# **Safety and Immunogenicity of ChAdOx1 nCoV-19 (AZD1222) vaccine administered in a prime-boost regimen in older adults (COV002): a Phase 2/3 single blind, randomised controlled trial**

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# **Summary**

**Background**

Older adults are at higher risk of severe disease and death if they develop COVID-19 and are therefore a priority for immunisation should an efficacious vaccine be developed. Immunogenicity of vaccines is often poorer in older adults as a result of immunosenescence. We recently reported the immunogenicity of a novel viral vectored vaccine, ChAdOx1 nCoV-19 (AZD1222), in young adults, and now describe the safety and immunogenicity of this vaccine in a wider age range including adults aged over 70 years.

**Methods**

Healthy adults aged 18-55, 56-69 or 70+ years were enrolled at 2 UK clinical research facilities in immunogenicity subgroups of a phase 2 component of a Phase 2/3 randomised controlled trial,. They were randomised to receive either intramuscular ChAdOx1 nCoV-19 (at either low [LD] or standard dose [SD]) or a control vaccine, MenACWY, using block randomisation. Participants aged over 55 years were further randomised to receive single or two dose schedules spaced 28 days apart. The specific objectives were to assess the safety and humoral and cellular immunogenicity of a single or two-dose schedule in adults aged over 55 years. Humoral responses at baseline and following vaccination were assessed using an in-house standardised ELISA, a multiplex immunoassay (MIA), and a live SARS-CoV-2 microneutralisation assay (MNA80). Cellular responses were assessed using an *ex-vivo* interferon-γ enzyme-linked immunospot assay. The co-primary outcomes were efficacy, as measured by cases of symptomatic virologically confirmed COVID-19, and safety. Participants, but not trial staff, were blinded to vaccine allocation. Analyses were by group allocation. Here, we report the preliminary findings on safety, reactogenicity, and cellular and humoral immune responses. The study is ongoing and is registered at Clinicaltrials.gov, NCT 04400838, and ISRCTN, 15281137.

**Findings**

From 30th May to 8th August 2020, 560 participants (420 given ChAdOx1 nCoV-19 and 140 given MenACWY) were enrolled into study subgroups in each of three age bands 18-55, 56-69 or 70+ years respectively. Local and systemic reactions were more common in ChAdOx1 nCoV-19 recipients than control vaccine recipients, were similar in nature to those previously reported (injection site pain, feeling feverish, muscle ache, headache), but were less common in older adults than younger adults. In those receiving two standard doses (SD) of ChAdOx1 nCoV-19, local reactions were reported in 88%, 73%, and 61% of participants aged 18-55, 56-69, and 70+ years respectively, and systemic reactions in 86%, 77%, and 65% of participants after the first dose. Thirteen serious adverse events occurred during the study period, none of which were considered related to either study vaccine. Anti-spike IgG responses 28 days after a booster dose were similar across the three age cohorts, SD groups: 18-55 years, median 20713, IQR 13898-33550; 56-69 years, median 16170, IQR 10233-40353; 70+ years median 17561, IQR 9705-37796, p=0·6834).

Neutralising antibody titres after a booster dose were similar across all age groups: MNA80 at day 42 in SD groups, 18-55 years: median 193, IQR, 113, 238; 56-69 years: median 144, IQR 119, 347; 70+ years: median 161 IQR, 73, 323; p=0·400). By 14 days after boosting, 208 of 209 boosted participants had neutralising antibody.

T cell responses peaked at day 14 after a single standard dose of ChAdOx1 nCov-19 (18-55 median 1187 SFC IQR 841-2428 n=24; 56-69 median 797 IQR 383-1817 n=29; 70+ median 977 IQR 458-1914 n=48). Higher anti-ChAdOx1 vector neutralising antibody at the time of the booster dose was associated with lower anti-spike IgG antibody responses after the booster (p=0·0374) but there was no significant association with T cell responses (p=0·221).

**Interpretation**

ChAdOx1 CoV-19 appears to be better tolerated in older adults than younger adults and has similar immunogenicity across all age groups after a booster dose.

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**Research in context**

**Evidence before this study**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the causative agent of COVID-19 in January, 2020. There are currently no licensed vaccines to prevent COVID-19. We have previously demonstrated that ChAdOx1 nCoV-19 elicits potent neutralising antibody and T cell responses after booster vaccination in adults aged 18-55 years. We searched PubMed for research articles published between database inception and October 14, 2020, using the terms “SARS-CoV-2”, “vaccine”, “clinical trial”, and “phase”. No language restrictions were applied. We identified published clinical trial data on seven other vaccine candidates using these criteria. Two recombinant viral vectored vaccines have been tested in clinical trials. A single dose adenovirus-5 (Ad5) vector-based vaccine (CanSino Biological/Beijing Institute of Biotechnology, China) elicited neutralising antibodies and T cell responses in a dose dependent manner, but was less immunogenic in individuals >55 years of age. A heterologous prime-boost Ad5/Ad26 vectored vaccine schedule (Gamaleya Research Institute, Russia) generated neutralising antibody and cellular responses in adults <60 years of age. Two clinical trials utilised a nucleoside-modified mRNA vaccine in a 2-dose regimen. One vaccine (Pfizer, USA) generated neutralising antibodies in adults 18-55 years old in a dose dependent manner, at similar levels to convalescent sera. A further mRNA vaccine, (Moderna, USA) was given to older adults. The vaccine was tolerated, with neutralising antibodies induced in a dose-dependent manner which increased after a second dose. Binding- and neutralizing-antibody responses appeared to be similar to those previously reported among vaccine recipients between the ages of 18 and 55 years. Two inactivated viral vaccines have also demonstrated neutralising antibody in a dose dependent manner in adults aged 18-59 years (SinoPharm, China) or adults 18-59 and >60 years (SinoPharm, China). Lastly, a clinical trial of a nanoparticle vaccine composed of trimeric SARS-CoV-2 spike glycoproteins and Matrix-M1 adjuvant (Novavax, USA) reported results of a two-dose schedule given three weeks apart, in healthy adults less than 60 years of age. This vaccine was well tolerated and induced neutralization responses that exceeded those measured in convalescent serum of symptomatic patients.

**Added value of this study**

This study is the fourth published clinical trial of a vaccine against SARS-CoV-2 tested in an older adult population. The vaccine was safe and well tolerated, with reduced reactogenicity in older adults. Antibody responses against the SARS-CoV-2 spike protein were induced in all age groups and were boosted and maintained at 28 days post booster vaccination, including those in the over 70-year group. Cellular immune responses were also induced in all age and dose groups, peaking at day 14 post vaccination.

**Implications of the available evidence**

The populations at greatest risk of serious Covid-19 disease include people with coexisting health conditions and older adults. The immune correlates of protection against SARS-CoV-2 have not yet been determined but it is presumed that neutralizing antibodies are associated with protection and in a Covid-19 nonhuman primate challenge model, neutralizing antibody correlated with protection. This has led to the use of neutralization assays to assess immune responses in recent human Covid-19 vaccine trials. Immunisation with ChAdOx1 nCoV-19 results in development of neutralizing antibodies against SARS-CoV-2 in almost 100% of participants including older adults without severe co-morbidities, with higher levels in boosted compared with non-boosted groups. Further assessment of the efficacy of this vaccine is warranted in all age groups and individuals with co-morbidities .

**Introduction**

As of 24th October 2020, over 41 million people have been diagnosed with COVID-19 disease worldwide, with over 1.1 million confirmed deaths 1. Severe COVID-19 disease is more common in older adults and in individuals with co-morbidities such as hypertension, diabetes, cardiovascular disease and COPD 2. A safe and effective vaccine against SARS-CoV2 will be an important tool in controlling the global COVID-19 pandemic. While there are currently no licensed vaccines against SARS-CoV-2, 44 potential vaccine candidates based on a variety of platforms including lipid nanoparticle mRNA, DNA, adjuvanted protein, inactivated virus particles and non-replicating viral vectors are currently in clinical trials (of which 9 candidates are in Phase 3 trials) and a further 154 candidates are undergoing pre-clinical testing.3

The WHO Global Target Product Profile of critical characteristics for pre-qualification of a COVID-19 vaccine requires vaccine candidates to be targeted at the most at-risk groups including older adults, to have a favourable safety profile, to provide efficacy as measured by prevention of virologically confirmed disease and/or transmission and to provide at least 6 months of protection for individuals at ongoing risk of COVID-19 exposure. 4 On 25th September 2020 the UK Joint Committee on Vaccination and Immunisation (JCVI) gave interim recommendations for the national prioritisation of COVID-19 vaccines. 5 The following groups were provisionally prioritised: firstly, older adults living in residential care homes and residential care home workers; secondly, all adults 80 or more years of age and health and social care workers; and thirdly all adults over the age of 70. However, it was acknowledged that this priority ranking could change significantly if the first available vaccines were not considered safe or effective in older adults.

Immunosenescence refers to the gradual deterioration and decline of the immune system brought on by aging. Age-dependent differences in the functionality and availability of T and B cell populations are thought to play a key role in the decline of immune response.6 Immunosenescence is associated with an increased susceptibility to infection and reduced vaccine responses in older adults and may contribute to the poor health outcomes in this age group. There has been a drive to develop vaccines and adjuvant formulations tailored for older adults to overcome this diminished immune response post-vaccination. Assessment of immune responses in older adults is therefore essential in development of COVID-19 vaccines that could protect this vulnerable population.

The spike protein of SARS-CoV-2 binds to ACE2 receptors on target cells during viral entry. Analysis of convalescent patients suggests that the spike protein is an immunodominant antigen, eliciting both antibody and T cell responses.7 The majority of candidate vaccines for COVID-19 have been developed to induce anti-spike protein immune responses. Clinical trials using several different vaccine platforms including mRNA,8,9 adenoviral vectored vaccines,10,11 inactivated virus,12,13 and adjuvanted spike glycoprotein14 have shown neutralising antibody after immunisation.

 Replication deficient adenoviruses vectors containing a pathogen specific transgene have been used as novel vaccines due to their ability to induce strong humoral and cellular responses.15 However, pre-existing immunity may reduce the immunogenicity of vectors derived from human viruses, hence use of Simian adenoviruses may be preferable. ChAdOx1 nCOV-19 is a replication defective chimpanzee adenovirus vectored vaccine expressing the full-length SARS-CoV-2spike glycoprotein gene (GenBank accession number MN908947). Vaccination of Rhesus macaques with a single dose of ChAdOx1 nCOV-19 generates humoral and cellular immune responses and protects from lower respiratory infection after subsequent challenge with SARS-CoV-2.16 Preliminary results of a Phase 1/2 clinical trial of ChAdOx1 nCoV-19 in adults aged 18-55 years show that the vaccine is well tolerated and generates robust neutralising antibody and cellular immune responses against spike glycoprotein.17 Here we present the safety and immunogenicity results of a Phase 2 component of a Phase 2/3 multi-centre study using ChAdOx1 nCoV-19 at 2 different doses, in adults including those 56-69 years and over 70 years, and in a 1 or 2 dose regimen.

**Methods**

**Study design**

This is a phase 2/3, participant-blinded, multicentre, randomised controlled trial, assessing safety and efficacy of the ChAdOx1 nCov-19 vaccine with sequential age-escalation immunogenicity sub-studies performed in older age groups. It is being conducted at twenty centres in the UK. The groups reported in this manuscript were part of the phase 2 component and were enrolled at two sites: the Oxford Vaccine Centre, Centre for Clinical Vaccinology and Tropical Medicine, University of Oxford, and the NIHR Southampton Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton. Data on the participants from the Phase 3 component will be published subsequently. Adult participants aged 18–55 years, 56-69 years, and 70+ years, without severe or uncontrolled medical comorbidities, as defined in the Clinical Study Plan (supplementary) were recruited through local advertisements. Participants aged 65 years and older with a high Clinical Frailty Score were excluded. Participants were enrolled into one of 10 different groups (Figure S1). Those aged 18-55 years were recruited first to the LD/LD group. Those aged 56-69 years were recruited subsequently, and further extension to the 70+ age group only occurred after safety review by the independent DSMB. The 56-69 years and 70+ year cohorts were randomised to receive either a single dose or two doses of vaccine as well as being randomised to receive the experimental vaccine or the control. Recruitment was sequential with low dose (LD) groups recruited first and standard dose (SD) cohorts recruited after a protocol amendment was approved which incorporated the new higher dose level. All participants underwent a screening visit where a full medical history, targeted examination, a blood test for SARS-CoV-2 exposure and a urinary pregnancy test in women of childbearing potential were performed. Volunteers who were seropositive to SARS-CoV-2 before enrolment were excluded from participating in all groups aside from 18-55 SD/SD. In addition, all volunteers presented here aside from the age 18-55 LD/LD group had additional safety tests (blood tests for HIV; hepatitis B and C serology; full blood count; kidney and liver function tests). Full details of the eligibility criteria are described in the trial protocol provided in the Appendix.

Written informed consent was obtained from all participants, and the trial is being conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The study was sponsored by the University of Oxford and approved in the UK by the Medicines and Healthcare products Regulatory Agency (reference 21584/0428/001-0001) and the South-Central Berkshire Research Ethics Committee (reference 20/SC/0179). Vaccine use was authorised by Genetically Modified Organisms Safety Committees at each participating site. An independent data and safety monitoring board (DSMB) reviewed all interim safety reports. This study is registered with [ClinicalTrials.gov](http://clinicaltrials.gov/), NCT04400838, and with ISRCTN, 15281137.

**Randomisation & masking**

Participants were randomly assigned to receive either the ChAdOx1 nCoV-19 vaccine or the quadrivalent MenACWY protein-polysaccharide conjugate vaccine. MenACWY was used as a comparator vaccine rather than a saline placebo to maintain blinding of participants who experienced local or systemic reactions. Participants were randomised to receive ChAdOx1 nCoV-19 or MenACWY in the following ratios: those aged 18-55 years were randomised 1:1 in the LD/LD group and 5:1 in the SD/SD group. Those aged 56-69 years were randomised to single ChAdOx1 nCoV-19, single MenACWY, 2 dose ChAdOx1 nCoV-19, or 2 dose MenACWY using a 3:1:3:1 ratio, and those aged 70 or older were randomised using a 5:1:5:1 ratio.

Randomisation lists, using block randomisation stratified by age and dose group and study site, were generated by the study statistician. Block sizes were chosen to align with the age and dose group sizes. Computer randomisation was done with full allocation concealment within the secure web platform used for the study electronic case report form (REDCap version 9.5.22; Vanderbilt University, Nashville, TN, USA). The trial staff administering the vaccine prepared vaccines out of sight of the participants and syringes were covered with an opaque material until ready for administration to ensure blinding of participants. Clinical investigators and the laboratory team remained blinded to group allocation.

**Procedures**

In the previous Phase 1/2 study, a single standard dose of 5x1010 virus particles(vp) ChAdOx1 nCoV-19 was used, based on previous experience with a ChAdOx1 MERS construct. In this study we assessed a lower dose of 2·2 x1010 vp or a standard dose of 3·5-6·5 x1010 vp in adults of different age cohorts. Due to the need to rapidly produce large numbers of doses of GMP-manufactured vaccine to allow timely enrolment into the Phase 2/3 clinical trial, two different batches of vaccine were used in this study: one manufactured and vialed by Advent.r.I. (Pomezia, Italy), and one manufactured by COBRA Biologics Ltd (Keele, UK) and vialed by Symbiosis. Both were manufactured according to Good Manufacturing Practice, as described in the Investigational Medicinal Product Dossier and approved by the regulatory agency in the UK, the MHRA. The 18-55 SD/SD cohort received vaccine manufactured by COBRA for both prime and boost doses and all other cohorts received prime and boost doses manufactured by Advent. Analytical comparability assessment of the batches indicates that the batches are comparable. Formal batch-to-batch comparison studies are ongoing and results will be reported when available.

ChAdOx1 nCoV-19 was administered as a single or two-dose regimen (4-6 weeks apart) at either a low dose (LD) of 2·2x1010 vp or a standard dose (SD) of between 3·5 and 6·5 × 1010 vp. It was administered as a single intramuscular injection into the deltoid, according to specific study standard operating procedures (SOPs). The MenACWY vaccine was provided by the UK Department of Health and Social Care and administered as per summary of product characteristics at the standard dose..18

Safety data from animal studies and our previous Phase 1/2 clinical trial of ChAdOx1 nCoV-19 were reviewed prior to participant recruitment. Volunteers were considered enrolled into the trial at the point of vaccination. Participants were observed in the clinic for a minimum of 15 minutes after the vaccination procedure in case of any immediate adverse events.

Participants from each group were instructed to complete a diary card to record solicited local and systemic adverse reactions for 7 days. Protocol defined solicited local adverse events included injection site pain, tenderness, warmth, redness, swelling, induration, and itch and solicited systemic adverse events included malaise, muscle ache, joint pain, fatigue, nausea, headache, chills, feverishness (i.e. a self-reported feeling of having a fever), and objective fever defined as an oral temperature of 38°C or higher. All participants were given the emergency 24-hour telephone number to contact the on-call study physician as required. Serious adverse events will be recorded throughout the follow-up period of 1 year after the last dose of vaccine.

Severity of adverse events was graded with the following criteria: mild (transient or mild discomfort for <48 h, no interference with activity, and no medical intervention or therapy required), moderate (mild to moderate limitation in activity, and no or minimal medical intervention or therapy required), severe (marked limitation in activity and medical intervention or therapy required), or potentially life-threatening (requires assessment in emergency department or hospitalisation). All participants in in the 56-69 year and 70+ year age groups and participants in the 18-55 SD/SD groups had clinical and immunogenicity assessments at 0, 7, 14 and 28 days after their prime and booster vaccinations. Participants in the 18-55 LD/LD group had clinical and immunogenicity assessments at baseline, pre-booster and at 14 and 28 days after their booster vaccination.

Humoral responses at baseline and following vaccination were assessed using a multiplexed immunoassay (Meso Scale Discovery multiplexed immunoassay [MIA] against spike and receptor binding domain), a standardised total IgG ELISA against trimeric SARS CoV-2 spike protein, and a live SARS-CoV-2 neutralisation assay (Public Health England [PHE]), as described previously.17 Cellular responses were assessed using an *ex-vivo* interferon-γ (IFN γ) enzyme-linked immunospot (ELISpot) assay to enumerate antigen-specific T cells.17 Neutralising antibody to the ChAdOx1 vector was measured using a secreted embryonic alkaline phosphatase-reporter (SEAP) assay which measures the reciprocal of the serum dilution required to reduce *in vitro* expression of vector-expressed SEAP by 50%, 24 hours post transduction.19 Owing to the labour-intensive nature of neutralisation assays, we prioritised analysis of samples from the ChAdOx1 nCoV-19 groups, randomly selecting more samples from ChAdOx1 nCoV-19 participants than control samples to be sent for blinded analysis.

**Outcomes**

The co-primary outcomes are to assess efficacy as measured by cases of symptomatic virologically confirmed COVID-19 and safety of the vaccine as measured by the occurrence of serious adverse events. Secondary outcomes include safety, reactogenicity, and immunogenicity profiles of ChAdOx1 nCoV-19 in older adults, efficacy against hospital-attended COVID-19, death, and seroconversion against non-spike proteins (see protocol for full description of outcomes).

Preliminary results for selected secondary endpoints are reported here, comparing local and systemic reactogenicity and cellular and humoral immunogenicity of ChAdOx1 nCoV-19 between different age groups, after one or two doses and at low or standard dose. Efficacy analyses are not included in this report.

**Statistical analysis**

Safety endpoints are described as frequencies (%) with 95% binomial exact CIs. Medians and IQRs are presented for immunological endpoints. Participants were analysed according to the vaccine received. (Figure S1).

Comparison across three age groups were made using Kruskal Wallis tests within each dose level of the vaccine (LD or SD) for antibody responses or unadjusted analysis of variance applied to log-transformed values for neutralisation titres. Comparisons between low and standard dose groups were made using Wilcoxon Rank Sum tests (antibody response) or independent samples t-tests applied to log-transformed values for neutralisation titres. Baseline characteristics were not statistically compared. We present unadjusted p values for a small number of statistical comparisons to avoid issues of multiplicity.

To assess the relationship between responses on different assays, unadjusted linear regression was used to analyse log-transformed post-baseline values. Statistical analyses were performed using SAS version 9.4 and R version 3.6.1 or later.

**Role of funding source**

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication

**Results**

Between 30th May and 8th August 2020, 560 participants were enrolled in the study (420 randomised to ChAdOx1 nCoV-19 and 140 randomised to MenACWY). In those aged 18-55 years 160 participants were enrolled (ChAdOx1 nCoV-19: 100, MenACWY: 60), in those aged 56-69 years 160 participants were enrolled (ChAdOx1 nCoV-19: 120, MenACWY: 40) and in those aged 70 years and older 240 were enrolled (ChAdOx1 nCoV-19: 200, MenACWY: 40). All randomised participants were vaccinated. One participant received the incorrect vaccine after randomisation and was excluded from the analysis. Seven participants randomised to receive two doses of vaccine chose not to continue with the second dose and were excluded. Three participants were excluded from immunology analyses due to incorrectly labelled samples (either incorrect participant ids or incorrect timepoints or both) (Figure S1). The baseline characteristics of the participants eligible for inclusion in the analysis in each group are shown in Tables S1a and S1b. Almost all participants were white and non-smokers. A large proportion of health care workers who were predominantly female were enrolled in the 18-55 years and 56-69 years age groups. The median age in the oldest age groups ranged from 73 to 74 years with the oldest participants being 83 years old.

Injection site pain and tenderness were the most common solicited local adverse reactions and occurred most frequently in the first 48 hours after vaccination (Figure 1). In those aged 56 or older a standard dose of ChAdOx1 nCoV-19 prime or boost elicited a greater number of local or systemic reactions than MenACWY (Figures S2-S5). The difference was less clear with low dose vaccine in the older age groups, and numbers are small in the control groups (Table S14). At least one local symptom was reported after prime vaccination with SD ChAdOx1 nCoV-19 by 88%, 73%, and 61% of participants aged 18-55, 56-69, and 70+ years respectively (Table S13). Similar proportions of local symptoms were reported after SD ChAdOx1 nCoV-19 booster vaccination (SD/SD groups) with 76%, 72%, and 55% of participants aged 18-55, 56-69, and 70+ years respectively reporting at least one local symptom. A similar pattern was seen across the age groups in participants receiving a single low dose ChAdOx1 nCoV-19 (LD) and after low dose boost (LD/LD), but with fewer total adverse reactions (Table S13, Figure S2). No severe local symptoms were reported by ChAdOx1 nCoV-19 recipients. In the two-dose control groups, local symptoms were experienced by 57%, 25%, and 35% of individuals aged 18-55, 56-69, and 70+ years after prime vaccination with MenACWY and by 86%, 37%, and 20% after booster vaccinations with MenACWY respectively. (Table S13)

Fatigue, headache, feverishness and myalgia were the most commonly solicited systemic adverse reactions (Figure 2). At least one systemic symptom was reported after SD prime vaccination by 86%, 77%, and 65% of participants in the 18-55 SD/SD group, 56-69 SD/SD group, and 70+ SD/SD group respectively (Table S13). The severity of symptoms experienced in the SD/SD group was reduced after booster vaccination with only one participant (1%) reporting a severe reaction compared with 6 (5%) after the prime dose. 65%, 72%, and 43% of participants in the 18-55 SD/SD group, 56-69 SD/SD group, and 70+ SD/SD group respectively reported at least one systemic adverse reaction after a ChAdOx1-nCoV-19 booster. The incidence of objectively measured fever was low at 24% in the 18-55 SD/SD group, and no fevers were recorded in either the 56-69 SD/SD or 70+ SD/SD groups after prime vaccination with ChAdOx1 nCoV-19 (Table S6-S8, Table S12). No participants of any age who received SD experienced objective fever after booster vaccination. A similar pattern of decreasing reactogenicity with increasing age was seen in the LD groups (Tables S9 - S13, Figure S3). There have been 13 serious adverse events to date (across all age and vaccine groups), none of which are considered related to either study vaccine as assessed by the investigators (Table S15).

Using a multiplex immunoassay (MIA) which detected total IgG against receptor binding domain and trimeric spike protein, we observed that participants who received a standard dose prime with ChAdOx1 nCoV-19 had similar anti-spike antibody titres by day 28 after their first vaccine to those who received a low dose, p=0·1086 adjusted for age (Figure 3, Table S2). In both dose levels anti-spike IgG responses were lower at day 28 in those who were older. (Low dose groups: 18-55 years median 6439 Arbitrary units per ml [AU/ml], IQR 4338-10640, 56-69 years median 4553, IQR 2657-12462, 70+ years median 3565, IQR 1507-6345, p=0·0037. Standard dose groups: 18-55 years median 9807, IQR 5847-17220, 56-69 years median 5496, IQR 2548-12061, 70+ years median 4156, IQR 2122-12595, p=0·0044). By 28 days after booster vaccination, similar antibody titres were seen across all two dose groups regardless of age or vaccine dose and were higher than for those who did not receive a booster dose. Similar results were seen with anti-RBD antibodies (Figure 3, Table S2) and with an in-house standardised ELISA (Figure S4, Table S3).

In a live virus microneutralization assay (MNA80) performed at Public Health England, median titres peaked in most boosted groups by day 42 (Figure 4). There were no statistically significant differences in normalized titres between age groups at day 42 (low-dose groups: 18-55 years: median 161 IQR 99, 233; 56-69 years: median 143, IQR, 79, 220; 70+ years: 150, IQR, 103, 255; p=0·899. Standard dose groups, 18-55 years: median 193, IQR, 113, 238; 56-69 years: median 144, IQR 119, 347; 70+ years: median 161 IQR, 73, 323; p=0·400). Within each age group there was no statistically significant differences in neutralization titres between low and standard dose vaccine recipients at the same timepoint (18-55 years: p=0·3287, 56-69 years: p=0·1240, 70+ years: p=0·6195). Figure 4, Table S4. Neutralising titres were achieved by 14 days after the booster dose in 208 of 209 booster dose recipients. The one participant with a non-neutralizing level was in the 70+ LD/LD group.

Anti-spike IgG levels after vaccination were highly correlated with neutralizing titres in all age groups and for both low and standard dose vaccines (r2 from linear regression range 0·42 to 0·75, all p < 0·0001, Figure S7).

IFN γ ELISpot responses against SARS-CoV-2 spike protein peaked 14 days after the first dose and did not rise significantly after the second dose (Figure 5 p=0·4622 from paired t-test of day 28 v day 42). ELISpot data were unavailable for the 18-55 LD/LD cohort as peripheral blood mononuclear cells (PBMCs) were not collected in this group. In those who received two standard doses, there was a statistically significant difference across age groups with those aged 56-69 years having higher responses at day 42 than other age groups receiving the same vaccine, (median 413, IQR 245-675 spot-forming cells per million PBMCs (SFCs) in those 18-55 years, compared with a median of 798, IQR 462-1186 SFCs in those 56-69 years, and a median of 307, IQR 161-516 SFCs in those 70 years or older, p<0.0001) as shown in Table S5.

Anti-ChAdOx1 neutralising antibody titres across different age and dose groups are shown in Figure 6a. Titres increased with the ChAdOx1 priming vaccination in all groups to comparable levels but were not increased further after a second vaccine dose at day 28. This was in contrast to the anti-SARS-CoV-2 spike protein antibodies, which were boosted 28 days after the second vaccine dose. Anti-ChAdOx1 neutralising titres at the time of the booster vaccine were negatively correlated with standardised ELISA values 28 days after boost (p=0·0374, Figure 6b) but there was no statistically significant correlation between pre-boost anti-ChAdOx1 neutralising titres and ELISpot responses 14 days after the booster dose (p=0·221, Figure 6c).

**Discussion**

Our findings show that the ChAdOx1 nCoV-19 vaccine was safe and well tolerated with a lower reactogenicity profile in older adults than in younger adults. Immunogenicity was similar across age groups after booster vaccination. If these responses correlate with protection in humans, these findings are encouraging as older individuals are at disproportionate risk of severe COVID-19 disease and it is therefore essential that any vaccine adopted for use against SARS-CoV-2 is effective in older adults.

The majority of the reported local and systemic adverse events were mild to moderate in severity, in line with our previous phase 1 study of the ChAdOx1 nCoV-19 vaccine 17 and previously reported studies of ChAdOx1 vectored vaccines 20-22. Fewer adverse events were experienced after booster vaccination than after prime vaccination and reactogenicity reduced with increasing age. The lower dose vaccine was less reactogenic than standard dose vaccine across all age groups.

The serious adverse events observed during the trial in these study groups were judged unrelated to the study vaccines and occurred at frequencies expected for these conditions in the general population. There were no suspected unexpected serious adverse reactions (SUSARs) notified in the groups reported in this manuscript. In the phase 3 component of the trial SUSARs occurred in groups not described in this paper. Details of these events will be included in reports of the phase 3 trial subsequently. SUSARs and other adverse events are carefully monitored to ensure that there is no pattern of unexplained illnesses that emerge which could indicate a safety concern. These independent assessments have led to the recommendation that the trial is safe to continue.

ChAdOx1 nCoV-19 vaccine induced specific antibody to the SARS-CoV-2 spike glycoprotein and receptor binding domain at 28 days after a single dose across all age groups, including adults over 70. There was a clear effect of a booster on antibody titres at day 56 which was unrelated to dose regimen or age cohort. Similar patterns were observed with neutralizing antibody responses, with no difference in the magnitude of the response at day 28 after a prime vaccine regardless of age or vaccine dose, but a booster effect measured in individuals who received a second dose of vaccine.

These findings are similar to those reported for an Ad5-vector-based SARS-CoV-2 vaccine which also had reduced reactogenicity in older adults after a single dose of vaccine, although immunogenicity was concurrently reduced in this older age group10. A prime-boost mRNA SARS-CoV-2 vaccine has also been shown to be immunogenic in older adults with dose dependent immune responses and similar neutralising antibody titres and cellular immune responses to younger adults. However, in contrast to the observations here, reactogenicity was more common after a second dose of the mRNA vaccine.8

T cell responses are important in controlling disease in natural infection7 and generation of a robust cellular immune response is therefore a desirable attribute for a vaccine against SARS-CoV2 . Here we show that spike-specific T cell responses measured by ELISpot peaked at 14 days after prime vaccination, consistent with previous studies of simian adenovirus vectored vaccines,23 and were similar in all groups regardless of age and vaccine dose. Spike protein T cell responses measured by ELISpot have also been reported in studies with other adenoviral vectored vaccines against SARS-CoV211 including in adults aged over 55.10 Theoretical concerns about vaccine enhanced disease have led to a view that a Th1 biased CD4 response is a preferred coronavirus vaccine characteristic.24 An adjuvanted nanoparticle vaccine has been shown to induce spike-specific CD4 T cell cytokine responses with a predominantly Th1 profile,14 as has a mRNA vaccine in small numbers of adults aged 56-70 and 71+ years.8 More detailed investigations of antigen specific T cell responses in our study participants are ongoing.

The robust humoral and cellular immune responses obtained in our older adult population were encouraging given that a number of studies have demonstrated that declining immune function with age leads to poorer immune responses to vaccines. This holds true for vaccines such as influenza where pre-existing immune memory exists25 and vaccines that induce primary immune responses such as hepatitis B.26 Other adenoviral vector platforms against SARS-CoV-2 have either shown reduced immunogenicity in an older age group10 (although this was a single-dose regimen and so not directly comparable to a prime-boost regimen) or have not yet been tested in an older population.11

However, our results are consistent with previous studies of adenoviral vector-based vaccines against respiratory pathogens which evoke humoral and T cell responses in older adults including a human adenovirus vectored RSV vaccine27 and a simian adenovirus vectored RSV vaccine.28 Our results with ChAdOx1 nCOV-19 are also consistent with those of a ChAdOx1-vectored vaccine against influenza that demonstrated good immunogenicity in adults over 50 years.20

It is noteworthy that the anti-spike antibody responses in our study increased after booster vaccination at an interval of 1 month but the neutralising anti-vector antibody responses did not. There was also no difference in anti-vector immunity by age. There was a small negative correlation between anti-vector antibody titre and anti-spike total IgG, but not T cell ELISpot responses. Further work is needed to investigate if homologous boosting with adenoviral vectored vaccines can be undertaken without loss of immunogenicity to the pathogen specific transgene.

In the absence of a clear serological correlate of protection against SARS-CoV-2, clinical studies have focussed on neutralising antibodies which confer protection from challenge in animal models. 8-14 Live virus neutralisation assays are labour intensive and can only be performed in specialist laboratories under category 3 biological safety conditions. We show here that anti-spike IgG levels correlate with neutralising antibody titres for all age groups. This suggests that should neutralising antibody be shown to be protective in humans, routine serological assays could be used for the standardised evaluation of functional antibody by vaccine candidates in clinical trials.

A limitation of this study is the single-blind design. However, all laboratory analyses and clinical assessments reported in this manuscript were made in a blinded fashion. Furthermore, the selection of 70+ participants with a median age of 73-74 years between dose groups and with limited co-morbidities, may not be representative of the general older population including those living in residential care settings or >80 years of age. Early phase studies in older adults require healthy volunteers to be enrolled for demonstration of safety, and recruitment to the study occurred at a period of national lockdown when more vulnerable individuals were advised by Public Health England to self-isolate. We therefore excluded volunteers with significant co-morbidities or clinical frailty. Larger studies are now underway to evaluate immunogenicity, safety and efficacy in older adults with a wider range of comorbidities.

Ultimately, licensure of a vaccine relies on the demonstration of efficacy in preventing COVID-19 disease, and safety. Ongoing Phase 3 studies with ChAdOx1 nCoV-19 are underway in the UK, Brazil and the USA to evaluate vaccine efficacy and safety. The demonstration of similar safety and immunogenicity of ChAdOx1 nCoV-19 in older adults when compared with younger adults could support the use of this vaccine in this age group, if it is shown to be protective in the ongoing phase 3 trials.

**Contributors**

 AJP and SG conceived and designed the trial and AJP is the chief investigator.

AJP, AMM, HR, MNR, MV, and PMF contributed to the protocol and design of the study. AVH and SNF were the study site PIs. AF, CD, EC, KJE, RAM, and TL were responsible for laboratory testing and assay development. MV and NM conducted the statistical analysis, SG and TL were responsible for vaccine development. ADD, CG, and RDT were responsible for vaccine manufacture. AJP, AMM MNR, MV, NM, and TL contributed to the preparation of the report.

AMM, DO, HR, KJE, MNR, PKA and PMF contributed to the implementation of the study. All other authors contributed to the implementation of the study and data collection. All authors critically reviewed and approved the final version.

**Declaration of interests**

Oxford University has entered into a partnership with Astra Zeneca for further development of ChAdOx1 nCov-19. AZ reviewed the data from the study and the final manuscript prior to submission, but the authors retained editorial control. 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 consultant to Vaccitech. PMF is a consultant to Vaccitech. AJP is Chair of the UK Department of Health and Social Care's Joint Committee on Vaccination & Immunisation (JCVI), but does not participate in policy advice on coronavirus vaccines, and is a member of the WHO Strategic Advisory Group of Experts (SAGE). AVSH is a co-founder of and consultant to Vaccitech and is named as an inventor on a patent covering design and use of ChAdOx1-vectored vaccines. MS reports grants from Janssen, GlaxoSmithKline, Medimmune, Novavax, and MCM and grants and non-financial support from Pfizer, outside of the submitted work. CG reports personal fees from the Duke Human Vaccine Institute, outside of the submitted work. ADD reports grants and personal fees from AstraZeneca, outside of the submitted work. In addition, ADD has a patent manufacturing process for ChAdOx vectors with royalties paid to AstraZeneca, and a patent ChAdOx2 vector with royalties paid to AstraZeneca. The other authors declare no competing interests.

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**Data sharing**

The study protocol is provided in the appendix. Anonymised participant data will be made available when the trial is complete, upon requests directed to the corresponding author; after approval of a proposal, data can be shared through a secure online platform.

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