Single dose administration, and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine

Merryn Voysey[1]*, Sue Ann Costa Clemens[3]*, Shabir A. Madhi[4]*, Lily Y. Weckx[5]*, Pedro M. Folegatti[2]*,Parvinder K. Aley[1], Brian Angus[2], Vicky L. Baillie[4], Shaun L. Barnabas[9], Qasim E. Bhorat[9], Sagida Bibi[1], Carmen Briner[26], Paola Cicconi[2], Elizabeth A. Clutterbuck[1], Andrea M. Collins[10], Clare L. Cutland[4], Thomas C. Darton[11], Keertan Dheda[13], Alexander D. Douglas[2], Christopher J. A. Duncan[14], Katherine R. W. Emary[1], Katie J. Ewer[2], Amy Flaxman[2], Lee Fairlie[15], Saul N. Faust[16], Shuo Feng[1], Daniela M. Ferreira[10], Adam Finn[17], Eva Galiza[20], Anna L. Goodman[18], Catherine M. Green[7], Christopher A. Green[19], Melanie Greenland[1], Catherine Hill[4], Helen C. Hill[10], Ian Hirsch[6], Alane Izu[4], Daniel Jenkin[2], Simon Kerridge[1], Anthonet Koen[4], Gaurav Kwatra[4], Rajeka Lazarus[21], Vincenzo Libri[23], Patrick J. Lillie[24], Natalie G. Marchevsky, Richard P. Marshall[6], Ana V. A. Mendes[12], Eveline P. Milan[27], Angela M. Minassian[2], Alastair McGregor[25], Yama F Mujadidi[1], Anusha Nana[22], Sherman D. Padayachee[26], Daniel J. Phillips[1], Ana Pittella[28], Emma Plested[1], Katrina M. Pollock[29], Maheshi N. Ramasamy[1], Hannah Robinson[1],Alexandre V. Schwarzbold[32], Andrew Smith[30], Rinn Song[1], Matthew D. Snape[1], Eduardo Sprinz[31], Rebecca K. Sutherland[33], Emma C. Thomson[34], M. Estée Török[35], Mark Toshner[36], David P. J. Turner[37], Johan Vekemans[6], Tonya L. Villafana[6], Thomas White[6], Christopher J Williams[38], Adrian V. S Hill[2]*, Teresa Lambe[2]*, Sarah C. Gilbert[2]*, Andrew J Pollard[1]* and the Oxford COVID Vaccine Trial Group

*contributed equally

[1] Oxford Vaccine Group, Department of Paediatrics, University of Oxford, UK: A. J. Pollard FMedSci, M. Voysey DPhil, P. K. Aley DPhil, S. Bibi PhD, E. A. Clutterbuck PhD, K. R. W. Emary BM BCH, S. Feng PhD, M. Greenland MSc, S. Kerridge MSc, N. G. Marchevsky MSc, Y. F Mujadidi MSc, D. J. Phillips MMath, E. Plested, M. N. Ramasamy DPhil, H. Robinson RN, M. D. Snape MD, R. Song MD

[2] Jenner Institute, Nuffield Department of Medicine, University of Oxford, UK: A. D. Douglas DPhil, A. Flaxman DPhil, S. C. Gilbert PhD, T. Lambe PhD, A. V. S. Hill FMedSci, P. M. Folegatti MD, B. Angus MD, P. Cicconi MD PhD, K.J. Ewer PhD, D. Jenkin MRCP, A. M. Minassian DPhil

[3] Institute of Global Health, University of Siena, Brazil and Department of Paediatrics, University of Oxford: S. A. C. Clemens MD PhD

[4] South African Medical Research Council Vaccines and Infectious Diseases Analytics Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa and Department of Science and Innovation/National Research Foundation South African Research Chair Initiative in Vaccine Preventable Diseases Unit, University of the Witwatersrand, Johannesburg, South Africa: S. A. Madhi PhD, V. Baillie PhD, C. L. Cutland MD PhD, C. Hill BA Hons, A. Izu PhD, A. Koen MBChB, G. Kwatra PhD

[5] Universidade Federal de SaoPaulo, Brazil: L. Y. Weckx MD PhD

[6] AstraZeneca BioPharmaceuticals PLC: I. Hirsch PhD, R. P. Marshall MD, J. Vekemans MD PhD, T. L. Villafana PhD, T. White PhD

[7] Clinical BioManufacturing Facility, University of Oxford, UK: C. M. Green PhD

[8] Family Centre for Research with Ubuntu, Department of Paediatrics, University of Stellenbosch, Cape Town, South Africa: S. L. Barnabas PhD

[9] Soweto Clinical Trials Centre, Soweto, South Africa: Q. E. Bhorat MSc

[10] Department of Clinical Sciences, Liverpool School of Tropical Medicine and Liverpool University Hospitals NHS Foundation Trust: A. M. Collins PhD, D. M. Ferreira PhD, H. C. Hill PhD

[11] Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield and Department of Infection and Tropical Medicine, Sheffield Teaching Hospitals NHS Foundation Trust, UK: T. C. Darton DPhil

[12] Escola Bahiana de Medicina e Saúde Pública, Salvador, Braziland Hospital São Rafael, Salvador, Brazil and ID'OR, Brazil: A. V. A. Mendes MD PhD

[13] Division of Pulmonology, Groote Schuur Hospital and the University of Cape Town, South Africa and Faculty of Infectious and Tropical Diseases, Department of Immunology and Infection, London School of Hygiene and Tropical Medicine, London, UK: K. Dheda FRCPCH

[14] Department of Infection and Tropical Medicine, Newcastle upon Tyne Hospitals NHS Foundation Trust and Translational and Clinical Research Institute, Immunity and Inflammation Theme, Newcastle University: C. J. A. Duncan DPhil

[15] Wits Reproductive Health and HIV Institute, Faculty of Health Sciences, University of the Witwatersrand, Johanesburg, South Africa: L. Fairlie FCPaeds

[16] NIHR Southampton Clinical Research Facility and Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, and Faculty of Medicine and Institute for Life Sciences, University of Southampton, Southampton, UK: S. N. Faust PhD

[17] University Hospitals Bristol and Weston NHS Foundation Trust, UK: A. Finn FRCPCH

[18] Department of Infection, Guy's and St Thomas' NHS Foundation Trust, St Thomas' Hospital, London, UK and MRC Clinical Trials Unit, University College London, London, UK: A. L. Goodman FRCP

[19] NIHR/Wellcome Trust Clinical Research Facility, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK: C. A. Green DPhil

[20] St George's Vaccine Institute, St George's, University of London, UK: E. Galiza MBBS

[21] Severn Pathology, North Bristol NHS Trust: R. Lazarus DPhil

[22] Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa: C. Briner MBBCh, A. Nana BPharm

[23] NIHR UCLH Clinical Research Facility and NIHR UCLH Biomedical Research Centre, London, UK: V. Libri MD FRCP

[24] Hull University Teaching Hospitals NHS Trust, UK: P. J. Lillie PhD

[25] London Northwest University Healthcare, Harrow, UK: A. C. McGregor FRCPath

[26] Setshaba Research Centre, Pretoria, South Africa: S. D. Payadachee MBChB

[27] Universidade Federal do Rio Grande do Norte - UFRN, Brazil: E. P. Milan PhD

[28] Hospital Quinta D'OR, Rede D'OR, Brazil: A. Pittella MD

[29] NIHR Imperial Clinical Research Facility and NIHR Imperial Biomedical Research Centre, London, UK: K. M. Pollock PhD

[30] College of Medical, Veterinary & Life Sciences, Glasgow Dental Hospital & School, University of Glasgow: A. Smith FRCPath

[31] Infectious Diseases Service, Hospital de Clinicas de Porto Alegre; Universidade Federal do Rio Grande do Sul: E. Sprinz MD PhD

[32] Clinical Research Unit, Department of Clinical Medicine, Universidade Federal de Santa Maria, Brazil: A. V. Schwarzbold PhD

[33] Clinical Infection Research Group, Regional Infectious Diseases Unit, Western General Hospital, Edinburgh, UK: R. K. Sutherland FRCP

[34] MRC - University of Glasgow Centre for Virus Research & Department of Infectious Diseases, Queen Elizabeth University Hospital, Glasgow, UK: E. C. Thomson FRCP PhD

[35] Department of Medicine, University of Cambridge, UK and Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK: M. E. Török FRCP

[36] Heart Lung Research Institute, Dept of Medicine, University of Cambridge and NIHR Cambridge Clinical Research Facility, Cambridge University Hospital and Royal Papworth NHS Foundation Trusts UK: M. Toshner MD

[37] University of Nottingham and Nottingham University Hospitals NHS Trust, UK: D. P. J. Turner PhD

[38] Public Health Wales, Cardiff, Wales and Aneurin Bevan University Health Board, Wales: C. J Williams FFPH

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Author contributions

AJP and SCG conceived the trial and AJP is the chief investigator. AJP, PMF, DJ, and MV contributed to the protocol and design of the study. SACC, SAM, LYW, AVSH, ALG, VLB, SLB, QEB, AMC, MT, AS, KD, CJW, CJAD, PJL, ECT, LF, SNF, CAG, RL, TCD, EG, HH, DMF, VL, AM, AI, CB, AK, GK, MET, AP, EPM, AVS, AVAM, CLC, ALG, AN, SDP, KMP, AS, ES, RKS, MNR, MT and DPJT are study site principal investigators. PKA, EP, HR, DJ, PMF, SB, EAC, KRWE, BA, PC, AMM, TW, SK, KJE, AF, JV, IH, TLV, YFM, RS, and MDS contributed to the implementation of the study and/or data collection. MV, NGM, MG, DJP, and SF conducted the statistical analysis. CMG and ADD were responsible for vaccine manufacturing. MV, NGM, and AJP contributed to the preparation of the report. All authors critically reviewed and approved the final version.

Competing Interests Statement

Oxford University has entered into a partnership with Astra Zeneca for further development of ChAdOx1 nCoV-19. SCG is co-founder of Vaccitech (collaborators in the early development of this vaccine candidate) and named as an inventor on a patent covering use of ChAdOx1-vectored vaccines and a patent application covering this SARS-CoV-2 vaccine. TL is named as an inventor on a patent application covering this SARS-CoV-2 vaccine and was a consultant to Vaccitech for an unrelated project. PMF is a consultant to Vaccitech. AJP is Chair of UK Dept. Health and Social Care's (DHSC) Joint Committee on Vaccination & Immunisation (JCVI), but does not participate in discussions on COVID-19 vaccines, and is a member of the WHO's SAGE. AJP and SNF are NIHR Senior Investigator. The views expressed in this article do not necessarily represent the views of DHSC, JCVI, NIHR or WHO. AVSH reports personal fees from Vaccitech, outside the submitted work and has a patent on ChAdOx1 licensed to Vaccitech, and may benefit from royalty income to the University of Oxford from sales of this vaccine by AstraZeneca and sublicensees. MS reports grants from NIHR, non-financial support from AstraZeneca, during the conduct of the study; grants from Janssen, grants from GlaxoSmithKline, grants from Medimmune, grants from Novavax, grants and non-financial

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Research in Context

Evidence before this study

The ChAdOx1 nCoV-19 (AZD1222) vaccine was approved for emergency use authorisation by the MHRA based on interim efficacy results from 131 cases of primary symptomatic COVID-19, with efficacy based on two of the four trials of the vaccine. The planned rollout of the vaccine in the UK involves the administration of two doses, 12 weeks apart, a policy that has received substantial comment.

Added Value of this study

This report provides updated efficacy results after a further month of data collection, from 332 cases of primary symptomatic COVID-19. Efficacy estimates now include data from all four studies of the vaccine from 3 countries, and a breakdown by the interval between the two doses is provided. Furthermore, the efficacy of a single dose of vaccine is explored.

Implications of the available evidence

These analyses show that higher vaccine efficacy is obtained with a longer interval between the first and second dose, and that a single dose of vaccine is highly efficacious in the first 90 days, providing further support for current policy.

Abstract

Background

The ChAdOx1 nCoV-19 (AZD1222) vaccine has been approved for emergency use by the UK regulatory authority, MHRA, with a regimen of two standard doses given with an interval of between 4 and 12 weeks. The planned rollout in the UK will involve vaccinating people in high risk categories with their first dose immediately, and delivering the second dose 12 weeks later.

Here we provide both a further prespecified pooled analysis of trials of ChAdOx1 nCoV-19 and exploratory analyses of the impact on immunogenicity and efficacy of extending the interval between priming and booster doses. In addition, we show the immunogenicity and protection afforded by the first dose, before a booster dose has been offered.

Methods

We present data from phase III efficacy trials of ChAdOx1 nCoV-19 in the United Kingdom and Brazil, and phase I/II clinical trials in the UK and South Africa, against symptomatic disease caused by SARS-CoV-2. The data cut-off date for these analyses was 7th December 2020. The accumulated cases of COVID-19 disease at this cut-off date exceeds the number required for a pre-specified final analysis, which is also presented. As previously described, individuals over 18 years of age were randomised 1:1 to receive two standard doses (SD) of ChAdOx1 nCoV-19 ($5x10^{10}$ viral particles) or a control vaccine/saline placebo. In the UK trial efficacy cohort a subset of participants received a lower dose (LD, $2.2x10^{10}$ viral particles) of the ChAdOx1 nCoV-19 for the first dose. All cases with a nucleic acid amplification test (NAAT) were adjudicated for inclusion in the analysis, by a blinded independent endpoint review committee.

Studies are registered at ISRCTN89951424 and ClinicalTrials.gov; NCT04324606, NCT04400838, and NCT04444674.

Findings

17,177 baseline seronegative trial participants were eligible for inclusion in the efficacy analysis, 8948 in the UK, 6753 in Brazil and 1476 in South Africa, with 619 documented NAAT +ve infections of which 332 met the primary endpoint of symptomatic infection >14 days post dose 2.

The primary analysis of overall vaccine efficacy >14 days after the second dose including LD/SD and SD/SD groups, based on the prespecified criteria was 66.7% (57.4%, 74.0%). There were no hospitalisations in the ChAdOx1 nCoV-19 group after the initial 21 day exclusion period, and 15 in the control group.

Vaccine efficacy after a single standard dose of vaccine from day 22 to day 90 post vaccination was 76% (59%, 86%), and modelled analysis indicated that protection did not wane during this initial 3 month period. Similarly, antibody levels were maintained during this period with minimal waning by day 90 day (GMR 0.66, 95% CI 0.59, 0.74).

In the SD/SD group, after the second dose, efficacy was higher with a longer prime-boost interval: VE 82.4% 95%CI 62.7%, 91.7% at 12+ weeks, compared with VE 54.9%, 95%CI 32.7%, 69.7% at <6 weeks. These observations are supported by immunogenicity data which showed binding antibody responses more than 2-fold higher after an interval of 12 or more weeks compared with and interval of less than 6 weeks GMR 2.19 (2.12, 2.26) in those who were 18-55 years of age.

Interpretation

ChAdOx1 nCoV-19 vaccination programmes aimed at vaccinating a large proportion of the population with a single dose, with a second dose given after a 3 month period is an effective strategy for reducing disease, and may be the optimal for rollout of a pandemic vaccine when supplies are limited in the short term.

Introduction

The widespread morbidity and mortality associated with the 2020 COVID-19 pandemic, precipitated the most extensive and rapid global vaccine development programme in history[1], culminating in development of several vaccines reaching phase 3 efficacy milestones and receiving emergency use authorisation by the end of that year.[2-4] Widespread vaccination programmes have commenced in several countries as new vaccines are licensed for emergency use by regulators in each setting, with a focus primarily on high-risk groups such as the elderly, those with co-morbidities or front line workers.

Vaccine supply is likely to be limited, at least initially, and so policy-makers must decide how best to deliver available doses to achieve greatest public health benefit, and different approaches have been taken in different settings. In the UK second doses of both available vaccines (a viral vector and mRNA vaccine) are being delivered with an interval of up to 12 weeks[5,6], and this regimen is also being considered by several other countries.[7,8] By contrast, WHO has recently recommended a maximum 6 week interval between the 2 doses of the same mRNA vaccine[9].

The ChAdOx1 nCoV-19 vaccine (AZD1222) is a chimpanzee adenoviral vectored vaccine with full length SAR-CoV-2 spike insert which was developed at the University of Oxford. The safety and immunogenicity of the vaccine were assessed in four randomised controlled trials in the UK, Brazil and South Africa, and results in healthy adults, and in older aged cohorts, have been published[10-14]. Efficacy of two doses of the vaccine was demonstrated at the interim analysis of 131 cases which pooled data from Brazil and the UK, to be 70.4% (95.8% CI 54.8–80.6%) overall.[14] ChAdOx1 nCoV-19 was authorised for emergency use in the United Kingdom on 30th December 2020, based on data presented in an interim analysis with a data cut off date of 4th November 2020[14], in a regimen of two standard doses administered 4-12 weeks apart for adults over 18 years of age, and has since been authorised for use in many other countries.

The University of Oxford sponsored studies were initially planned as single dose studies but were amended to incorporate a second dose after review of the phase 1 immunogenicity data which showed a substantial increase in neutralising antibody with a second dose of vaccine.[12] After initially providing consent to participate in a single dose study, some participants chose not to receive the second dose, providing a self-selected cohort of single dose recipients.

Additionally, due to the time required to manufacture the second dose, there were delays in administration of the second dose for a large number of trial participants who received the two dose schedule. These two situations, provide an opportunity to explore the immunogenicity and efficacy of a single dose of vaccine, and the impact of an extended interval before delivery of the second dose. In addition, data from an additional month of follow up is now available for inclusion in the analysis, providing greater precision in estimates due to the larger number of cases for analysis in comparison with the previous report.[14]

Methods

Data from three single-blind randomised controlled trials in the UK (COV001/COV002), Brazil (COV003), and one double-blind study in South Africa (COV005) are included in this exploratory analysis as all four trials now meet the required criteria for inclusion of having at least 5 primary outcome cases. The data cut-off date for cases to be included in the current report was December 7, 2020.

A full description of the safety, immunogenicity and interim efficacy of the four studies has been previously published in detail, including full study protocols.[12-14] Briefly, participants in efficacy cohorts were randomised 1:1 to receive either ChAdOx1 nCoV-19 vaccine or a control product (MenACWY in the UK, MenACWY prime and saline boost in Brazil, and saline only in South Africa). One group of participants in the COV002 study in the UK received a low dose (LD) as their first dose followed by a standard dose (SD) as discussed previously.[14] Other participants received two standard doses (SD/SD).

The primary outcome was symptomatic COVID-19 disease defined as a NAAT+ swab combined with at least one qualifying symptom (fever ≥ 37.8°C; cough; shortness of breath; anosmia or ageusia). The primary analysis was of cases occurring more than 14 days after the second dose, with a secondary analysis of cases occurring more than 21 days after the first dose. In all studies, participants were asked to contact the study site if they had symptoms of COVID-19, and were then invited to attend for clinical review and a swab. Additionally, in the UK, asymptomatic infections were measured by means of weekly self-administered nose and throat swabs using kits provided by the Department of Health and Social Care. All endpoints were adjudicated for inclusion in the analysis by an independent blinded endpoint review committee.

The current report details additional exploratory analyses of single dose efficacy which have been added at the request of regulators and policy-makers. These are considered as supportive analyses to the previously published interim efficacy analysis, and were not pre-specified. In addition, the impact of the timing of the second dose is explored in more detail.

For the primary analysis, which we present here updated with additional cases from an extra month of follow up, randomised participants enrolled in efficacy cohorts were included in the analysis according to the vaccine received. Events were included that occurred more than 14 days after the second dose, in participants who were seronegative to SARS-CoV-2 N protein at baseline and had at least 14 days of follow up after the second dose and no previous evidence of SARS-CoV-2 infection from NAAT swabs.

For the analysis of single dose efficacy, randomised participants enrolled in efficacy cohorts were included in the analysis according to the vaccine they received as their first dose. Events were included if they occurred more than 21 days after the first dose. Participants were excluded if they had a NAAT+ swab in the first 21 days after the first dose, or had less than 22 days of follow up. Participants who received a second dose were censored in the analysis at the time of their booster dose. Participants who did not receive a second dose are censored in the analysis at the data cut-off date.

Vaccine efficacy was calculated as 1 – the adjusted relative risk (ChAdOx1 nCoV-19 vs control groups) computed using a robust Poisson regression model. The model contained terms for study, treatment group, and age group at randomisation. The logarithm of the period at risk was used as an offset variable in the model to adjust for volunteers having different follow up times during which the events occurred.

To explore the impact of varying the timing of the second dose of vaccine, we fit separate efficacy models, using unadjusted log-binomial models, for each 20 day interval starting with an interval of 20 to 40 days (midpoint for plot: 30 days) and incrementing by one day for each model. Participants who received their second dose within the window were included in that model. Vaccine efficacy for each window was plotted with 95% confidence intervals.

To explore the potential for waning of efficacy after the first dose, before a booster dose was received, a similar approach was taken with separate efficacy models fitted to 28 day windows of the time from vaccination. Cases occurring outside the windows were censored.

Potential differences in population baseline characteristics between those who received a second dose of vaccine and those who did not are explored descriptively, with comparisons made between groups using Chi-squared tests, Wilcoxon Rank Sum tests, or Cochran-Armitage tests as appropriate.

The persistence of anti-spike IgG responses after a single dose were measured in the UK by standardised ELISA. Decay of antibody over time was modelled for low dose and standard dose recipients using a linear model.

Baseline serum samples were measured for nucleocapsid reactivity with the Roche Elecsys Anti-SARS-CoV-2 serology test and a multiplexed immunoassay was used to measure the spike-specific response to ChAdOx1 nCoV-19 vaccination and/or natural SARS-CoV-2 infection. Antibody neutralisation was measured with a lentivirus-based pseudovirus particle expressing the SARS CoV-2 spike protein as described[12]

Data analysis was done using R version 3.6.1 or later. Robust Poisson models were fitted using "*proc genmod*" function in SAS version 9.4.

Results

There were 17177 participants included in the efficacy analysis (8597 ChAdOx1 nCoV-19 and 8580 control participants). 8948 from UK, 6753 from Brazil and 1476 from South Africa (Figure S1).

There were 332 cases of primary symptomatic COVID-19 occurring more than 14 days after a booster dose. In the SDSD cohort, 74 (0.8%) cases occurred in the ChAdOx1 nCoV-19 group and 197 (1.9%) in the control group, with vaccine efficacy of 63.1% 95% CI (51.8%, 71.7%). 61 cases were available for analysis in the LDSD cohort with VE of 80.7% 95% CI (62.1%, 90.2%), and overall efficacy across both cohorts combined was 66.7% (57.4%, 74.0%).(Table 1)

From the day of vaccination there were 2 hospitalisations in the ChAdOx1 nCoV-19 and 22 in the control group, 3 of whom were considered severe, see Table S1.

There were 130 cases of asymptomatic infection occurring more than 14 days after the booster dose (COV002 UK cohort only). In the SDSD cohort there was no evidence of protection with VE of 2.0%, 95%CI (-50.7%, 36.2%, 41 ChAdOx1 nCoV-19 versus 42 control cases). However, in the LDSD cohort there were 47 cases and VE was higher at 49.3%, 95%CI (7.4%, 72.2%, 16 ChAdOx1 nCoV-19 versus 31 control cases). (Table 1)

Overall reduction in any PCR+ was 54.1% (44.7%, 61.9%), indicating the potential for a reduction of transmission with a regimen of two SDs.

Protection against primary symptomatic COVID-19 with a single SD vaccine was modelled against time since the first dose and showed no evidence of waning of protection in the first 3 months after vaccination (Figure 2A). A single standard dose of vaccine provided protection against primary symptomatic COVID-19 in the first 90 days of 76%, (95%CI, 59%, 86%), but did not provide protection against asymptomatic infection in the same period (VE 16%, 95% CI -88%, 62%). (Table 2)

However, overall cases of any PCR+ were reduced by 67% (95%CI 49%, 78%) after a single SD vaccine suggesting the potential for a substantial reduction in transmission.

Participants included in the analysis of a single dose were further explored to identify differences in baseline characteristics between those who received a booster dose (and are censored in the analysis at that time point) and those who did not receive a booster dose (and have longer follow up). Statistically significant differences between these groups were found for age, sex, health or social care worker status, dose (LD/SD, SD/SD), country, ethnicity, and follow up time (all $p<0.001$) (Table S1). Participants receiving a booster dose were older (median age 40 years versus 36 years), with a higher proportion of males (44.2% versus 39.0%) and non-white (24.1% versus 20.8%), and a lower proportion of health or social care workers (60.1% versus 65.7%) when compared with the group of participants who did not receive a booster dose. A lower proportion of UK COV002 participants receiving a low dose prime vaccination belonged to the boosted group, compared with the non-boosted group (33.4% versus 40.9%). Follow up time differed between the two groups, as expected due to the censoring of participants at the time of booster dose (median time 41 days versus 111 days in boosted and non-boosted groups, respectively).

Modelling of the change in vaccine efficacy against primary symptomatic COVID-19 (from 2 weeks after the second dose) showed that efficacy was high after a 2 month interval and continued to increase with longer dose interval. (Figure 1). There was less variation in the time between doses for the LD/SD cohort with most data accruing in those who had approximately 3 months between first and second doses, and efficacy remained high during this period (Figure 1C).Vaccine efficacy after 2 standard doses rose from 54.9% (32.7%, 69.7%) with an interval < 6 weeks, to 82.4% (62.7%, 91.7%) when spaced more than 12 weeks apart (Table 1).

Efficacy against asymptomatic infections in the UK showed a similar pattern with efficacy estimates increasing with the interval between doses, however the number of cases available for each analysis was limited within each dose interval bracket and confidence intervals were wide. (Table 1, Figure S2)

Anti-SARS-CoV-2 spike IgG responses to a single dose of vaccine measured by standardised ELISA decayed log-linearly over a 6 month period. Geometric mean antibody decay estimated in a linear model showed a decline from the peak at day 28, of 33% by day 90 (GMR 0.66, 95% CI 0.59, 0.74) and by 64% by day 180 (GMR 0.36, 95% CI 0.27, 0.47) (Figure 2B).

Participants aged 18 to 55 years who received the second vaccine more than 12 weeks after the first had antibody titres 2-fold higher than those who received the second dose within 6 weeks of their initial vaccination (GMR 2.05, 95%CI 1.99, 2.12), Figure 3, Table S4.

Similarly, neutralising antibody titres measured by pseudovirus were higher after a longer interval before the second dose. Figure S3, Table S3.

Plotting SARS-CoV-2 spike IgG against vaccine efficacy for each dose interval showed a clear relationship between binding antibody and vaccine protection, as well as between neutralisation antibody and vaccine efficacy, suggesting potential correlates of protection (Figure 4).

Discussion

Here we report a prespecified full primary analysis of the efficacy of the ChAdOx1 nCoV-19 vaccine, including 332 symptomatic cases of COVID19 in an analysis population of 17,177 study participants, confirming the efficacy reported in our published interim analysis[14] (131 cases reported in the interim analysis). In this updated analysis there were no additional hospitalisations or severe cases in the ChAdOx1 nCoV-19 vaccinated group with no cases from 10 days after the first dose of the vaccine compared with a total of 22 in the control group. These new analyses provide important verification of the interim data that underpinned the emergency use authorisation of the vaccine in the UK by the MHRA on 30th December 2020[15] and many other international regulators since the end of 2020 including India, Nepal, Bangladesh, Argentina, Brazil, Mexico and many others.

The analysis presented here provides strong evidence for the efficacy of two standard doses of the vaccine (SD/SD), which is the regimen approved by the MHRA and other regulators. Following regulatory approval, a key question for policymakers to plan the optimal approach to roll out, is the optimal dose interval, which is assessed in this report through post-hoc exploratory analyses. Two criteria which contribute to decision-making in this area are the impact of prime-boost interval on protection after the second dose; and the degree to which the vaccinated individual is at risk of infection during the pre-boost period, either due to reduced efficacy with a single dose, or rapid waning of efficacy prior to the second vaccination.

Exploratory analyses are presented in this report that show protection with dosing intervals between 4 weeks and ≥12 weeks and that a longer interval provides better protection post-boost, without compromising protection in the three month period until the second dose is administered.

A single standard dose of ChAdOx1 nCoV-19 provided 76% protection overall against symptomatic COVD-19 in the first 90 days after vaccination and with no evidence of significant waning of protection during this period. It is not clear how long protection might last with a single dose as follow up is currently limited to the time periods described here, and, for this reason, a second dose of vaccine is recommended.

A second dose of ChAdOx1 nCoV-19 induces increased neutralising antibody levels[10,12] and is likely necessary for long lasting protection. However, where there is a limited supply of vaccine, a policy of initially vaccinating a larger cohort with a single dose may provide better overall population protection than vaccinating half the number of individuals with 2 doses in the short term. With the evidence available at this time, it is anticipated that a second dose is still required to potentiate long-lived immunity. Recent modelling of delayed boosting suggests that even in the presence of substantial waning of first dose efficacy, programmes that delay a second dose in order to vaccinate a larger proportion of the population, result in greater immediate overall population protection.[16]

In our study, vaccine efficacy was higher, after the second dose, in those with a longer prime-boost interval, reaching 82.4% in those with a dosing interval of 12 weeks or more. Point estimates of efficacy were lower with shorter dosing intervals, though it should be noted that there is some uncertainty as confidence intervals overlap. Higher binding and neutralising antibody titres were observed in sera at the longer prime-boost interval, suggesting that, assuming there is a relationship between the humoral immune response and efficacy, these may be true findings and not artefacts of the data. Greater protective efficacy associated with stronger immune responses after a wider prime-boost interval have been seen with other vaccines such as influenza, Ebola, malaria[17-19]. The findings presented here for the ChAdOx1 nCoV-19 vaccine are consistent with current policy recommendations in different countries to use dose intervals from 4-12 weeks for this vaccine.

In our interim analysis, we identified a higher efficacy in a subgroup analysis of those who received the LD/SD regimen[14]. This finding is confirmed in the current analysis, but with further

data available, we show that the enhanced immunogenicity and efficacy with this regimen may be partly driven by the longer dosing interval that was a feature of this group, further supporting the observation of a relationship between dose interval and efficacy in the SD/SD group discussed above and supported by emergency use authorisation. The SD/SD regimen is preferred operationally as it is more straightforward to deliver a vaccine with one dosage, and because there are more immunogenicity and efficacy data to support its use.

A further important question is whether vaccines can provide impact against transmission, and therefore combined with physical distancing measures contribute to reductions in human to human transmission of the virus. While transmission studies per se were not included in the analysis, swabs were obtained from volunteers every week in the UK study, regardless of symptoms, to allow assessment of the overall impact of the vaccine on risk of infection and thus a surrogate for potential onward transmission. If there was no impact of a vaccine on asymptomatic infection, it would be expected that an efficacious vaccine would simply convert severe cases to mild cases and mild cases to asymptomatic, with overall PCR positivity unchanged. A measure of overall PCR positivity is appropriate to assess whether there is a reduction in the burden of infection. Analyses presented here show that a single standard dose of the vaccine reduced PCR positivity by 67%, and that, after the second dose, the SD/SD schedule reduced PCR positivity by 49.5% overall. These data indicate that ChAdOx1 nCoV-19, used in the authorised schedules, may have a substantial impact on transmission by reducing the number of infected individuals in the population.

No correlate of protection has yet been defined for COVID-19 vaccines, however the data presented here on the relationship between antibody levels and efficacy suggest that humoral immunity may play a role. In contrast, high protective efficacy recorded early after a single dose of vaccine in this study, and also seen with other vaccines from different manufacturers[3], suggests other immunological mechanisms may be at play early after the first dose, as lower levels of neutralising antibody are detected after a single dose. Further study of correlates of protection is ongoing.

Limitations

There are some limitations to the analyses presented in this report. The studies were not designed to determine if vaccine efficacy differed by dose interval and the presence of data of varying intervals arose due to the logistics of running large-scale clinical trials in a pandemic setting. These are therefore post-hoc exploratory analyses only with potential for multiple sources of bias, and were not pre-specified. However, the analyses are presented here to provide a rigorous peer-reviewed interrogation of updated data that reflect the approach that is currently being used to underpin the deployment of ChAdOx1 nCoV-19 in the response to the pandemic. The previous interim analysis was carefully considered by regulators and policy-makers and is aligned with the findings presented here.

In our data, there is currently limited length of follow-up after the second dose and follow-up tends to be longer in those who were boosted early and thus have shorter prime-boost intervals. Furthermore, the participants who contribute to the analysis of single dose efficacy are a mixture of participants with events occurring prior to their boost dose, and participants who did not receive a boost dose. These two cohorts differ in some key characteristics.

It is not clear what effect each of these individual sources of variation in the data have on vaccine efficacy estimates. However, the same trend seen with efficacy is also seen in the immunological data, suggesting an underlying biological mechanism.

Conclusion

Vaccination programmes aimed at vaccinating a large proportion of the population with a single dose, with a second dose given after a 3 month period may be an effective strategy for reducing disease, and may be the optimal for rollout of a pandemic vaccine when supplies are limited in the short term.

Tables and Figures

Table 1 Efficacy of ChAdOx1 nCoV-19 after two doses

Cases > 14 days after second dose	N cases	ChAdOx1 nCoV-19	Control	Vaccine Efficacy (95% CI)
Primary symptomatic COVID-19	332	84/8597 (1.0%)	248/8580 (2.9%)	66.7% (57.4%, 74.0%)
SD/SD	271	74/7201 (1.0%)	197/7178 (2.7%)	63.1% (51.8%, 71.7%)
LD/SD	61	10/1396 (0.7%)	51/1402 (3.6%)	80.7% (62.1%, 90.2%)¥
Asymptomatic/Unknown infection (COV002 UK only)	130	57/4071 (1.4%)	73/4136 (1.8%)	22.2% (-9.9%, 45.0%)
SD/SD	83	41/2692 (1.5%)	42/2751 (1.5%)	2.0% (-50.7%, 36.2%)
LD/SD	47	16/1379 (1.2%)	31/1385 (2.2%)	49.3% (7.4%, 72.2%)¥†
Any PCR+	507	161/8597 (1.9%)	346/8580 (4.0%)	54.1% (44.7%, 61.9%)
SD/SD	390	132/7201 (1.8%)	258/7178 (3.6%)	49.5% (37.7%, 59.0%)
LD/SD	117	29/1396 (2.1%)	88/1402 (6.3%)	67.6% (50.8%, 78.7%)¥
Symptomatic COVID-19 Cases > 14 days after second dose	**N cases**	**ChAdOx1 nCoV-19**	**Control**	**Vaccine Efficacy (95% CI)**
Time between first and second dose SD/SD				
< 6 weeks	111	35/3900 (0.9%)	76/3860 (2.0%)	54.9% (32.7%, 69.7%)
6-8 weeks	64	20/1103 (1.8%)	44/1004 (4.4%)	59.9% (32.1%, 76.4%)*
9-11 weeks	43	11/905 (1.2%)	32/957 (3.3%)	63.7% (28.0%, 81.7%)¥
≥12 weeks	53	8/1293 (0.6%)	45/1356 (3.3%)	82.4% (62.7%, 91.7%)†
Time between first and second dose SD/SD or LD/SD				
< 6 weeks	111	35/3915 (0.9%)	76/3875 (2.0%)	54.9% (32.7%, 69.7%)
6-8 weeks	64	20/1115 (1.8%)	44/1018 (4.3%)	59.7% (31.7%, 76.2%)*
9-11 weeks	66	14/1529 (0.9%)	52/1593 (3.3%)	72.3% (50.0%, 84.6%)¥
≥12 weeks	91	15/2038 (0.7%)	76/2093 (3.6%)	80.7% (66.5%, 88.9%)†
Asymptomatic COVID-19 Cases > 14 days after second dose (COV002 only)	**N cases**	**ChAdOx1 nCoV-19**	**Control**	**Vaccine Efficacy (95% CI)**
Time between first and second dose SD/SD				
< 6 weeks	17	9/728 (1.2%)	8/733 (1.1%)	-11.4% (-189.2%, 57.1%)
6-8 weeks	21	14/528 (2.7%)	7/476 (1.5%)	-80.4% (-348.1%, 27.4%)
9-11 weeks	17	6/599 (1.0%)	11/666 (1.7%)	39.9% (-62.3%, 77.8%)¥

≥12 weeks	28	12/837 (1.4%)	16/876 (1.8%)	22.8% (-63.3%, 63.5%)¥
Time between first and second dose SD/SD or LD/SD				
< 6 weeks	17	9/728 (1.2%)	8/733 (1.1%)	-11.4% (-189.2%, 57.1%)
6-8 weeks	21	14/538 (2.6%)	7/488 (1.4%)	-81.9% (-351.8%, 26.8%)
9-11 weeks	43	17/1223 (1.4%)	26/1302 (2.0%)	31.6% (-26.0%, 62.8%)¥
≥12 weeks	49	17/1582 (1.1%)	32/1613 (2.0%)	47.2% (5.0%, 70.7%)¥

VE and 95% confidence intervals have been calculated via robust Poisson models, adjusting for study (COV001, COV002, COV003, COV005) and age group (18-55 years, 56-69 years, ≥70 years). Models for asymptomatic/unknown infections do not adjust for study.
¥ Calculated from an unadjusted robust Poisson model.

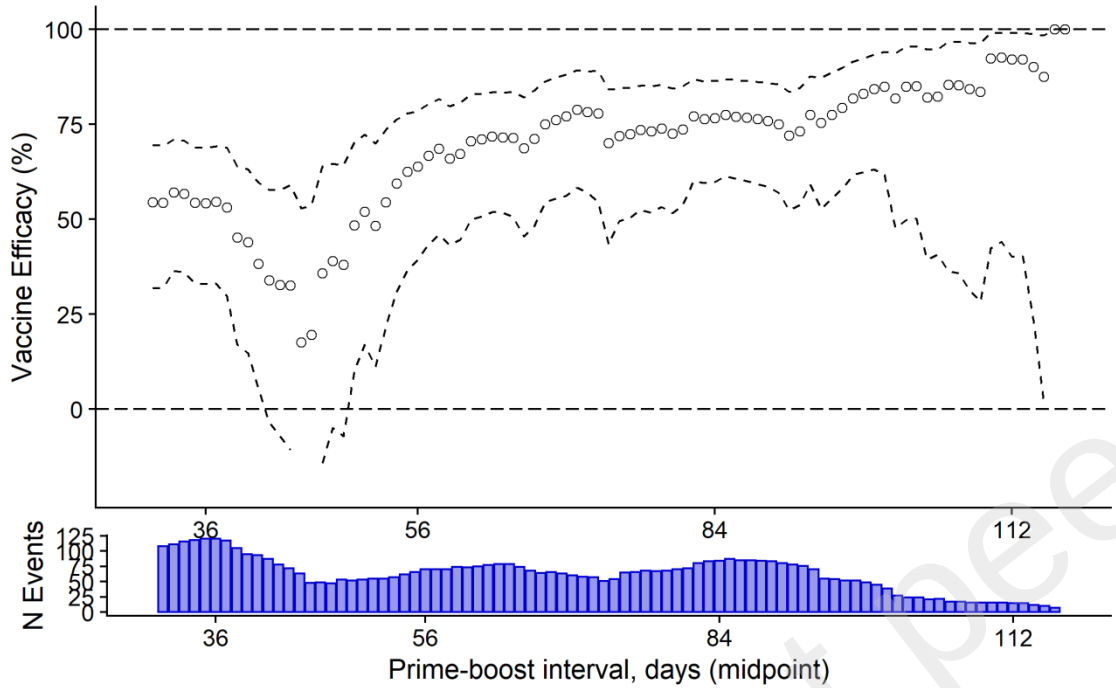
Table 2 Efficacy of ChAdOx1 nCoV-19 after a single dose

Symptomatic COVID-19 Cases > 21 days after a single SD dose	**N cases**	**ChAdOx1 nCoV-19**	**Control**	**Vaccine Efficacy (95% CI)**
Time since first standard dose				
22 to 30 days	37	7/ 9257	30/ 9237	77% (47%, 90%)
31 to 60 days	28	6/ 7147	22/ 7110	73% (33%, 89%)
61 to 90 days	23	4/ 2883	19/ 2974	78% (36%, 93%)
90 to 120 days	10	4/ 1368	6/ 1404	32% (-142%, 81%)
22 to 90 days	**88**	**17**	**71**	**76% (59%, 86%)**
Asymptomatic COVID-19 infections > 21 days after a single SD dose	**N cases**	**ChAdOx1 nCoV-19**	**Control**	**Vaccine Efficacy (95% CI)**
Time since first dose				
22 to 30 days	12	6/9257	6/9237	0.2% (-209%, 68%)
31 to 60 days	11	5/7147	6/7110	17% (-172%, 75%)
61 to 90 days	1	0/2883	1/2974	
90 to 120 days	5	1/1368	4/1404	
22 to 90 days	**24**	**11**	**13**	**16% (-88%, 62%)**
Any PCR+ 22 to 90 days	**112**	**28**	**84**	**67% (49%, 78%)**

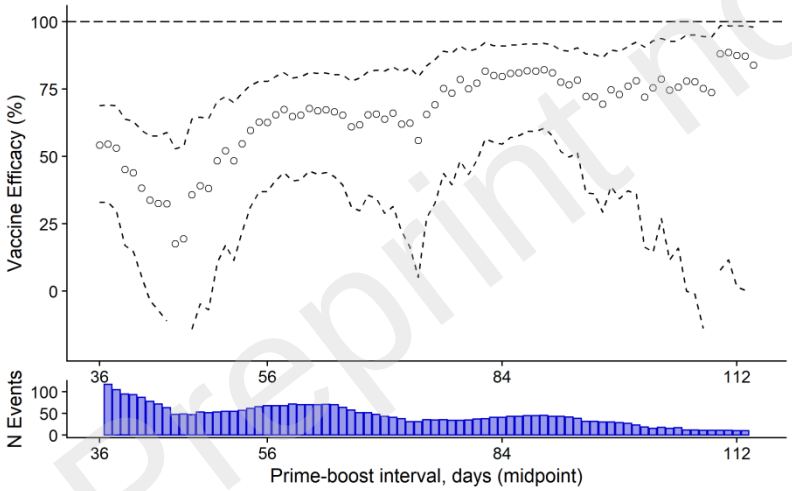
VE and 95% confidence intervals have been calculated via robust Poisson models. Participants were censored in the analysis at the upper limit of the time window.

Figure 1 Vaccine efficacy against primary symptomatic COVID-19 by interval between first and second dose, A) after SD/SD or LD/SD administration, B) after SD/SD, and C) after LDSD administration

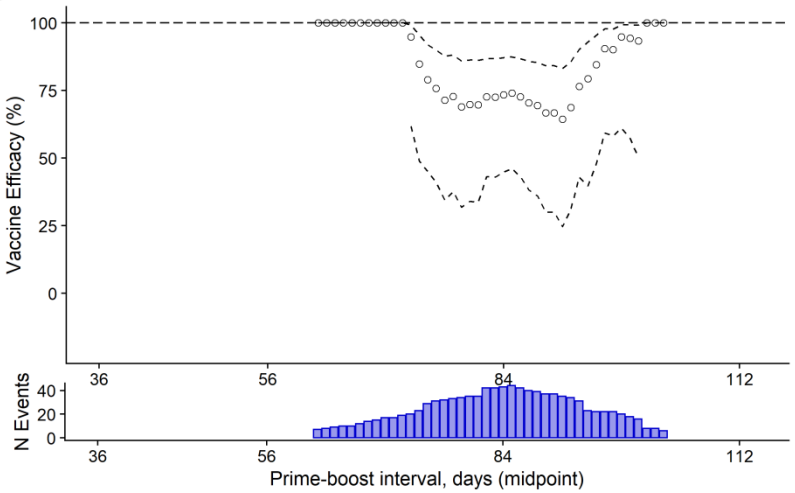
A)



B)



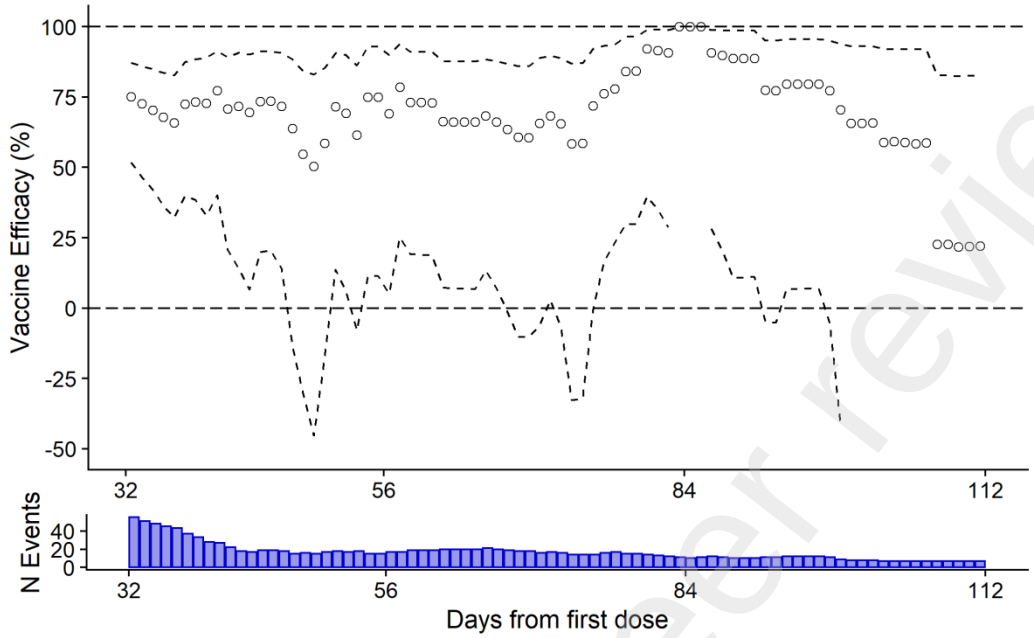
C)



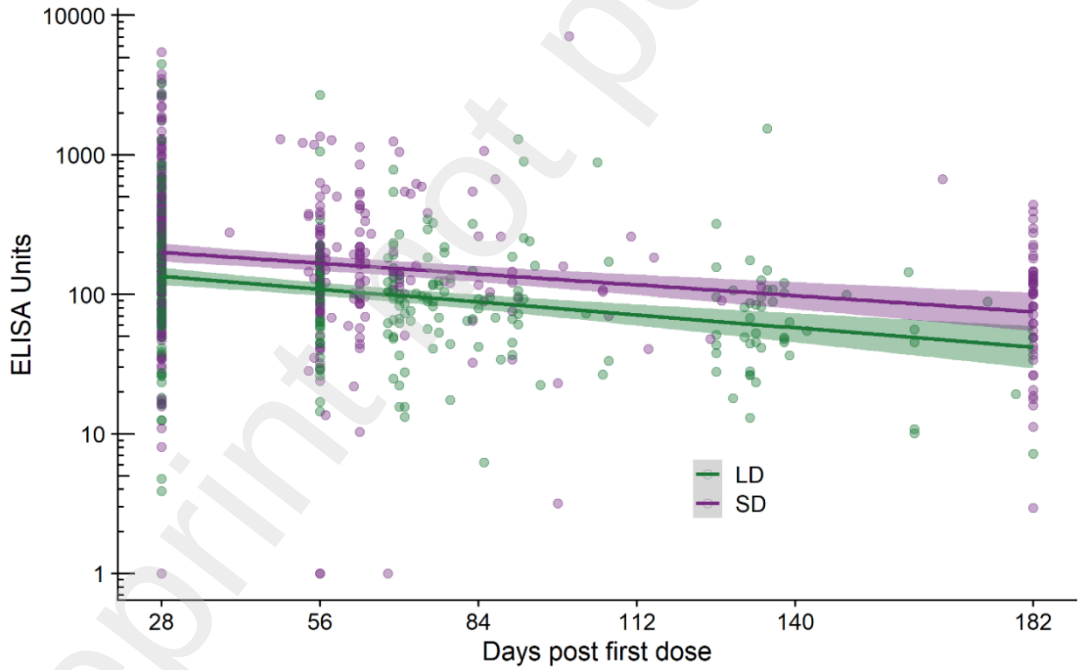
Each dot represents one estimate of vaccine efficacy in a subset of participants who received two doses of vaccine with a gap between first and second dose within a 20 day range. The x axis shows the midpoint of the 20 day range for dosing. Dotted lines show 95% confidence intervals for each dot point estimate of VE. Bar charts below each plot show the number of events included in each efficacy analysis.

Figure 2 Vaccine efficacy over time for standard dose ChAdOx1 nCoV-19 (A), and persistence of anti-SARS-CoV-2 spike IgG by standardised ELISA antibody (B), after a single dose of either standard of low dose ChAdOx1 nCoV-19

A)



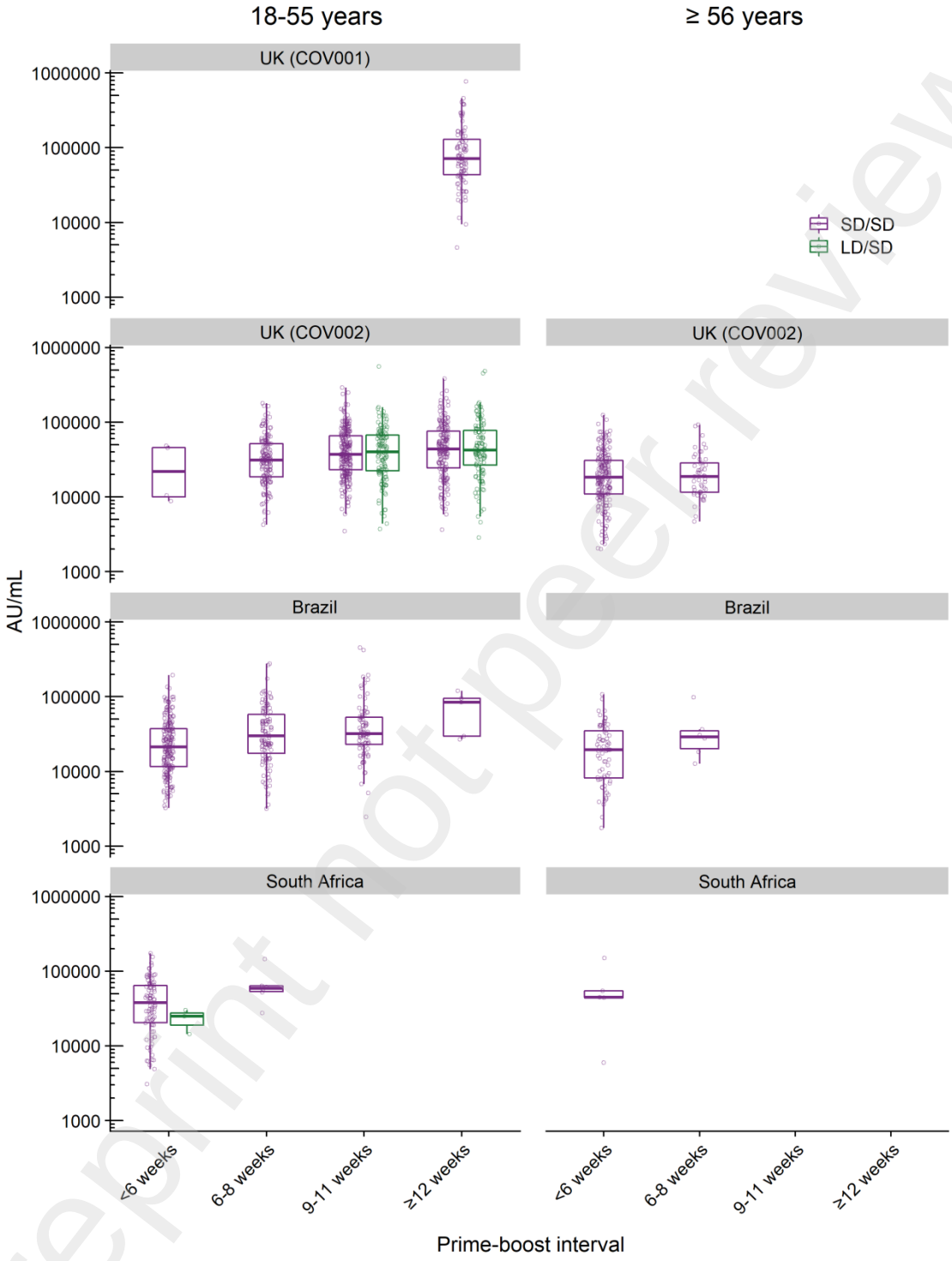
B)



A). Each dot represents a 28 day range of follow up with the x axis showing the midpoint of the range. For each estimate of VE (each dot), cases were included if they occurred within the 21 day range, or censored if not. Dotted lines show 95% confidence intervals for each dot point estimate of VE. The bar chart shows the number of cases included in each model. B). Solid line shows estimates from a linear model with shaded areas showing standard

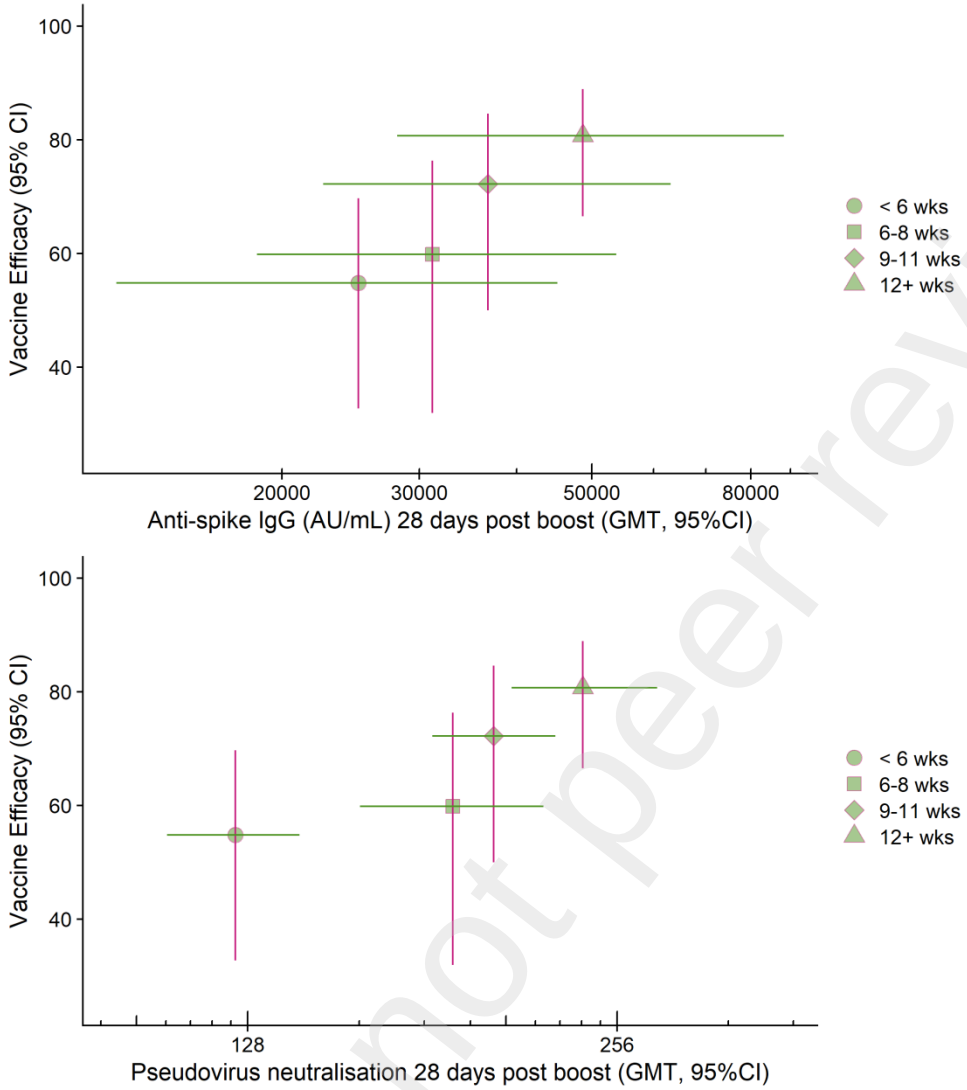
errors. Mean antibody decay estimated in the linear model showed a decline from the peak at day 28, of 33% by day 90 (GMR 0.66, 95% CI 0.59, 0.74) and by 64% by day 180 (GMR 0.36, 95% CI 0.27, 0.47).

Figure 3 SARS-CoV-2 anti-spike IgG responses by multiplex immunoassay at 28 days after the second dose in SD/SD and LD/SD recipients by interval between first and second dose



*participants who were PCR+ prior to the blood sample taken at day 28 post boost were removed from the analyses

Figure 4 Relationship between binding and neutralising antibody 28 days post second dose, and vaccine efficacy against primary symptomatic COVID-19



Vaccine efficacy with 95% CI against primary symptomatic COVID-19 in SD/SD and LD/SD participants combined are shown plotted against A) the GMT (95% CI) of anti-SARS-CoV-2 spike IgG from an immunoassay, and B) the GMT (95%CI) pseudovirus neutralisation, for each prime boost interval.

Supplementary tables and figures

Figure S1 CONSORT diagram

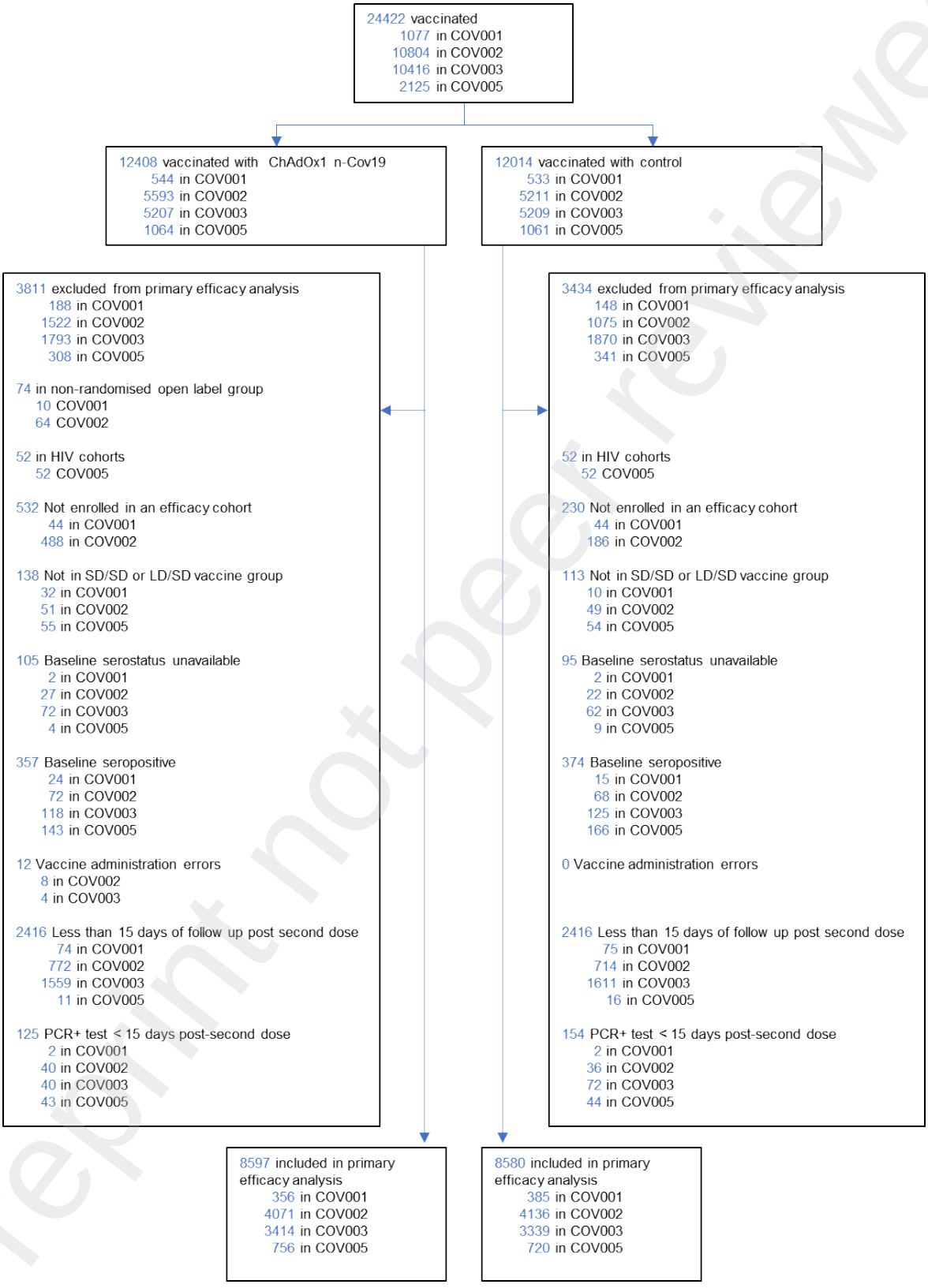


Table S1 Hospitalisation for COVID-19 (safety population, any dose)

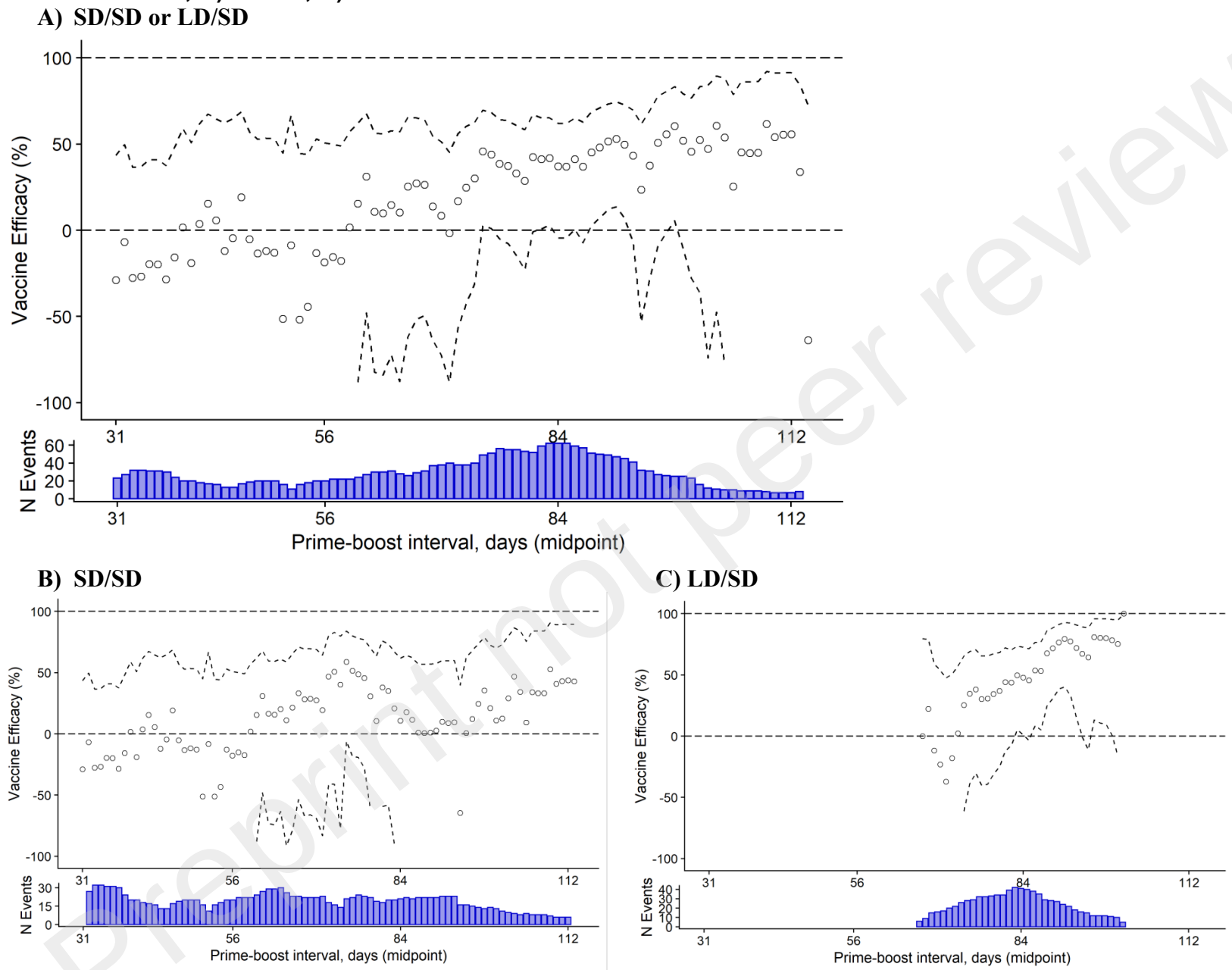
	N cases	ChAdOx1 nCoV-19 N=12408	Control N=12104
< 22 days after a single dose	9	2	7
>= 22 days after the first dose and < 15 days post booster dose	6	0	6
>= 15 days post booster dose	9	0	9

Table S2 Factors related to receipt of a booster dose

	Participants who received booster N%	Participants who were not boosted N%	P value*
Age, median [IQR]	40.0 (30.1 - 52.0)	36.3 (28.0 - 48.0)	<0.001
18 – 55 years, n (%)	15841/19150 (82.7%)	2377/2752 (86.4%)	<0.001
56 – 69 years, n (%)	2218/19150 (11.6%)	247/2752 (9.0%)	
70+ years, n (%)	1091/19150 (5.7%)	128/2752 (4.7%)	
Sex			
Female, n (%)	10679/19150 (55.8%)	1680/2752 (61.0%)	<0.001
Male, n (%)	8471/19150 (44.2%)	1072/2752 (39.0%)	
Health or social care worker, n (%)	11518/19150 (60.1%)	1809/2752 (65.7%)	<0.001
Dose group (COV002 only)			
SD, n (%)	5782/8676 (66.6%)	693/1173 (59.1%)	<0.001
LD, n (%)	2894/8676 (33.4%)	480/1173 (40.9%)	
Country (single SD cohort only)			
UK (SD), n (%)	6566/16222 (40.5%)	838/2272 (36.9%)	<0.001
Brazil (SD), n (%)	8194/16222 (50.5%)	1389/2272 (61.1%)	
South Africa (SD), n (%)	1462/16222 (9.0%)	45/2272 (2.0%)	
Ethnicity			
White, n (%)	14532/19150 (75.9%)	2180/2751 (79.2%)	<0.001
Non-white, n (%)	4615/19150 (24.1%)	571/2751 (20.8%)	
Follow up time, days, median [IQR]	41.0 (31.0 - 79.0)	111.0 (44.0 - 178.0)	<0.001

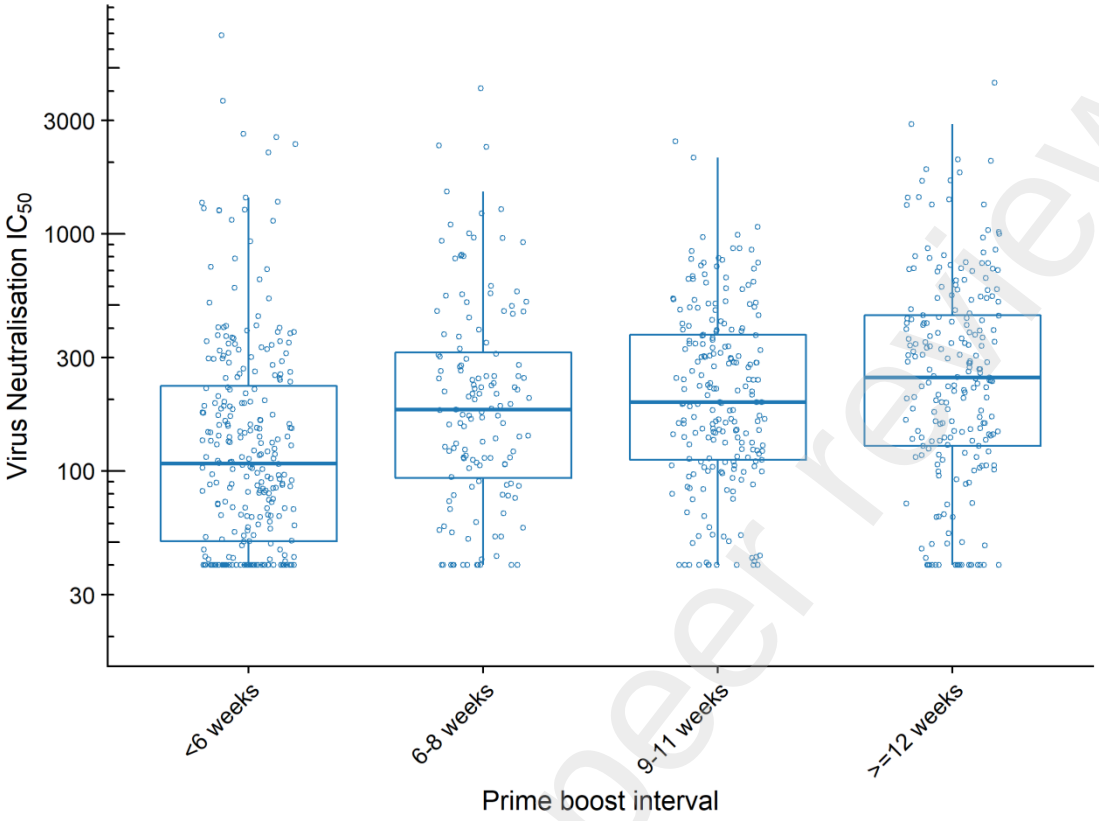
*p-values from Chi-squared tests, Wilcoxon Rank Sum tests (continuous age and follow-up time) and Cochran-Armitage tests (ordinal age groups).

Figure S2 Vaccine efficacy against asymptomatic/unknown infection by interval between first and second dose after, A) SD/SD or LD/SD, B) SD/SD, C) LD/SD administration



Each dot represents one estimate of vaccine efficacy in a subset of participants who received two doses of vaccine with a gap between first and second dose within a 20 day range. The x axis shows the midpoint of the 20 day range for dosing. Dotted lines show 95% confidence intervals for each dot point estimate of VE. Solid line shows a cubic spline smooth function for VE.

Figure S3 Neutralising antibody 28 days after a booster dose, measured in pseudovirus assay (Monogram IC50)



Participants who were PCR+ prior to the blood sample taken at day 28 post boost were removed from the analyses. Analysis includes SD/SD and LD/SD recipients.

Table S3 Neutralising antibody 28 days after a booster dose, measured in pseudovirus assay (Monogram IC50)

Prime-boost interval	N	Median [IQR]	GMT (95% CI)
<6 weeks	272	107 [50, 228]	125 (110, 141)
6-8 weeks	136	181 [93, 315]	188 (158, 223)
9-11 weeks	210	194 [111, 375]	203 (181, 228)
≥12 weeks	217	248 [128,452]	240 (210, 276)

Table S4 SARS-CoV-2 anti-spike IgG responses by multiplex immunoassay at 28 days after the second dose in SD/SD recipients by interval between first and second dose

Age group	Study	Prime-boost interval	ChAdOx1 nCoV-19				Control			
			N	Median [IQR]	GMT (95% CI)	GMR (95% CI)	N	Median [IQR]	GMT (95% CI)	GMR (95% CI)
18-55 years	Overall (SD/SD)	<6 weeks	297	25338 [12252, 45396]	23467 (21031, 26185)	ref	295	67 [33, 136]	78 (66, 92)	ref
		6-8 weeks	267	31115 [18540, 53382]	29450 (26149, 33168)	1.25 (1.19, 1.32)	196	56 [16, 169]	71 (58, 86)	0.91 (0.80, 1.02)
		9-11 weeks	323	36109 [22958, 61687]	37446 (34430, 40726)	1.60 (1.54, 1.65)	232	50 [16, 101]	62 (51, 75)	0.79 (0.68, 0.90)
		≥12 weeks	283	51329 [28835, 93582]	51401 (46276, 57094)	2.19 (2.12, 2.26)	173	53 [16, 98]	56 (47, 66)	0.72 (0.61, 0.83)
	Overall (SD/SD and LD/SD)	<6 weeks	300	25198 [12267, 45202]	23453 (21040, 26142)	ref	300	68 [33, 137]	78 (66, 91)	ref
		6-8 weeks	267	31115 [18540, 53382]	29450 (26149, 33168)	1.26 (1.19, 1.33)	196	56 [16, 169]	71 (58, 86)	0.92 (0.80, 1.03)
		9-11 weeks	447	36758 [22588, 63086]	36761 (33917, 39843)	1.57 (1.51, 1.62)	323	48 [16, 95]	57 (49, 67)	0.74 (0.64, 0.83)
		≥12 weeks	397	48658 [28131, 88231]	47942 (43638, 52670)	2.04 (1.98, 2.11)	259	46 [16, 90]	51 (45, 59)	0.66 (0.56, 0.75)
≥56 years	Overall (SD/SD)	<6 weeks	279	20371 [10553, 35752]	18909 (16930, 21120)	ref	273	34 [16, 78]	40 (35, 46)	ref
		6-8 weeks	55	20561 [12978, 34178]	21947 (18180, 26495)	1.16 (1.05, 1.27)	56	35 [16, 75]	42 (32, 55)	1.05 (0.91, 1.18)
Country Level Estimates										
18-55 years	COV001 (UK) SD/SD	≥12 weeks	92	71270 [43306, 129621]	76070 (62987, 91872)		52	47 [16, 120]	52 (37, 73)	
	COV002 (UK) SD/SD	<6 weeks	4	27818 [10052, 45897]	21119 (4900, 91029)		2	74 [68, 79]	73 (10, 539)	
		6-8 weeks	151	31115 [18540, 51312]	29257 (25264, 33880)		81	38 [16, 113]	52 (39, 70)	
		9-11 weeks	238	36896 [23014, 65786]	38421 (35006, 42169)		155	47 [16, 98]	54 (44, 66)	
		≥12 weeks	186	43936 [24332, 76216]	42170 (37386, 47566)		114	57 [16, 92]	57 (46, 69)	
	COV002 (UK) LD/SD	9-11 weeks	124	39994 [21988, 67187]	35034 (28890, 42485)		91	39 [16, 86]	47 (37, 60)	
		≥12 weeks	114	42138 [24638, 77156]	40326 (33103, 49127)		86	38 [16, 70]	43 (34, 53)	
	COV003 (Brazil) SD/SD	<6 weeks	202	21104 [11651, 37236]	20675 (18222, 23458)		202	70 [33, 155]	81 (67, 98)	
		6-8 weeks	110	29108 [16760, 56978]	28586 (23264, 35125)		113	76 [40, 206]	90 (69, 117)	
		9-11 weeks	85	31871 [22997, 53258]	34847 (28912, 42000)		77	60 [16, 102]	81 (54, 122)	
		≥12 weeks	5	84281 [29585, 94946]	59814 (25145, 142286)		7	95 [16, 100]	73 (14, 394)	
	COV005 (South Africa) SD/SD	<6 weeks	91	37316 [19675, 63656]	31229 (25273, 38588)		91	54 [16, 112]	71 (52, 99)	
		6-8 weeks	6	59070 [53276, 63377]	59982 (34400, 104587)		2	28 [22, 33]	25 (0, 5993)	
	COV005 (South Africa) LD/SD	<6 weeks	3	24956 [19684, 27528]	22121 (8548, 57250)		5	115 [16, 172]	65 (13, 319)	
≥56 years	COV002 (UK) SD/SD	<6 weeks	202	19860 [11688, 33899]	19282 (17144, 21688)		202	25 [16, 72]	38 (33, 45)	
		6-8 weeks	49	20356 [12462, 31414]	20907 (17168, 25460)		54	34 [16, 70]	39 (30, 51)	
	COV003 (Brazil) SD/SD	<6 weeks	72	21019 [8503, 37859]	16898 (12967, 22021)		67	37 [16, 82]	43 (33, 56)	
		6-8 weeks	6	31811 [22330, 38513]	32632 (15397, 69159)		2	269 [236, 302]	261 (11, 6286)	

	COV005 (South Africa) SD/SD	<6 weeks	5	49287 [48849, 60514]	43366 (9756, 192765)		4	345 [83, 618]	164 (10, 2691)	

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