	0
Colitis ulcerative	2 (1.1%)	1 (0.8%)	1 (11%)	0
Colon cancer	1 (0.6%)	0	0	1 (2.7%)
Dyspepsia	1 (0.6%)	1 (0.8%)	0	0
Intestinal obstruction	1 (0.6%)	0	0	1 (2.7%)
Oesophageal achalasia	1 (0.6%)	1 (0.8%)	0	0
Small intestinal obstruction	1 (0.6%)	1 (0.8%)	0	0
Vomiting	1 (0.6%)	1 (0.8%)	0	0
General disorders and administration site conditions	**34 (20%)**	**25 (20%)**	**2 (22%)**	**7 (19%)**
Malaise	1 (0.6%)	0	0	1 (2.7%)
No adverse event*	30 (17%)	22 (17%)	2 (22%)	6 (16%)
Unevaluable event	3 (1.7%)	3 (2.3%)	0	0
Hepatobiliary disorders	**3 (1.7%)**	**3 (2.3%)**	**0**	**0**
Bile duct stone	1 (0.6%)	1 (0.8%)	0	0
Cholecystitis acute	1 (0.6%)	1 (0.8%)	0	0
Cholelithiasis	1 (0.6%)	1 (0.8%)	0	0
Immune system disorders	**1 (0.6%)**	**1 (0.8%)**	**0**	**0**
Anaphylactic reaction	1 (0.6%)	1 (0.8%)	0	0
Infections and infestations	**20 (11%)**	**13 (10%)**	**1 (11%)**	**6 (16%)**
Appendicitis	3 (1.7%)	1 (0.8%)	0	2 (5.4%)
COVID-19	4 (2.3%)	1 (0.8%)	1 (11%)	2 (5.4%)
Diverticulitis intestinal haemorrhagic	1 (0.6%)	0	0	1 (2.7%)
Ear lobe infection	1 (0.6%)	0	0	1 (2.7%)
Gastroenteritis	2 (1.1%)	2 (1.6%)	0	0
Intervertebral discitis	1 (0.6%)	1 (0.8%)	0	0
Peritonitis	1 (0.6%)	1 (0.8%)	0	0
Pneumonia	1 (0.6%)	1 (0.8%)	0	0
Postoperative wound infection	1 (0.6%)	1 (0.8%)	0	0
Pyelonephritis	1 (0.6%)	1 (0.8%)	0	0
Tubo-ovarian abscess	1 (0.6%)	1 (0.8%)	0	0
Urinary tract infection	2 (1.1%)	2 (1.6%)	0	0
Viral infection	1 (0.6%)	1 (0.8%)	0	0

System Organ Class Preferred Term	Total N = 174	ChAd & mRNA N = 128	ChAd only N = 9	mRNA only N = 37
Injury, poisoning and procedural complications	**14 (8.0%)**	**8 (6.3%)**	**0**	**6 (16%)**
Animal bite	1 (0.6%)	1 (0.8%)	0	0
Ankle fracture	2 (1.1%)	1 (0.8%)	0	1 (2.7%)
Clavicle fracture	1 (0.6%)	0	0	1 (2.7%)
Hip fracture	1 (0.6%)	1 (0.8%)	0	0
Humerus fracture	1 (0.6%)	0	0	1 (2.7%)
Lower limb fracture	1 (0.6%)	1 (0.8%)	0	0
Road traffic accident	1 (0.6%)	1 (0.8%)	0	0
Skull fracture	1 (0.6%)	0	0	1 (2.7%)
Snake bite	1 (0.6%)	0	0	1 (2.7%)
Spinal compression fracture	1 (0.6%)	1 (0.8%)	0	0
Spinal cord injury	1 (0.6%)	1 (0.8%)	0	0
Tendon rupture	1 (0.6%)	1 (0.8%)	0	0
Wrist fracture	1 (0.6%)	0	0	1 (2.7%)
Metabolism and nutrition disorders	**1 (0.6%)**	**0**	**0**	**1 (2.7%)**
Type 2 diabetes mellitus	1 (0.6%)	0	0	1 (2.7%)
Musculoskeletal and connective tissue disorders	**3 (1.7%)**	**3 (2.3%)**	**0**	**0**
Intervertebral disc degeneration	1 (0.6%)	1 (0.8%)	0	0
Lumbar spinal stenosis	1 (0.6%)	1 (0.8%)	0	0
Periarthritis	1 (0.6%)	1 (0.8%)	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**36 (21%)**	**29 (23%)**	**2 (22%)**	**5 (14%)**
Acral lentiginous melanoma	1 (0.6%)	1 (0.8%)	0	0
Angiosarcoma	1 (0.6%)	1 (0.8%)	0	0
Astrocytoma	1 (0.6%)	1 (0.8%)	0	0
Breast cancer	7 (4.0%)	6 (4.7%)	0	1 (2.7%)
Cholangiocarcinoma	1 (0.6%)	1 (0.8%)	0	0
Colorectal cancer metastatic	1 (0.6%)	1 (0.8%)	0	0
Endometrial cancer stage I	1 (0.6%)	0	1 (11%)	0
Gastrointestinal carcinoma	1 (0.6%)	1 (0.8%)	0	0
Intraductal proliferative breast lesion	1 (0.6%)	1 (0.8%)	0	0
Invasive lobular breast carcinoma	1 (0.6%)	1 (0.8%)	0	0
Lung adenocarcinoma	1 (0.6%)	1 (0.8%)	0	0
Lung cancer metastatic	1 (0.6%)	0	1 (11%)	0
Malignant melanoma	1 (0.6%)	1 (0.8%)	0	0
Malignant neoplasm of unknown primary site	1 (0.6%)	1 (0.8%)	0	0
Non-Hodgkin's lymphoma	1 (0.6%)	1 (0.8%)	0	0
Osteoma	1 (0.6%)	1 (0.8%)	0	0
Ovarian cancer recurrent	1 (0.6%)	1 (0.8%)	0	0
Pancreatic carcinoma	1 (0.6%)	1 (0.8%)	0	0
Pancreatic carcinoma metastatic	1 (0.6%)	1 (0.8%)	0	0
Plasma cell myeloma	1 (0.6%)	1 (0.8%)	0	0
Prostate cancer	7 (4.0%)	4 (3.1%)	0	3 (8.1%)
Prostate cancer metastatic	1 (0.6%)	0	0	1 (2.7%)
Tongue neoplasm malignant stage unspecified	1 (0.6%)	1 (0.8%)	0	0
Urinary tract neoplasm	1 (0.6%)	1 (0.8%)	0	0
Nervous system disorders	**18 (10%)**	**13 (10%)**	**1 (11%)**	**4 (11%)**
Basal ganglia infarction	1 (0.6%)	1 (0.8%)	0	0
Cauda equina syndrome	1 (0.6%)	1 (0.8%)	0	0
Cerebrovascular accident	5 (2.9%)	4 (3.1%)	0	1 (2.7%)

System Organ Class Preferred Term	Total N = 174	ChAd & mRNA N = 128	ChAd only N = 9	mRNA only N = 37
Coma	1 (0.6%)	1 (0.8%)	0	0
Guillain-Barre syndrome	1 (0.6%)	1 (0.8%)	0	0
Headache	1 (0.6%)	1 (0.8%)	0	0
Ischaemic stroke	1 (0.6%)	0	0	1 (2.7%)
Memory impairment	1 (0.6%)	1 (0.8%)	0	0
Motor neurone disease	1 (0.6%)	0	1 (11%)	0
Multiple sclerosis	1 (0.6%)	1 (0.8%)	0	0
Parkinson's disease	1 (0.6%)	1 (0.8%)	0	0
Syncope	1 (0.6%)	0	0	1 (2.7%)
Transient global amnesia	1 (0.6%)	0	0	1 (2.7%)
VIth nerve paralysis	1 (0.6%)	1 (0.8%)	0	0
Pregnancy, puerperium and perinatal conditions	**7 (4.0%)**	**5 (3.9%)**	**1 (11%)**	**1 (2.7%)**
Abortion spontaneous	5 (2.9%)	4 (3.1%)	1 (11%)	0
Complication of pregnancy	1 (0.6%)	0	0	1 (2.7%)
Ectopic pregnancy	1 (0.6%)	1 (0.8%)	0	0
Psychiatric disorders	**1 (0.6%)**	**1 (0.8%)**	**0**	**0**
Post-traumatic stress disorder	1 (0.6%)	1 (0.8%)	0	0
Respiratory, thoracic and mediastinal disorders	**5 (2.9%)**	**5 (3.9%)**	**0**	**0**
Chronic respiratory disease	1 (0.6%)	1 (0.8%)	0	0
Pleural effusion	1 (0.6%)	1 (0.8%)	0	0
Pulmonary embolism	3 (1.7%)	3 (2.3%)	0	0
Skin and subcutaneous tissue disorders	**1 (0.6%)**	**1 (0.8%)**	**0**	**0**
Rash	1 (0.6%)	1 (0.8%)	0	0
Surgical and medical procedures	**6 (3.4%)**	**3 (2.3%)**	**0**	**3 (8.1%)**
Finger amputation	1 (0.6%)	1 (0.8%)	0	0
Hip arthroplasty	1 (0.6%)	1 (0.8%)	0	0
Inguinal hernia repair	1 (0.6%)	0	0	1 (2.7%)
Intestinal resection	1 (0.6%)	0	0	1 (2.7%)
Knee arthroplasty	1 (0.6%)	1 (0.8%)	0	0
Transurethral prostatectomy	1 (0.6%)	0	0	1 (2.7%)
Vascular disorders	**1 (0.6%)**	**1 (0.8%)**	**0**	**0**
Hypertensive crisis	1 (0.6%)	1 (0.8%)	0	0

* 30 SAEs entered as surgical procedures rather than the underlying cause were assigned the PT “no adverse event”.

Table B4. AESIs related to SARS-CoV2 infection.

Sex	Age	Ethnicity	Group	Diagnosis	Outcome	Causality	Relationship to ChAdOx1 nCoV-19	Severity	SOC	PT	Duration of AESI (days)	Last COVID-19 vaccine before AESI	Days since last COVID-19 vaccine
Male	33	White	ChAd only	COVID-19	Recovered / resolved	No relationship	Not related	Grade 4	Infections and infestations	COVID-19	2	ChAdOx1	473
Male	26	White	ChAd & mRNA	COVID-19 illness	Recovered / resolved	No relationship	Not related	Grade 1	Infections and infestations	COVID-19	5	Other	296
Female	35	White	ChAd only	COVID-19 illness	Recovered / resolved	No relationship	Not related	Grade 2	Infections and infestations	COVID-19	7	ChAdOx1	392
Male	24	White	ChAd & mRNA	Idiopathic brachial plexopathy - Parsonage - Turner Syndrome	Ongoing Recovering / resolving	No relationship	Not related	Grade 3	Nervous system disorders	Neuralgic amyotrophy		ChAdOx1	348
Female	65	White	ChAd & mRNA	Shingles: mainly on the left side of the back	Recovered / resolved	No relationship	Not related	Grade 1	Infections and infestations	Herpes zoster	8	Pfizer	40
Male	72	White	ChAd & mRNA	COVID-19 illness	Recovered / resolved	No relationship	Not related	Grade 2	Infections and infestations	COVID-19	14	Pfizer	259
Male	75	White	ChAd & mRNA	COVID-19	Recovered / resolved	No relationship	Not related	Grade 2	Infections and infestations	COVID-19	15	Pfizer	183
Male	47	White	ChAd & mRNA	COVID-19	Recovered / resolved	No relationship	Not related	Grade 2	Infections and infestations	COVID-19	35	Pfizer	127
Female	54	White	ChAd & mRNA	COVID-19 illness	Ongoing Not recovered / not resolved	No relationship	Not related	Grade 3	Infections and infestations	COVID-19		Pfizer	290
Male	35	White	mRNA only	COVID-19	Recovered / resolved	No relationship	Not related	Grade 2	Infections and infestations	COVID-19	7	Pfizer	149
Female	72	White	ChAd & mRNA	COVID-19	Recovered / resolved	No relationship	Not related	Grade 2	Infections and infestations	COVID-19	21	Pfizer	170
Female	73	White	ChAd & mRNA	COVID-19	Recovered / resolved	No relationship	Not related	Grade 2	Infections and infestations	COVID-19	14	Pfizer	157
Male	74	White	ChAd & mRNA	COVID-19 illness	Recovered / resolved	No relationship	Not related	Grade 1	Infections and infestations	COVID-19	6	Pfizer	3
Female	70	White	ChAd & mRNA	Pulmonary embolus	Recovered / resolved	Unlikely	Not related	Grade 4	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	104	Pfizer	134
Male	56	White	ChAd & mRNA	COVID-19 illness	Recovered / resolved	No relationship	Not related	Grade 2	Infections and infestations	COVID-19	6	Pfizer	226
Female	40	White	ChAd & mRNA	Pulmonary embolus	Recovered / resolved with sequelae	Unlikely	Not related	Grade 4	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	3	Pfizer	19

Sex	Age	Ethnicity	Group	Diagnosis	Outcome	Causality	Relationship to ChAdOx1 nCoV-19	Severity	SOC	PT	Duration of AESI (days)	Last COVID-19 vaccine before AESI	Days since last COVID-19 vaccine
Male	74	White	ChAd & mRNA	COVID-19 positive, on chemo for mesothelioma, admitted with spikes of temp and SOB	Recovered / resolved	No relationship	Not related	Grade 3	General disorders and administration site conditions	Unevaluable event	10	Moderna	21
Male	42	White	mRNA only	COVID-19	Recovered / resolved	No relationship	Not related	Grade 1	Infections and infestations	COVID-19	15	Pfizer	78

Table B5. AESIs by system organ class and preferred term.

System Organ Class Preferred Term	Total N = 71	ChAd & mRNA N = 54	ChAd only N = 7	mRNA only N = 10
Cardiac disorders	**2 (2.8%)**	**1 (1.9%)**	**0**	**1 (10%)**
Myocardial infarction	1 (1.4%)	1 (1.9%)	0	0
Supraventricular tachycardia	1 (1.4%)	0	0	1 (10%)
Ear and labyrinth disorders	**1 (1.4%)**	**1 (1.9%)**	**0**	**0**
Vertigo	1 (1.4%)	1 (1.9%)	0	0
Endocrine disorders	**1 (1.4%)**	**1 (1.9%)**	**0**	**0**
Basedow's disease	1 (1.4%)	1 (1.9%)	0	0
Gastrointestinal disorders	**6 (8.5%)**	**3 (5.6%)**	**2 (29%)**	**1 (10%)**
Coeliac disease	1 (1.4%)	1 (1.9%)	0	0
Colitis	1 (1.4%)	0	1 (14%)	0
Colitis ulcerative	2 (2.8%)	1 (1.9%)	1 (14%)	0
Colon cancer	1 (1.4%)	0	0	1 (10%)
Crohn's disease	1 (1.4%)	1 (1.9%)	0	0
General disorders and administration site conditions	**3 (4.2%)**	**3 (5.6%)**	**0**	**0**
Fatigue	1 (1.4%)	1 (1.9%)	0	0
No adverse event	1 (1.4%)	1 (1.9%)	0	0
Unevaluable event	1 (1.4%)	1 (1.9%)	0	0
Hepatobiliary disorders	**2 (2.8%)**	**1 (1.9%)**	**1 (14%)**	**0**
Bile duct stone	1 (1.4%)	1 (1.9%)	0	0
Hepatic steatosis	1 (1.4%)	0	1 (14%)	0
Infections and infestations	**18 (25%)**	**12 (22%)**	**2 (29%)**	**4 (40%)**
Appendicitis	1 (1.4%)	0	0	1 (10%)
COVID-19	14 (20%)	10 (19%)	2 (29%)	2 (20%)
Diverticulitis intestinal haemorrhagic	1 (1.4%)	0	0	1 (10%)
Herpes zoster	2 (2.8%)	2 (3.7%)	0	0
Musculoskeletal and connective tissue disorders	**3 (4.2%)**	**3 (5.6%)**	**0**	**0**
Axial spondyloarthritis	1 (1.4%)	1 (1.9%)	0	0
Polymyalgia rheumatica	1 (1.4%)	1 (1.9%)	0	0
Rheumatoid arthritis	1 (1.4%)	1 (1.9%)	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**6 (8.5%)**	**5 (9.3%)**	**1 (14%)**	**0**
Astrocytoma	1 (1.4%)	1 (1.9%)	0	0
Breast cancer	1 (1.4%)	1 (1.9%)	0	0
Colorectal cancer metastatic	1 (1.4%)	1 (1.9%)	0	0
Endometrial cancer stage I	1 (1.4%)	0	1 (14%)	0
Hypergammaglobulinaemia benign monoclonal	1 (1.4%)	1 (1.9%)	0	0
Ovarian cancer recurrent	1 (1.4%)	1 (1.9%)	0	0
Nervous system disorders	**18 (25%)***	**13 (24%)***	**1 (14%)**	**4 (40%)**
Basal ganglia infarction	1 (1.4%)	1 (1.9%)	0	0
Cerebrovascular accident	4 (5.6%)	3 (5.6%)	0	1 (10%)
Facial paralysis	1 (1.4%)	0	0	1 (10%)
Guillain-Barre syndrome	1 (1.4%)	1 (1.9%)	0	0
Headache	1 (1.4%)	1 (1.9%)	0	0
Ischaemic stroke	1 (1.4%)	0	0	1 (10%)
Memory impairment	1 (1.4%)	1 (1.9%)	0	0
Motor neurone disease	1 (1.4%)	0	1 (14%)	0
Multiple sclerosis	1 (1.4%)	1 (1.9%)	0	0
Myasthenia gravis	1 (1.4%)	1 (1.9%)	0	0
Neuralgic amyotrophy	1 (1.4%)	1 (1.9%)	0	0

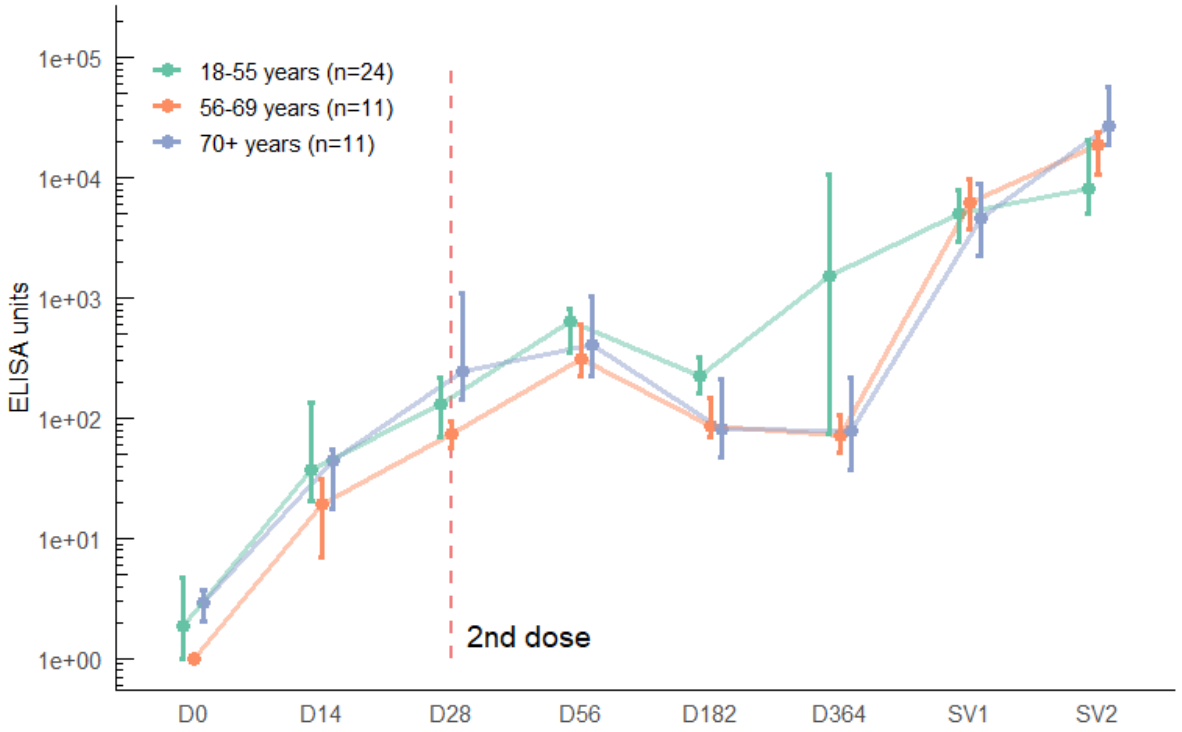
System Organ Class Preferred Term	Total N = 71	ChAd & mRNA N = 54	ChAd only N = 7	mRNA only N = 10
Transient epileptic amnesia	1 (1.4%)	1 (1.9%)	0	0
Transient ischaemic attack	2 (2.8%)	1 (1.9%)	0	1 (10%)
VIth nerve paralysis	1 (1.4%)	1 (1.9%)	0	0
Respiratory, thoracic and mediastinal disorders	**4 (5.6%)**	**4 (7.4%)**	**0**	**0**
Dyspnoea	1 (1.4%)	1 (1.9%)	0	0
Pulmonary embolism	3 (4.2%)	3 (5.6%)	0	0
Skin and subcutaneous tissue disorders	**3 (4.2%)**	**3 (5.6%)**	**0**	**0**
Angioedema	1 (1.4%)	1 (1.9%)	0	0
Rash	1 (1.4%)	1 (1.9%)	0	0
Vitiligo	1 (1.4%)	1 (1.9%)	0	0
Surgical and medical procedures	**1 (1.4%)**	**1 (1.9%)**	**0**	**0**
Finger amputation	1 (1.4%)	1 (1.9%)	0	0
Vascular disorders	**3 (4.2%)**	**3 (5.6%)**	**0**	**0**
Giant cell arteritis	1 (1.4%)	1 (1.9%)	0	0
Thrombosis	2 (2.8%)	2 (3.7%)	0	0

*One participant reported two AESIs in SOC "Nervous system disorders".

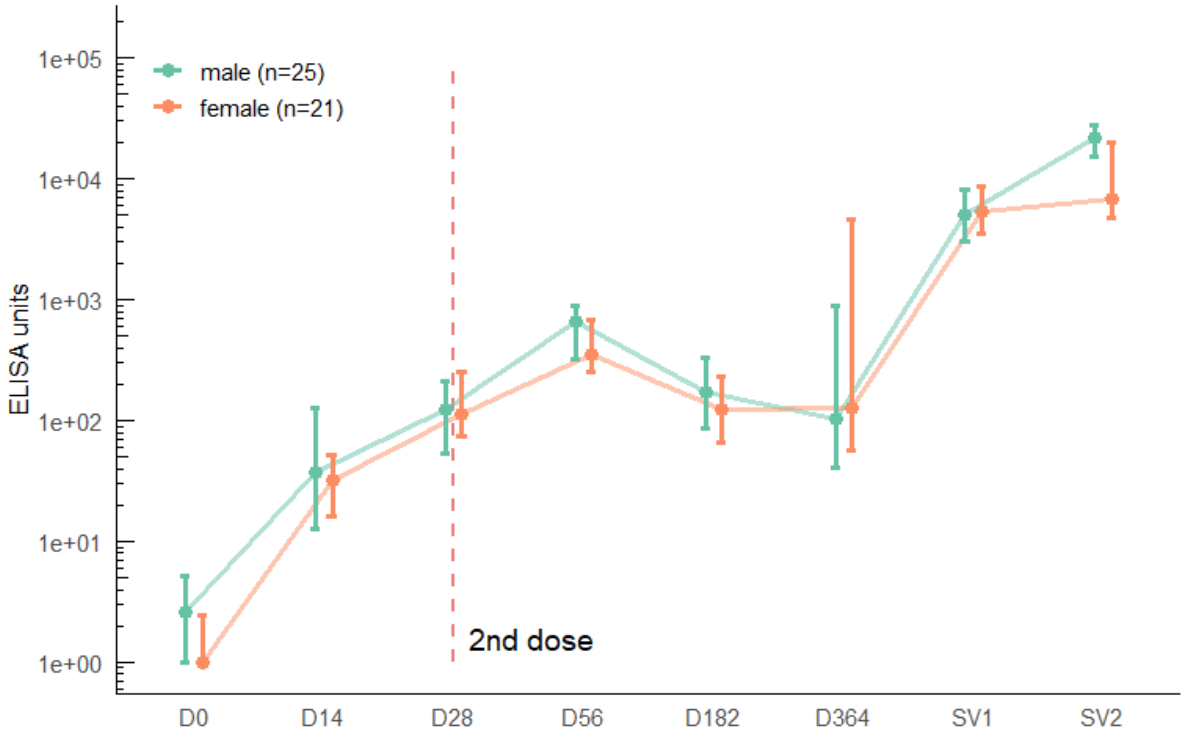
APPENDIX C. Antibody response results.

Figure C1. Antibody responses over a 2-year period in 46 participants who received a second dose of ChAdOx1 nCoV-19 at 28 days after the first dose – subgroup analysis by (A) age group, (B) sex, and (C) dosage in COV001/COV002.

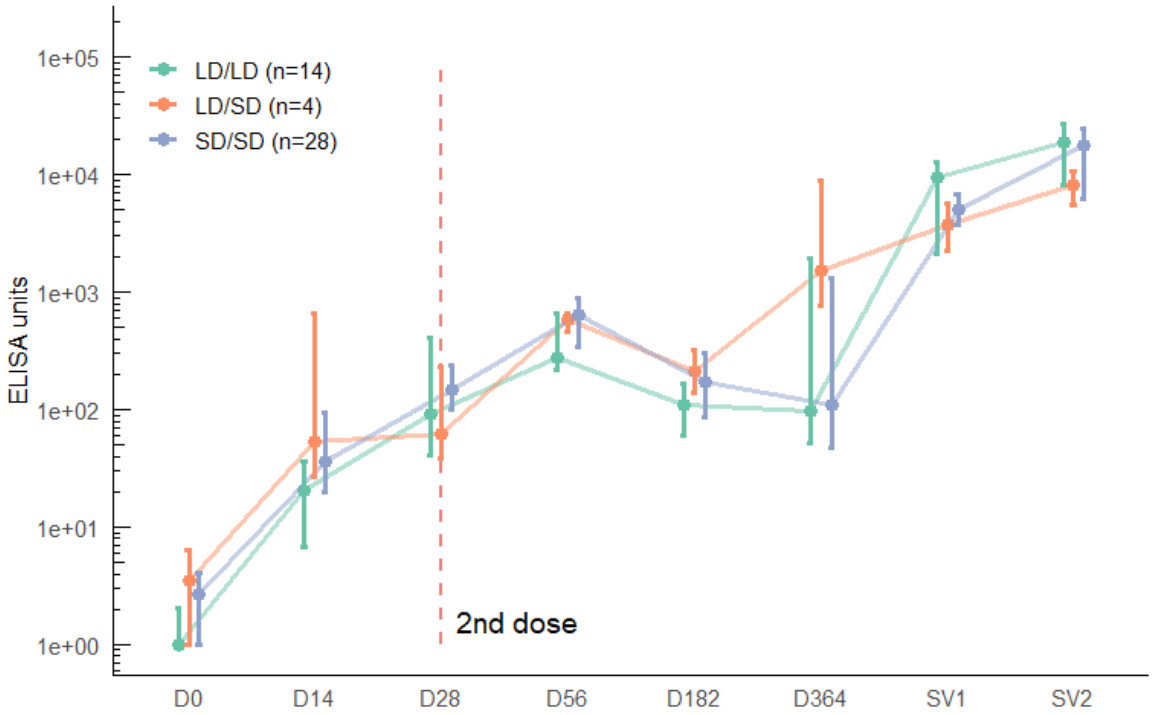
(A)



(B)



(C)



Antibody responses measured using total IgG ELISA against trimeric SARS-CoV-2 spike protein.

Bars show IQR.

D0, D14, D28, D56, D182, D364: Timepoints in COV001/COV002. D0 was when the first dose of ChAdOx1 nCov-19 was given. Numbers in subsequent D timepoints indicate number of days after first dose.

SV1, SV2: Timepoints in COV009. First (SV1) and second (SV2) study visits.

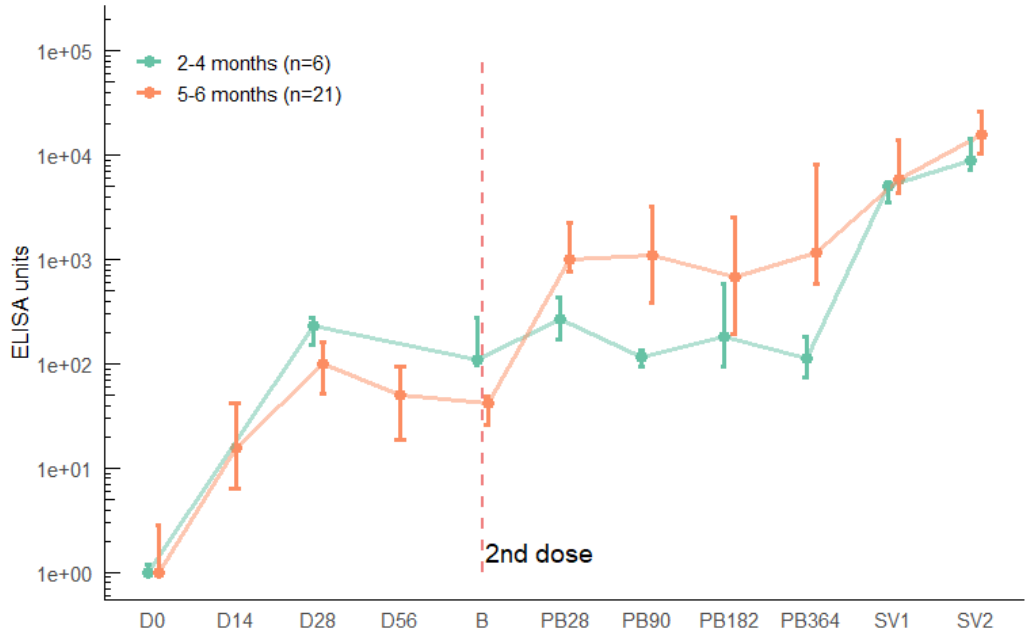
Timepoint	D0	D14	D28	D56	D182	D364	SV1	SV2
Number of participants with data for analysis	46/46	39/46	44/46	44/46	35/46	38/46	40/46	37/46

LD: Low dose ChAdOx1 nCoV-19 ($2.2x10^{10}$ vp),

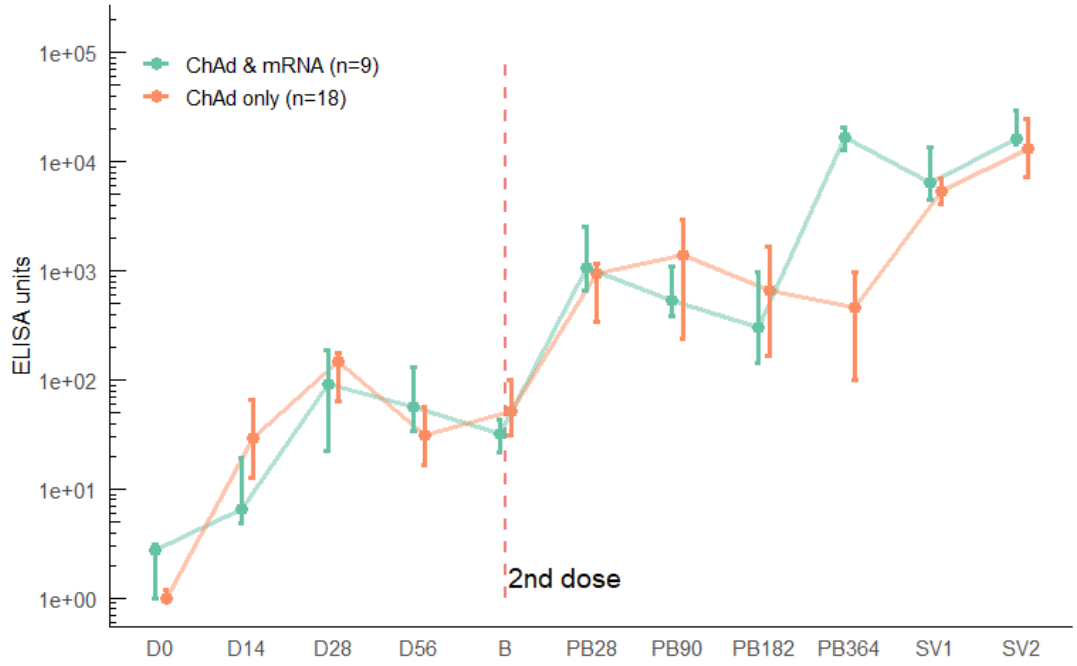
SD: Standard dose ChAdOx1 nCoV-19 ($3.5\text{-}6.5x10^{10}$ vp).

Figure C2. Antibody responses over a 2-year period in 27 participants who received a second dose of ChAdOx1 nCoV-19 at 2 to <6 months after receiving the first dose in COV001/COV002 – subgroup analysis by (A) interval between first and second dose, (B) vaccine platform across the follow-up period, and (C) dosage in COV001/COV002.

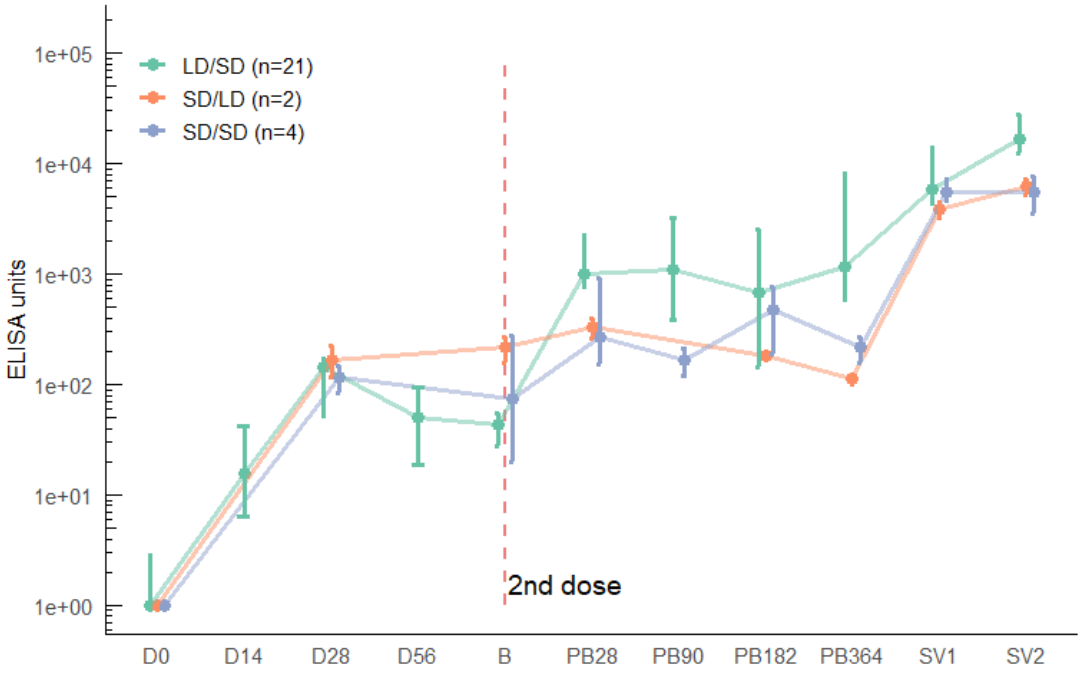
(A)



(B)



(C)



Antibody responses measured using total IgG ELISA against trimeric SARS-CoV-2 spike protein.

Bars show IQR.

D0, D14, D28, D56: Timepoints in COV001/COV002. D0 was when the first dose of ChAdOx1 nCov-19 was given. Numbers in subsequent D timepoints indicate number of days after first dose.

B, PB28, PB90, PB182, PB364: Timepoints in COV001/COV002. B was when the second dose of ChAdOx1 nCov-19 was given. Numbers in subsequent PB timepoints indicate number of days after second dose.

SV1, SV2: Timepoints in COV009. First (SV1) and second (SV2) study visits.

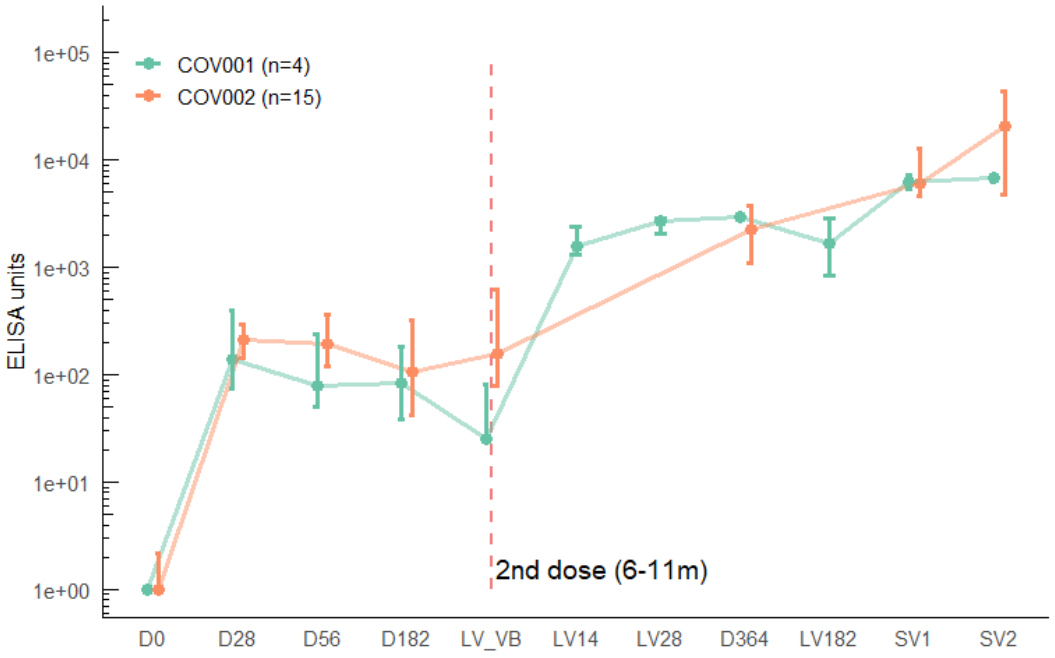
Timepoint	D0	D14	D28	D56	B	PB28	PB90	PB182	PB364	SV1	SV2
Number of participants with data for analysis	27/27	20/27	25/27	12/27	27/27	26/27	23/27	25/27	14/27	25/27	24/27

LD: Low dose ChAdOx1 nCoV-19 ($2.2x10^{10}$ vp),

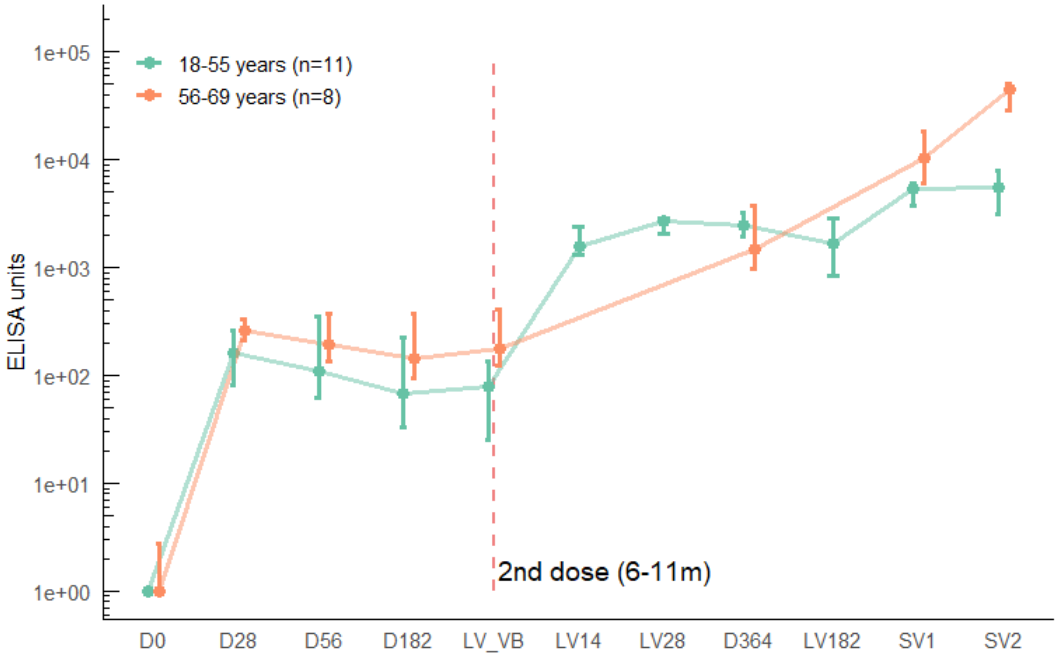
SD: Standard dose ChAdOx1 nCoV-19 ($3.5\text{-}6.5x10^{10}$ vp).

Figure C3. Antibody responses over a 2-year period in 19 participants who received a late second dose of ChAdOx1 nCoV-19 at 6 to 11 months after receiving a standard first dose in COV001/COV002 – subgroup analysis by (A) study (COV001 or COV002), and (B) age group.

(A)



(B)



Antibody responses measured using total IgG ELISA against trimeric SARS-CoV-2 spike protein.

Bars show IQR.

D0, D14, D28, D56, D182, D364: Timepoints in COV001/COV002. D0 was when the first dose of ChAdOx1 nCov-19 was given. Numbers in subsequent timepoints indicate number of days after first dose.

LV_VB, LV14, LV28, LV182: Timepoints in COV001/COV002. LV_VB was when the second dose of ChAdOx1 nCov-19 was given. Numbers in subsequent timepoints indicate number of days after second dose.

SV1, SV2: Timepoints in COV009. First (SV1) and second (SV2) study visits.

Timepoint	D0	D28	D56	D182	LV_VB	LV14	LV28	D364	LV182	SV1	SV2
Number of participants with data for analysis	19/19	19/19	19/19	19/19	16/19	3/19	3/19	16/19	3/19	16/19	16/19