COVAX

Window 2

Information Fact Pack

23 December 2020

COVAX

CEPI Gavi The Vaccine Alliance World Health Organization

Information Fact Pack

Candidate	AstraZeneca ChAdOx1 nCoV-19 (AZD1222)
Manufacturer	AstraZeneca
Headquarter location	United Kingdom

Technical information

Technology platform	Non-replicating adenoviral vector
Antigen / adjuvant	Unmodified full-length spike protein No adjuvant
Vaccine presentation	Liquid, ready to use Multi-dose vial (10 dose, 6R and 10R)
Expected dose regimen	2-dose schedule, 28 days apart
Route of administration	Intramuscular (IM) injection
Target population	Expected indication: for the prevention of COVID-19 for adults ≥18 years of age. Of the 11,636 participants included in the interim efficacy analysis (using only data from UK and Brazil, as the study in South Africa had not yet met the pre-specified criteria for inclusion in the efficacy analysis), 10,218 (87·8%) were aged 18–55 years. Only 1,418 (12.1%) of those assessed for efficacy were older than 55 years, meaning that from the interim analysis of these trials, it is not yet possible to infer efficacy in older adults. Additional demographic information: most participants were white (n=9,625 [82·7%]) and female (n=7,045 [60·5%]).
Labelling / Packaging	WHO-agreed standard English label and English carton. A single Patient Information Leaflet will be supplied per carton. Secondary packaging will include barcodes, including serialization, which are in compliance with WHO´s serialization requirements. Secondary packaging: Cartons of 10 vials, totaling 100 doses. Tertiary packaging: Shippers containing 24 cartons each, so 240 vials totaling 2,400 doses. *Note: This may be subject to change, depending on supply source.*
Cold chain requirements	2-8°C, with 6-month shelf life (may be updated later in 2021, based on ongoing stability test results). Vials must be used within 6 hours of first puncture when stored at room temperature, or within 48 hours of first puncture when stored at 2-8°C.
Efficacy data	Pooled interim analysis of Phase II/III results suggest the vaccine has an efficacy of 70.4% [95.8% CI 54.8 to 80.6], based on analysis of two of four of the ongoing Phase II/III trials (from UK and Brazil) including 11,636 participants. The primary outcome was virologically confirmed, symptomatic COVID-19 more than 14 days after the second dose. Within this, a subset of participants (n=2,741) received a half-dose of the vaccine followed by a full dose (“LD/SD”), while the remaining participants received two standard full doses (“SD/SD”). Vaccine efficacy was 62.1% [95% CI 41·0 to 75·7] in the SD/SD cohort and 90.0% [95% CI 67·4 to 97·0] in the LD/SD cohort. No COVID-19-related hospital admissions occurred in ChAdOx1 nCoV-19 recipients, whereas ten (of which two were severe) occurred in the placebo groups.

Safety / reactogenicity data	The overall safety of the ChAdOx1 nCoV-19 vaccine is based on an interim analysis of pooled data from four clinical trials conducted in the United Kingdom, Brazil, and South Africa. At the time of analysis, 23,745 participants ≥18 years old had been randomized and received either the ChAdOx1 nCoV-19 vaccine or the control (12,021 ChAdOx1 nCoV-19 recipients and 11,724 control recipients). The most frequently reported adverse reactions were injection site tenderness (>60%); injection site pain, headache, fatigue (>50%); myalgia, malaise (>40%); pyrexia, chills (>30%); and arthralgia, nausea (>20%). The majority of adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination. When compared with the first dose, adverse reactions reported after the second dose were milder and reported less frequently.

Clinical and regulatory timelines

Clinical development overview	Phase I or I/II sites UK, South Africa, Kenya (sponsored by the University of Oxford), Japan Phase II/III sites Brazil, UK (sponsored by the University of Oxford); India (sponsored by SIIPL/ICMR); Chile, Japan, Peru, Russia, USA (sponsored by AstraZeneca)
Date of 1st pivotal efficacy data	November 23, 2020; published in *Lancet* on December 8, 2020
Regulatory strategy	UK MHRA: Emergency use authorization expected by end-December 2020. EMA: Rolling submission started on October 1, 2020. Earliest expected approval in February 2021. WHO EUL: Rolling submission ongoing. Earliest expected approval in February – April 2021. *Note: Given timing of regulatory review and availability of doses, Participants must be prepared to accept doses that have received either Emergency Use Authorization (EUA) or Conditional Marketing Authorization approval (CMA) from a regulatory authority listed below, or Emergency Use Listing (EUL) from the WHO (together, "Conditional Regulatory Approval"). The relevant countries are: Australia, Austria, Belgium, Bulgaria, Canada, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Japan, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Kingdom, United States of America.*

COVAX Facility deal and supply terms

Total supply volume to COVAX Facility, doses by end of 2021[1]	170M committed doses *Supply volumes to individual participants to be determined as described in the Participant's Commitment Agreement.*
Projected delivery schedule, doses[2]	Q1: 64M Q2: 94M Q3: 12M Q4: 0
Estimated date of first delivery	c. February – April 2021 (depending on regulatory approval)
Manufacturing network	Drug Substance sites SK Bioscience (Republic of South Korea) WuXi Biologics (China) Drug Product sites SK Bioscience (Republic of South Korea) Catalent (Italy) WuXi Biologics (Germany) IDT Biologika (Germany) CHEMO (Spain)
Price	Price per dose will be equivalent to AstraZeneca's Cost of Goods for these doses ("COGs"), which will be capped at $4.00. In addition to this price, Participants will be responsible for (i) indirect tax, customs, excise duties and similar taxes; and (ii) costs associated with delivering the Product from the Distribution Centre (as defined below) to the point of delivery to the Participant. All COVAX Participants will face these same terms and there will be no tiering of prices across income groups.
Delivery and distribution (draft)	AstraZeneca shall set up and operate a distribution centre in the Netherlands at the Schiphol International Airport (the "Distribution Centre"). When placing binding purchase orders for doses that have received Conditional Regulatory Approval, the Participants shall be required to confirm to AstraZeneca that the AZD1222 Vaccine (i) meets the requirements attached to the Conditional Regulatory Approval; and (ii) will be able to receive and administer AZD1222 Vaccine granted such Conditional Regulatory Approval.

[1] Schedule corresponds to projected release of doses from the Distribution Centre, under best reasonable efforts. Delivery to countries will be affected by several elements including, but not limited to, regulatory approvals and country readiness.

[2] Schedule corresponds to projected release of doses from the Distribution Centre, under best reasonable efforts. Delivery to countries will be affected by several elements including, but not limited to, regulatory approvals and country readiness.

Indemnification Requirements

Self-Financing Participants must agree to AstraZeneca's Standard Indemnity provision below, unless they have previously entered into a bilateral arrangement with AstraZeneca which includes an alternative indemnity provision. In that case, AstraZeneca may require the relevant Self-Financing Participant to comply with the indemnity provisions under the bilateral arrangement in respect of the COVAX Doses.

1 Indemnification.

1.1 Purchaser. The Purchaser shall indemnify and hold harmless AstraZeneca, its Affiliates, sub-contractors, licensors, and sub-licensees, and officers, directors, employees and other agents and representatives of each (collectively, the "**Indemnified Persons**") from and against any and all damages and liabilities, including settlements for which the Indemnifying party has given its consent pursuant to the provisions set forth herein, and necessary legal costs relating to, resulting from or associated with claims for death, physical, mental, or emotional injury, illness, disability, or condition, fear of the foregoing, property loss or damage, and business interruption of the injured party or a Related Person of such injured person (together, "**Losses**") relating to or arising from the use or administration of the Vaccine shipped or allocated to its jurisdiction. Such indemnification will be available regardless of where the Vaccine is administered, where the claim is brought, and whether the claim of a Defect originates from the distribution, administration and use, clinical testing or investigation, manufacture, labelling, formulation, packaging, donation, dispensing, prescribing or licensing of the Vaccine in its jurisdiction. Such indemnification will not be available to Indemnified Persons (a) to the extent such Losses are the result of such Indemnified Person's Wilful Misconduct, or (b) to the extent that there has been a final determination by a court of competent jurisdiction that a defect in the Vaccine has arisen from AstraZeneca's failure to comply with current Good Manufacturing Practices or EMA pharmacovigilance regulations.

Indemnification under this Agreement will be available for Losses arising from the use and administration of vaccines supplied under this Agreement, regardless of when or where vaccination occurred and regardless of when or where the injury leading to the Losses occurs or is reported.

1.2 Process. The Indemnified Person shall give (or cause AstraZeneca to give) the Purchaser (the "Indemnifying Party"), prompt notice of any claim or lawsuit served upon the Indemnified Person (a "Third Party Claim") stating the nature and basis of such Third Party Claim and the maximum estimated amount (in United States Dollars) of such Third Party Claim, to the extent known (which estimate may be updated from time to time). Notwithstanding the foregoing, no delay or deficiency on the part of the Indemnified Person in so notifying the other shall limit any right of any Indemnified Person to indemnification under this Agreement, except to the extent such failure materially prejudices the defense of such Third Party Claim. AstraZeneca shall assume and control the defense of any Third Party Claim using legal counsel reasonably chosen by AstraZeneca. Each of the Parties shall (i) use commercially reasonable efforts to mitigate the effects of the claim and (ii) fully cooperate with AstraZeneca and its legal representatives in the investigation and defense of any matter which is the subject of indemnification, at the Indemnifying Party's cost and expense. AstraZeneca shall keep the Indemnifying Party reasonably informed of the progress of the defense of the Third Party Claim. AstraZeneca shall pay the invoices of legal counsel and other expenses of AstraZeneca arising from defending the Third Party Claim promptly upon presentment of an invoice and in any case within ninety (90) days of presentment thereof. AstraZeneca shall have the right to seek settlement or compromise of, and to so settle or compromise, the Third Party Claim; provided that AstraZeneca shall not settle or compromise a Third Party Claim without the prior written consent of the Indemnifying Party and AstraZeneca shall not unreasonably withhold, condition or delay its approval of the settlement of any claim, liability or action covered by the provisions set forth herein.

2 Release; Limitation of Liability for claims other than third party indemnification; Disclaimer of Warranties.

2.1 Limitation of Liability for claims other than third party indemnification. The aggregate liability of AstraZeneca and its Affiliates in respect of claims made by the Purchaser or any affiliates acting on the Purchaser's behalf (as distinguished from claims for third party indemnification), whether for breach of contract, another contractual-based claim, arising in tort (including negligence) or otherwise, arising out of, under or in connection with this Agreement shall not exceed the amounts actually paid by the Purchaser to AstraZeneca under this Agreement.

3 Definitions.

3.1 **"Defect"** means the characteristic of a product that does not provide the safety which a person is entitled to expect taking all circumstances into account, including: (a) the presentation of the product; (b) the use to which it could reasonably be expected that the product would be put; and (c) the time when the product was put into circulation, in each case as such term is interpreted consistently with the term "defective" under Article 6 of the EU Product Liability Directive 85/374/EEC.

3.2 "**Related Persons**" means spouses, heirs, children (whether natural or adopted), descendants, successors and assigns, estates, or legal representatives, executors, administrators or any other person or entity representing the rights of the injured person or any of the foregoing.

"**Wilful Misconduct**" means an act or omission taken (a) intentionally to achieve a wrongful purpose; (b) knowingly without legal or factual justification; and (c) in disregard of a known or obvious risk that is so great as to make it highly probable that the harm will outweigh the benefit. Each of the foregoing conditions must be proven with clear and convincing evidence.

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Appendix: Publications

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Appendix

Candidate AstraZeneca ChAdOx1 nCoV-19 (AZD1222)

List of scientific publications

Journal	Author	Date of publication
The Lancet	Folegatti, *et al.*	July 20, 2020
The Lancet	Ramasamy, *et al.*	November 19, 2020
The Lancet	Voysey, *et al.*	December 8, 2020

List of press releases

Title	Date of release
AstraZeneca and Oxford University announce landmark agreement for COVID-19 vaccine	April 30, 2020
AstraZeneca advances response to global COVID-19 challenge as it receives first commitments for Oxford's potential new vaccine	May 21, 2020
AstraZeneca takes next steps towards broad and equitable access to Oxford University's COVID-19 vaccine	June 4, 2020
COVID-19 vaccine AZD1222 showed robust immune responses in all participants in Phase I/II trial	July 20, 2020
AstraZeneca's scientific and social commitment for COVID-19 vaccine	August 31, 2020
Development of COVID-19 vaccine AZD1222 expands into US Phase III clinical trial across all adult age groups	August 31, 2020
Statement on AstraZeneca Oxford SARS-CoV-2 vaccine, AZD1222, COVID-19 vaccine trials temporary pause	September 9, 2020
COVID-19 vaccine AZD1222 clinical trials resumed in the UK	September 12, 2020
COVID-19 vaccine AZD1222 clinical trial resumed in Japan, follows restart of trials in the UK, Brazil, South Africa and India	October 2, 2020
FDA authorises restart of the COVID-19 AZD1222 vaccine US Phase III trial	October 23, 2020
AZD1222 vaccine met primary efficacy endpoint in preventing COVID-19	November 23, 2020
AZD1222 Oxford Phase III trials interim analysis results published in The Lancet	December 8, 2020

Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial

Pedro M Folegatti, Katie J Ewer*, Parvinder K Aley, Brian Angus, Stephan Becker, Sandra Belij-Rammerstorfer, Duncan Bellamy, Sagida Bibi, Mustapha Bittaye, Elizabeth A Clutterbuck, Christina Dold, Saul N Faust, Adam Finn, Amy L Flaxman, Bassam Hallis, Paul Heath, Daniel Jenkin, Rajeka Lazarus, Rebecca Makinson, Angela M Minassian, Katrina M Pollock, Maheshi Ramasamy, Hannah Robinson, Matthew Snape, Richard Tarrant, Merryn Voysey, Catherine Green*, Alexander D Douglas*, Adrian V S Hill*, Teresa Lambe*, Sarah C Gilbert*, Andrew J Pollard*, on behalf of the Oxford COVID Vaccine Trial Group†*

Summary

Background The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) might be curtailed by vaccination. We assessed the safety, reactogenicity, and immunogenicity of a viral vectored coronavirus vaccine that expresses the spike protein of SARS-CoV-2.

Methods We did a phase 1/2, single-blind, randomised controlled trial in five trial sites in the UK of a chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) expressing the SARS-CoV-2 spike protein compared with a meningococcal conjugate vaccine (MenACWY) as control. Healthy adults aged 18–55 years with no history of laboratory confirmed SARS-CoV-2 infection or of COVID-19-like symptoms were randomly assigned (1:1) to receive ChAdOx1 nCoV-19 at a dose of 5×10^{10} viral particles or MenACWY as a single intramuscular injection. A protocol amendment in two of the five sites allowed prophylactic paracetamol to be administered before vaccination. Ten participants assigned to a non-randomised, unblinded ChAdOx1 nCoV-19 prime-boost group received a two-dose schedule, with the booster vaccine administered 28 days after the first dose. Humoral responses at baseline and following vaccination were assessed using a standardised total IgG ELISA against trimeric SARS-CoV-2 spike protein, a muliplexed immunoassay, three live SARS-CoV-2 neutralisation assays (a 50% plaque reduction neutralisation assay [$PRNT_{50}$]; a microneutralisation assay [MNA_{50}, MNA_{80}, and MNA_{90}]; and Marburg VN), and a pseudovirus neutralisation assay. Cellular responses were assessed using an ex-vivo interferon-γ enzyme-linked immunospot assay. The co-primary outcomes are to assess efficacy, as measured by cases of symptomatic virologically confirmed COVID-19, and safety, as measured by the occurrence of serious adverse events. Analyses were done by group allocation in participants who received the vaccine. Safety was assessed over 28 days after vaccination. Here, we report the preliminary findings on safety, reactogenicity, and cellular and humoral immune responses. The study is ongoing, and was registered at ISRCTN, 15281137, and ClinicalTrials.gov, NCT04324606.

Findings Between April 23 and May 21, 2020, 1077 participants were enrolled and assigned to receive either ChAdOx1 nCoV-19 (n=543) or MenACWY (n=534), ten of whom were enrolled in the non-randomised ChAdOx1 nCoV-19 prime-boost group. Local and systemic reactions were more common in the ChAdOx1 nCoV-19 group and many were reduced by use of prophylactic paracetamol, including pain, feeling feverish, chills, muscle ache, headache, and malaise (all $p<0\cdot05$). There were no serious adverse events related to ChAdOx1 nCoV-19. In the ChAdOx1 nCoV-19 group, spike-specific T-cell responses peaked on day 14 (median 856 spot-forming cells per million peripheral blood mononuclear cells, IQR 493–1802; n=43). Anti-spike IgG responses rose by day 28 (median 157 ELISA units [EU], 96–317; n=127), and were boosted following a second dose (639 EU, 360–792; n=10). Neutralising antibody responses against SARS-CoV-2 were detected in 32 (91%) of 35 participants after a single dose when measured in MNA_{80} and in 35 (100%) participants when measured in $PRNT_{50}$. After a booster dose, all participants had neutralising activity (nine of nine in MNA_{80} at day 42 and ten of ten in Marburg VN on day 56). Neutralising antibody responses correlated strongly with antibody levels measured by ELISA ($R^2=0\cdot67$ by Marburg VN; $p<0\cdot001$).

Interpretation ChAdOx1 nCoV-19 showed an acceptable safety profile, and homologous boosting increased antibody responses. These results, together with the induction of both humoral and cellular immune responses, support large-scale evaluation of this candidate vaccine in an ongoing phase 3 programme.

Funding UK Research and Innovation, Coalition for Epidemic Preparedness Innovations, National Institute for Health Research (NIHR), NIHR Oxford Biomedical Research Centre, Thames Valley and South Midland's NIHR Clinical Research Network, and the German Center for Infection Research (DZIF), Partner site Gießen-Marburg-Langen.

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This online publication has been corrected. The corrected version first appeared at thelancet.com on August 13, 2020, and further correction has been made on November 19, 2020

See **Comment** page 448

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See **Online** for appendix 1

See **Online** for appendix 2

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. ChAdOx1 nCoV-19 has previously been reported to be immunogenic and protective against pneumonia in a rhesus macaque challenge model. We searched PubMed for research articles published between database inception and July 6, 2020, using the terms "SARS-CoV-2", "vaccine", "clinical trial", and "phase". No language restrictions were applied. We identified one published clinical trial, describing a trial done in China of an adenovirus-5-vectored vaccine against SARS-CoV-2, using a single dose at three different dose levels. The vaccine was tolerated, with reactogenicity increased at the highest dose. Antibodies, neutralising antibodies in a proportion of vaccinees, and cellular responses were induced. A further clinical trial, which was done in the USA, has been reported on *medRxiv*. The vaccine was a lipid nanoparticle-formulated, nucleoside-modified, mRNA vaccine that encodes trimerised SARS-CoV-2 spike glycoprotein receptor binding domain administered at one or two doses of three dose levels. The vaccine was tolerated, with reactogenicity increased at the highest dose. Antibodies and neutralising antibodies were induced in a dose-dependent manner and increased after a second dose.

Added value of this study

We report the results of the first clinical study of ChAdOx1 nCoV-19 (AZD1222). The vaccine was safe and tolerated, with reduced reactogenicity when paracetamol was used prophylactically for the first 24 h after vaccination. Reactogenicity was reduced after a second dose. Humoral responses to SARS-CoV-2 spike protein peaked by day 28 post prime and cellular responses were induced in all participants by day 14. Neutralising antibodies were induced in all participants after a second vaccine dose. After two doses, potent cellular and humoral immunogenicity was present in all participants studied.

Implications of all the available evidence

A vaccine against SARS-CoV-2 could be used to prevent infection, disease, and death in the global population, with high-risk populations such as hospital workers and older adults (eg, ≥65 years of age) prioritised to receive vaccination. The immune correlates of protection against SARS-CoV-2 have not yet been determined. Immunisation with ChAdOx1 nCoV-19 results in rapid induction of both humoral and cellular immune responses against SARS-CoV-2, with increased responses after a second dose. Further clinical studies, including in older adults, should be done with this vaccine.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged as a zoonotic virus late in 2019 and is the causative agent of COVID-19. Exposure to SARS-CoV-2 can result in a range of clinical outcomes, varying from asymptomatic infection to severe acute respiratory distress and death. SARS-CoV-2 has spread globally and was declared a pandemic on March 11, 2020, by WHO. As of July 19, 2020, more than 14 million people globally have been infected with more than 597 000 deaths.[1] The pandemic has placed substantial pressures on health systems delivering care for patients with COVID-19 and caused disruption of non-COVID-19 health-care provision, in addition to negative effects on the global economy. Further health consequences are anticipated.

No vaccines have been approved for prevention of COVID-19. There are currently more than 137 candidates undergoing preclinical development and 23 in early clinical development, according to WHO.[2] An ideal vaccine against SARS-CoV-2 would be effective after one or two vaccinations; would protect target populations such as older adults and those with comorbidities, including immunocompromised individuals; would confer protection for a minimum of 6 months; and would reduce onward transmission of the virus to contacts. Replication-deficient viral vectored vaccines have been used in immunocompromised individuals with no safety concerns[3–5] and ChAdOx1 vaccines are immunogenic in older adults[6] and can be manufactured at large scale, making this platform technology a promising candidate to develop a vaccine for the prevention of COVID-19. Adenoviral vectors have previously been combined with DNA and poxviral vectors to attempt to improve immunogenicity, with adenovirus or modified vaccinia virus Ankara prime-boost regimens showing enhancement of both cellular and humoral immunity. Use of homologous adenoviral regimens has largely been avoided because of presumed induction of antivector immunity, inhibiting the potency of a second dose.

Coronaviruses are enveloped, positive sense single-stranded RNA viruses with a glycoprotein spike on the surface, which mediates receptor binding and cell entry during infection. The roles of the spike protein in receptor binding and membrane fusion make it an attractive vaccine antigen. We have previously shown that a single dose of ChAdOx1 MERS, a chimpanzee adenovirus-vectored vaccine that encodes the spike protein of Middle East respiratory syndrome coronavirus (MERS-CoV), protected non-human primates against MERS-CoV-induced disease,[7] and data from a phase 1 clinical trial showed that ChAdOx1 MERS was safe and well tolerated at all three doses tested (5×10^9 viral particles, $2{\cdot}5\times10^{10}$ viral particles, and 5×10^{10} viral particles).[8] In addition, the highest dose elicited both humoral and cellular responses

against MERS-CoV in all vaccinees within 1 month of vaccination.

The ChAdOx1 nCoV-19 vaccine (AZD1222) consists of the replication-deficient simian adenovirus vector ChAdOx1, containing the full-length structural surface glycoprotein (spike protein) of SARS-CoV-2, with a tissue plasminogen activator leader sequence. ChAdOx1 nCoV-19 expresses a codon-optimised coding sequence for the spike protein (GenBank accession number MN908947).

In rhesus macaques, a single vaccination with ChAdOx1 nCoV-19 induced humoral and cellular immune responses. Protection against lower respiratory tract infection was observed in vaccinated non-human primates after high-dose SARS-CoV-2 challenge.[9]

We did a phase 1/2 single-blind, randomised controlled trial of ChAdOx1 nCoV-19 compared with a licensed meningococcal group A, C, W-135, and Y conjugate vaccine (MenACWY; Nimenrix, Pfizer, UK), as control vaccine, in healthy adults in the UK. In this preliminary report, we describe the immunogenicity, reactogenicity, and safety of vaccination with 5×10^{10} viral particles of ChAdOx1 nCoV-19 in single-dose and two-dose regimens.

Methods

Study design and participants

This phase 1/2, participant-blinded, multicentre, randomised controlled trial is being done at five centres in the UK (Centre for Clinical Vaccinology and Tropical Medicine, University of Oxford; NIHR Southampton Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton; Clinical Research Facility, Imperial College London; St Georges University of London and University Hospital NHS Foundation Trust; and University Hospitals Bristol and Weston NHS Foundation Trust). Healthy adult participants aged 18–55 years were recruited through local advertisements. All participants underwent a screening visit where a full medical history and examination was taken in addition to blood and urine tests (HIV; hepatitis B and C serology; full blood count; kidney and liver function tests; and urinary screen for blood, protein, and glucose and a pregnancy test done in women of childbearing potential). Volunteers with a history of laboratory confirmed SARS-CoV-2 infection; those at higher risk for SARS-CoV-2 exposure pre-enrolment (ie, front-line health-care workers working in emergency departments, intensive care units, and COVID-19 wards, and close contacts of confirmed COVID-19 cases; see appendix 1 p 82 for further details); and those with a new onset of fever, cough, shortness of breath, and anosmia or ageusia since Feb 1, 2020, were excluded from the study. An amendment to the study protocol (amendment date April 21, 2020) allowed for recruitment of health-care workers with a negative SARS-CoV-2 serology at screening, once an antibody test became available. As it was not possible to screen for negative SARS-CoV-2 serology in all participants, some enrolled participants had high-level anti-spike antibodies at baseline and their data are included in all analyses. Full details of the eligibility criteria are described in the trial protocol provided in the appendix 1 (pp 80–82).

Written informed consent was obtained from all participants, and the trial is being done in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. This study was approved in the UK by the Medicines and Healthcare products Regulatory Agency (reference 21584/0424/001-0001) and the South Central Berkshire Research Ethics Committee (reference 20/SC/0145). Vaccine use was authorised by Genetically Modified Organisms Safety Committees at each participating site.

Randomisation and masking

Participants were randomly assigned (1:1) to receive either the ChAdOx1 nCoV-19 vaccine or the MenACWY vaccine. MenACWY was used as a comparator vaccine to maintain blinding of participants who experienced local or systemic reactions, since these reactions are a known association with viral vector vaccinations. Use of saline as a placebo would risk unblinding participants as those who had notable reactions would know they were in the ChAdOx1 nCoV-19 vaccine group.

Randomisation lists, using block randomisation stratified by study group and study site, were generated by the study statistician (MV). Block sizes of two and four were chosen to align with the study group sizes and the sequence of enrolment, and varied across study groups. 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

The recombinant adenovirus for ChAdOx1 nCoV-19 was produced as previously described.[10] The vaccine was manufactured according to current Good Manufacturing Practice by the Clinical BioManufacturing Facility (University of Oxford, Oxford, UK) as previously described,[11] with only minor modifications, as described in the Investigational Medicinal Product Dossier and approved by the regulatory agency in the UK. ChAdOx1 nCoV-19 was administered at a dose of 5×10^{10} viral particles. 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 of 0·5 mL. Vaccines were administered as a single intramuscular injection into the deltoid.

Participants were recruited and followed up according to groups. Participants were recruited first for groups 1

and 3, then group 2, and then group 4. Group 1 (the phase 1 component of the study) consisted of participants who had intensive early follow-up visits for safety and immunogenicity purposes at days 3, 7, 14, 28, and 56 after vaccination. Group 2 consisted of participants who had higher blood volumes drawn for humoral and cellular immunogenicity assessment than group 4, which consisted of participants who had a serum sample drawn for humoral immunology assessments only. Group 3 consisted of ten participants who were enrolled in a non-randomised prime-boost group and received a booster ChAdOx1 nCoV-19 administered 28 days after the first dose. These participants were not blinded and had extensive follow-up for safety and immunogenicity purposes, as per group 1, after each dose. A staggered-enrolment approach was used for the first two, six, and 90 participants recruited in groups 1 and 3 (appendix 1 p 89) and interim safety reviews with the independent Data and Safety Monitoring Board were done before proceeding with vaccinations in larger numbers of volunteers. Volunteers were considered enrolled into the trial at the point of vaccination.

Participants in all groups had blood samples drawn and clinical assessments for safety as well as immunology at days 0 and 28, and will also be followed up at days 184 and 364. A later amendment to the protocol (amendment date June 22, 2020) provided for additional testing of booster vaccinations in a subset of participants, the results of which are not yet available and are not included in this Article.

In two of the five trial sites (Oxford and Southampton), a protocol amendment (amendment date May 6, 2020) was implemented to allow prophylactic paracetamol to be administered before vaccination and participants were advised to continue with 1 g of paracetamol every 6 h for 24 h to reduce vaccine-associated reactions. All participants enrolled after the protocol amendment at these two sites were given prophylactic paracetamol and randomised equally to the vaccine or control arms of the study.

Participants were observed in the clinic for 30–60 min after the vaccination procedure and were asked to record any adverse events using electronic diaries during the 28-day follow-up period. Expected and protocol-defined local site reactions (injection site pain, tenderness, warmth, redness, swelling, induration, and itch) and systemic symptoms (malaise, muscle ache, joint pain, fatigue, nausea, headache, chills, feverishness [ie, a self-reported feeling of having a fever], and objective fever defined as an oral temperature of 38°C or higher) were recorded for 7 days. All other events were recorded for 28 days and serious adverse events are recorded throughout the follow-up period.

Severity of adverse events are 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 [some assistance might be needed] and no or minimal medical intervention or therapy required), severe (marked limitation in activity [some assistance usually required] and medical intervention or therapy required), and potentially life-threatening (requires assessment in emergency department or hospitalisation). Unsolicited adverse events are reviewed for causality by two clinicians blinded to group allocation, and events considered to be possibly, probably, or definitely related to the study vaccines were reported. Laboratory adverse events were graded by use of site-specific toxicity tables, which were adapted from the US Food and Drug Administration toxicity grading scale.

Cellular responses were assessed using an ex-vivo interferon-γ enzyme-linked immunospot (ELISpot) assay to enumerate antigen-specific T cells. Humoral responses at baseline and following vaccination were assessed using a standardised total IgG ELISA against trimeric SARS CoV-2 spike protein, a muliplexed immunoassay (Meso Scale Discovery multiplexed immunoassay [MIA] against spike and receptor binding domain), three live SARS-CoV-2 neutralisation assays (Public Health England [PHE] plaque reduction neutralisation test [PRNT IC_{50}], PHE microneutralisation assay [MNA IC_{50}, IC_{80}, IC_{90}], and Marburg virus neutralisation [VN IC_{100}]), and a pseudovirus neutralisation assay (PseudoNA IC_{50}). PHE PRNT is a live neutralisation assay and was done at PHE (Porton Down, UK). PHE MNA is a rapid microneutralisation assay, which was conducted in the same laboratory. The third assay, Marburg VN, was conducted at Marburg University (Marburg, Germany). Full details on the assays are provided in the appendix 1 (pp 31–34). Owing to the labour-intensive nature of some of these assays, we prioritised analysis of samples from the ChAdOx1 nCoV-19 group, randomly selecting more samples from ChAdOx1 nCoV-19 participants than control samples to be sent for analysis.

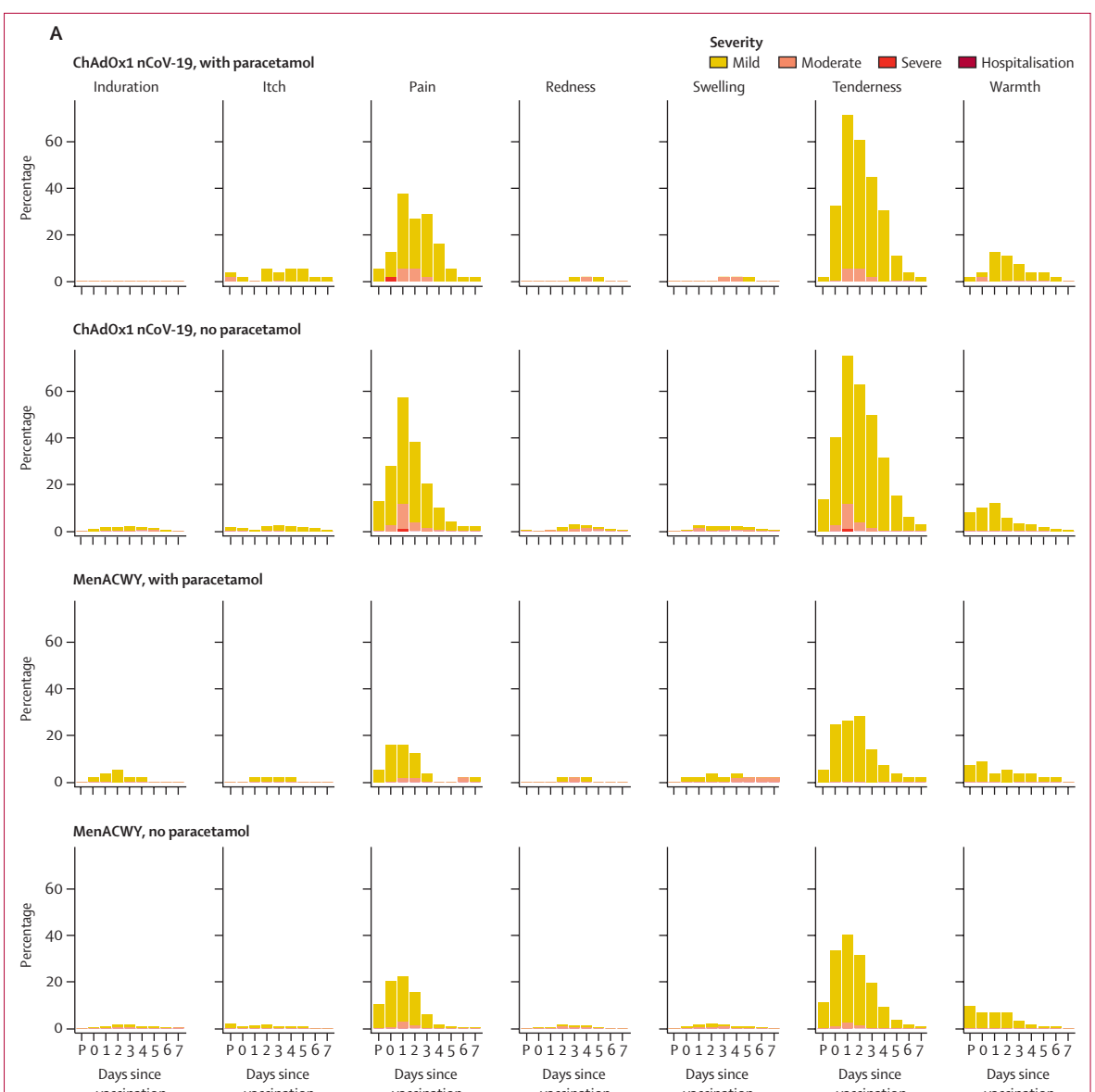
Convalescent plasma samples from adults (≥18 years) with PCR-positive SARS-CoV-2 infection were obtained from symptomatic patients admitted to hospital or from surveillance on health-care workers who did not have symptomatic infection. These samples were tested using standardised ELISA, MIA, PseudoNA, and Marburg VN. Different samples were analysed across the assays, dependent on sample availability, laboratory capacity, and assay-specific requirements. Where multiple longitudinal samples were available for the same participant, only one timepoint is included in the analyses in this Article and the earliest timepoint (at least 20 days after initial symptoms) was selected.

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, and efficacy against hospital-attended COVID-19, death, and seroconversion against non-spike proteins (appendix 1 pp 72–73). Preliminary results for secondary endpoints are reported here: occurrence of local and systemic reactogenicity signs and symptoms for 7 days after vaccination; occurrence of unsolicited adverse events for 28 days after vaccination; change from day 0 (baseline) to day 28 for safety laboratory measures; and cellular and humoral immunogenicity of ChAdOx1 nCoV-19. Neutralising antibodies and laboratory adverse events were tested on participants in groups 1 and 3 only. Unsolicited adverse events are reported for group 1 only.

The convalescent sample collection of PCR-positive hospitalised patients with COVID-19 or asymptomatic health-care workers was done to characterise the immunological properties of COVID-19 and not for the purposes of the clinical trial (Gastrointestinal Illness in Oxford: COVID substudy [Sheffield Research Ethics Committee reference: 16/YH/0247], ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections [Oxford Research Ethics Committee C reference 13/SC/0149], and Sepsis Immunomics project [Oxford Research Ethics Committee C, reference 19/SC/0296]).



(Figure 1 continues on next page)

Statistical analysis

Safety endpoints are described as frequencies (%) with 95% binomial exact CIs. Medians and IQRs are presented for immunological endpoints and analyses are considered descriptive only, as the full set of samples have not yet been analysed on all platforms and therefore results reported here are preliminary. Participants were analysed according to the group to which they were randomised. To assess the effect of prophylactic paracetamol use, the occurence of adverse reactions in the first 2 days after vaccination was analysed as a binary variable using adjusted logistic regression with results presented as adjusted odds ratios. The model adjusted for age, sex, occupation (health-care worker or not), smoking, alcohol consumption, and body-mass index. To assess the relationship between responses on different assays, linear regression was used to analyse log-transformed post-baseline values. Statistical analyses were done using SAS version 9.4 and R version 3.6.1 or later.

The sample size for the study was determined by the number of doses of vaccine that were available for use after the initial clinical manufacturing process. Sample sizes for efficacy are based on the number of primary outcome events that accrue and are presented in the protocol

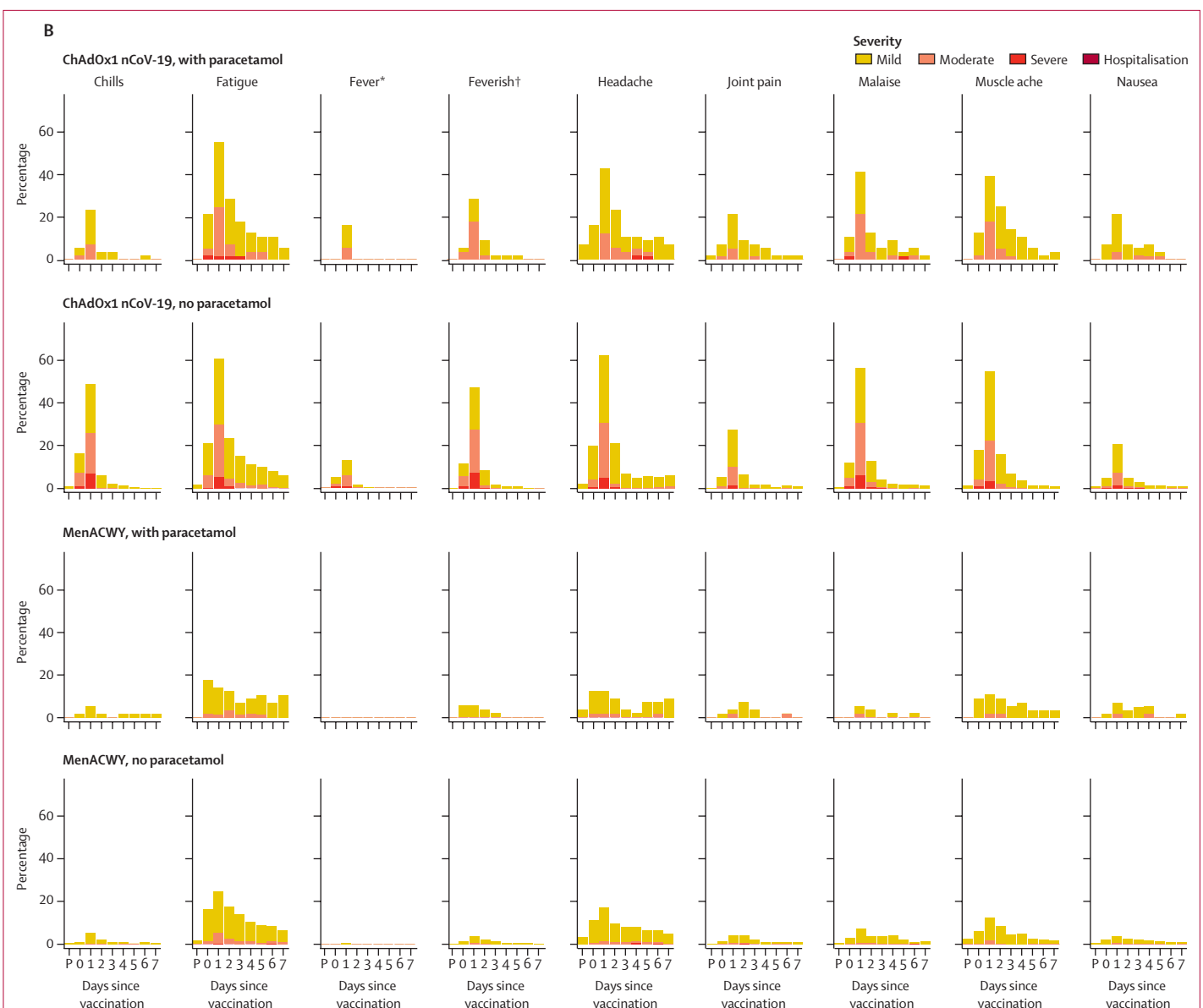


Figure 1: **Solicited local (A) and systemic (B) adverse reactions in first 7 days after vaccination as recorded in participant symptom electronic diaries**
Day 0 is the day of vaccination. P=60-min post-vaccination observation period in the clinic. MenACWY=meningococcal group A, C, W-135, and Y conjugate vaccine. *Mild: 38·0°C to <38·5°C; moderate: 38·5°C to <39·0°C; severe: ≥39·0°C. †Self-reported feeling of feverishness.

(appendix 1 pp 116–117). Efficacy analyses have not yet been done and are not included in this Article.

An independent data and safety monitoring board provided safety oversight (appendix 1 p 46). This study is registered with ClinicalTrials.gov, NCT04324606, and with ISRCTN, 15281137.

Role of the 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 April 23 and May 21, 2020, 1077 participants were enrolled into the study and assigned to vaccination with either ChAdOx1 nCoV-19 (n=543) or MenACWY (n=534; appendix 1 p 3); ten of these participants were enrolled in group 3, the prime-boost group, and thus were not randomly assigned. 88 participants were included in group 1, 412 in group 2, and 567 in group 4 (appendix 1

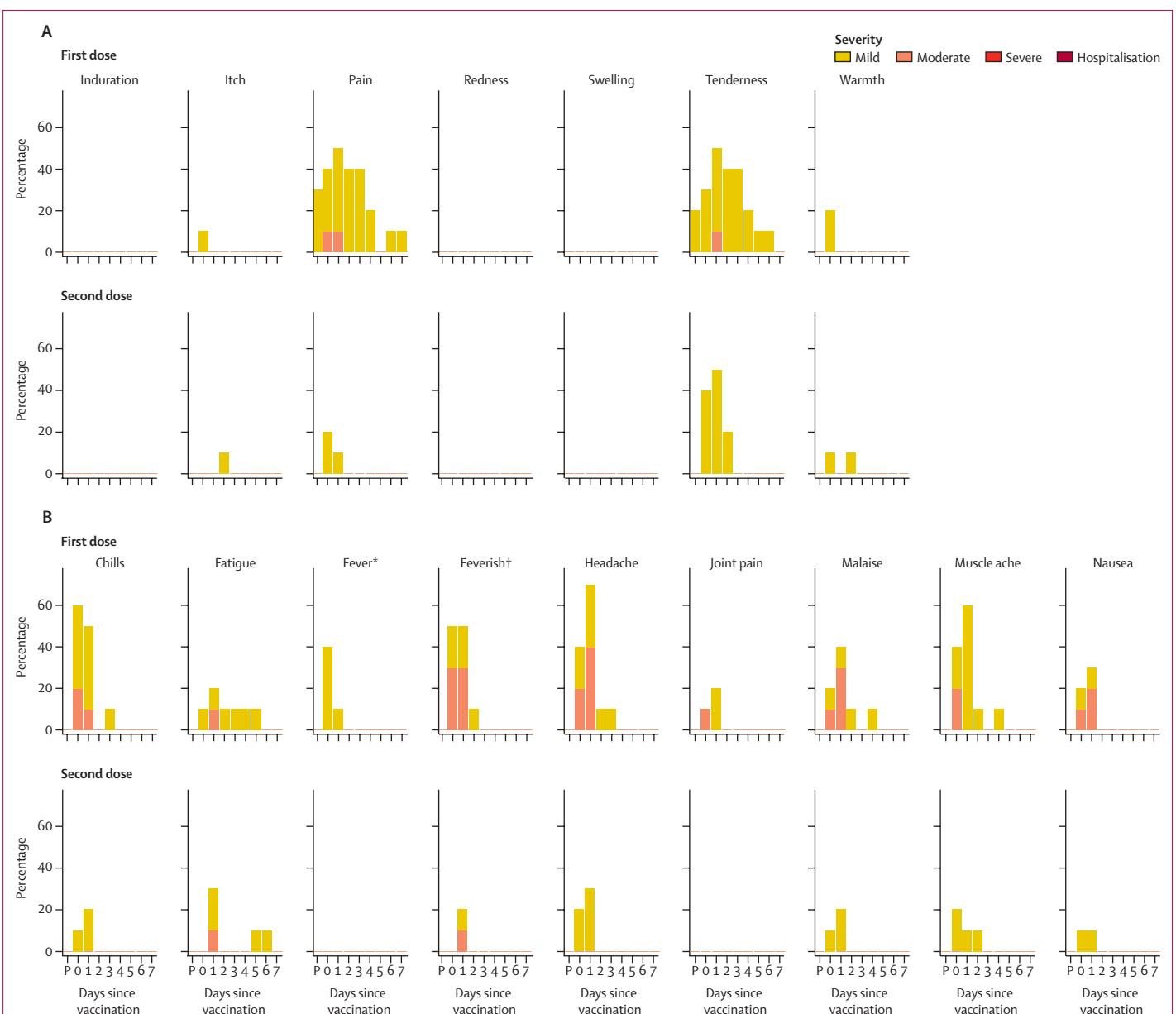


Figure 2: **Solicited local (A) and systemic (B) adverse reactions in first 7 days after priming and booster doses of ChAdOx1 nCoV-19 in the non-randomised subset of ten participants**
Day 0 is the day of vaccination. P=60-min post-vaccination observation period in the clinic. *Mild: 38·0°C to <38·5°C; moderate: 38·5°C to <39·0°C; severe: ≥39·0°C. †Self-reported feeling of feverishness.

p 3). All randomised participants were vaccinated; one participant in the MenACWY group received the ChAdOx1 nCoV-19 vaccine (appendix 1 p 3).

The median age of participants was 35 years (IQR 28–44 years), 536 (49·8%) participants were female and 541 (50·2%) were male, and the majority of participants (979 [90·9%]) were white (appendix 1 p 4). Baseline characteristics seemed similar between randomised groups (appendix 1 p 4).

56 participants in the ChAdOx1 nCoV-19 group and 57 in the MenACWY group received prophylactic paracetamol. In those who did not receive prophylactic paracetamol, 328 (67%) of 487 participants in the ChAdOx1 nCoV-19 group and 180 (38%) of 477 participants in the MenACWY group reported pain after vaccination, which was mostly mild to moderate in intensity (appendix 1 pp 5–7). With prophylactic paracetamol, pain was reported by fewer participants: 28 (50%) in the ChAdOx1 nCoV-19 group and 18 (32%) in the MenACWY group. Tenderness of mostly mild intensity was reported in the ChAdOx1 nCoV-19 group by 403 (83%) participants without paracetamol and 43 (77%) with paracetamol, and in the MenACWY group by 276 (58%) participants without paracetamol and 26 (46%) with paracetamol (figure 1; appendix 1 pp 5–7).

Fatigue and headache were the most commonly reported systemic reactions. Fatigue was reported in the ChAdOx1 nCoV-19 group by 340 (70%) participants without paracetamol and 40 (71%) with paracetamol and in the MenACWY group by 227 (48%) participants without paracetamol and 26 (46%) with paracetamol, whereas headaches were reported in the ChAdOx1 nCoV-19 group by 331 (68%) participants without paracetamol and 34 (61%) with paracetamol and in the MenACWY group by 195 (41%) participants without paracetamol and 21 (37%) participants with paracetamol.

Other systemic adverse reactions were common in the ChAdOx1 nCoV-19 group: muscle ache (294 [60%] participants without paracetamol and 27 [48%] with paracetamol), malaise (296 [61%] and 27 [48%]), chills (272 [56%] and 15 [27%]); and feeling feverish (250 [51%] and 20 [36%]). In the of ChAdOx1 nCoV-19 group, 87 (18%) participants without paracetamol and nine (16%) participants with paracetamol reported a temperature of at least 38°C, and eight (2%) patients without paracetamol had a temperature of at least 39°C. In comparison, two (<1%) of those receiving MenACWY reported a fever of at least 38°C, none of whom were receiving prophylactic paracetamol (figure 1; appendix 1 pp 5–7).

The severity and intensity of local and systemic reactions was highest on day 1 after vaccination (figure 1).

Adjusted analysis of the effect of prophylactic paracetamol on adverse reactions of any severity in the first 2 days after vaccination with ChAdOx1 nCoV-19 showed significant reductions in pain, feeling feverish, chills, muscle ache, headache, and malaise (appendix 1 pp 10–11).

All ten participants in the prime-boost group received their booster vaccine at day 28; solicited local and systemic reactions were measured in these participants for 7 days after both the prime and booster doses. The reactogenicity profile after the second dose appeared less severe in this subset, although the small number of participants in this group led to wide CIs (figure 2; appendix 1 pp 8–9).

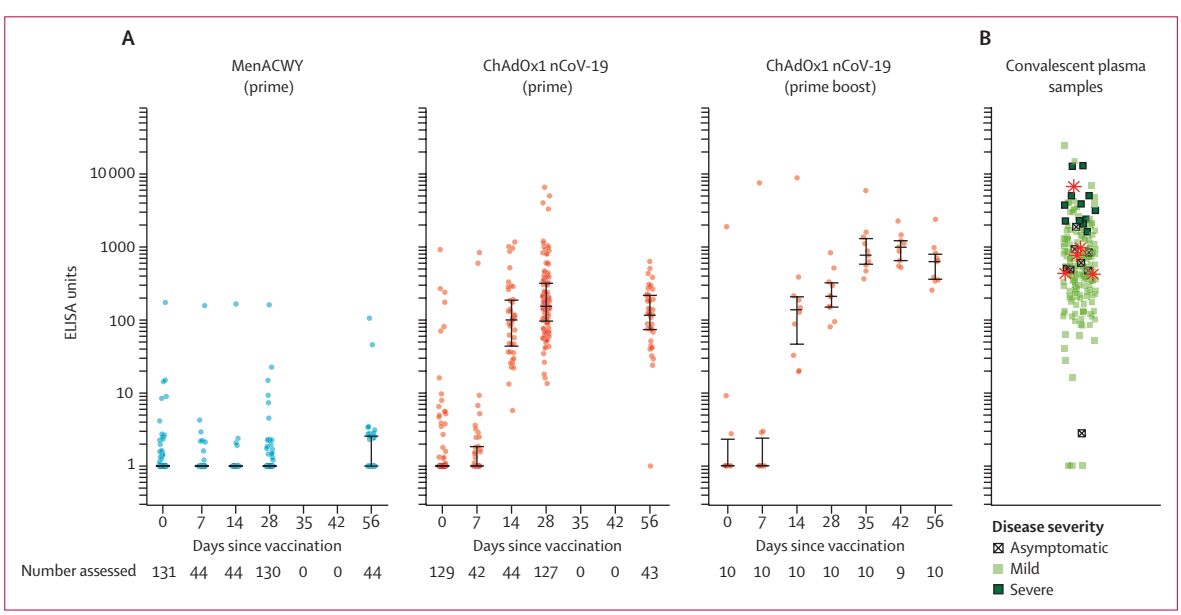


Figure 3: **SARS-CoV-2 IgG response by standardised ELISA to spike protein in trial participants (A) and in 180 convalescent plasma samples from 172 patients with PCR-confirmed COVID-19 and eight asymptomatic health-care workers (B)**

Error bars show median (IQR). Participants in the prime boost group received their second dose at day 28. Lower limit of quantification is 1 ELISA unit. Red stars in panel B show five samples also tested on the Marburg VN assay (see figure 4). MenACWY=meningococcal group A, C, W-135, and Y conjugate vaccine. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

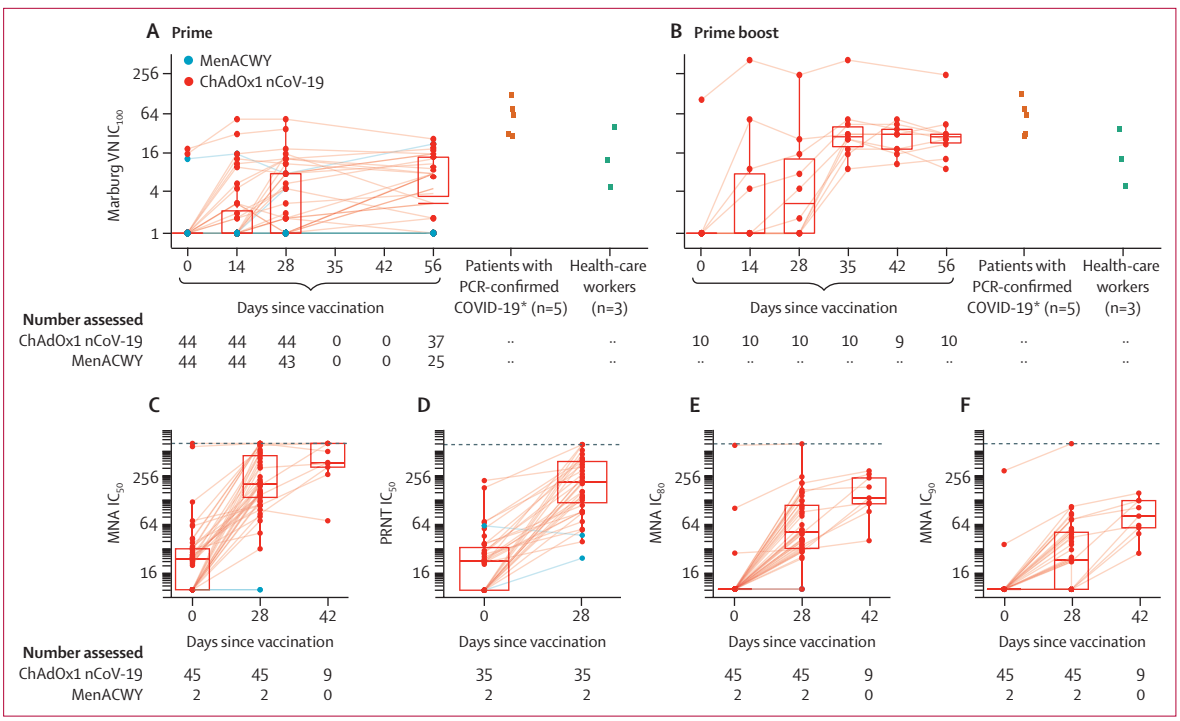


Figure 4: **Live SARS-CoV-2 neutralisation assays (Marburg VN and PHE PRNT$_{50}$) and microneutralisation assays (PHE MNA)**
Panels A and B show live SARS-CoV-2 neutralisation (Marburg VN) in prime (A) and prime boost (B) trial participants (boosted at day 28) and convalescent plasma from patients with PCR-confirmed COVID-19 and asymptomatic health-care workers. Panels C, E, and F show the PHE MNA (at IC$_{50}$, IC$_{80}$, and IC$_{90}$, respectively) and panel D the PHE PRNT$_{50}$. The day 42 timepoint was only measured in participants who received a booster dose at day 28. Solid lines connect samples from the same participant. Boxes show median (IQR). Dotted lines show upper limits of detection. MenACWY=meningococcal group A, C, W-135, and Y conjugate vaccine. PHE=Public Health England. MNA=microneutralisation assay. PRNT=plaque reduction neutralisation test. VN=virus neutralisation. IC=inhibitory concentration. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *ELISA results for these five convalescent plasma samples are shown in figure 3 as red stars.

Unsolicited adverse events in the 28 days following vaccination considered to be possibly, probably, or definitely related to ChAdOx1 nCoV-19 were predominantly mild and moderate in nature and resolved within the follow-up period (appendix 1 pp 12–15). Laboratory adverse events considered to be at least possibly related to the study intervention were self-limiting and predominantly mild or moderate in severity (data not shown). Transient haematological changes from baseline (neutropenia) were observed in 25 (46%) of 54 participants in the ChAdOx1 nCoV-19 group compared with three (7%) of 44 participants in the MenACWY group. There was one serious adverse event in the MenACWY group consisting of a new diagnosis of haemolytic anaemia, occurring 9 days after vaccination. The participant was clinically well throughout the study. The event was reported as a suspected unexpected serious adverse reaction relating to the MenACWY vaccine.

In the ChAdOx1 nCoV-19 group, antibodies against SARS-CoV-2 spike protein peaked by day 28 (median 157 ELISA units [EU], IQR 96–317; n=127) and remained elevated to day 56 (119 EU, 70–203; n=43) in participants who received only one dose, and increased to a median of 639 EU (360–792) at day 56 in the ten participants who received a booster dose (figure 3).

Similar increases in serum antibody levels to both the spike protein and the receptor binding domain by day 28 and after a booster dose were observed when measured by MIA (appendix 1 p 16). Immunogenicity among those who were advised to take paracetamol prophylactically was

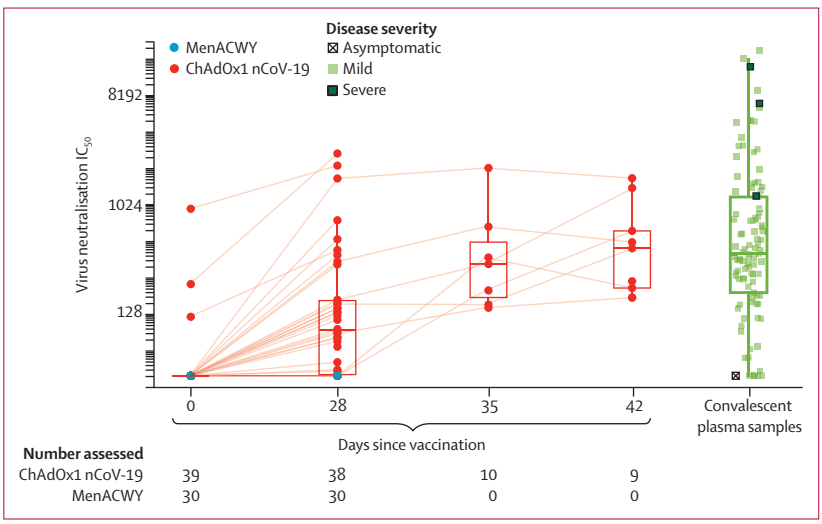


Figure 5: **PseudoNA results in trial participants and in convalescent plasma samples from 146 patients with PCR-confirmed COVID-19 and 24 asymptomatic health-care workers**
Solid lines connect samples from the same participant. Boxes show median (IQR). Results for days 35 and 42 are samples from participants who received a booster dose at day 28. IC=inhibitory concentration. MenACWY=meningococcal group A, C, W-135, and Y conjugate vaccine.

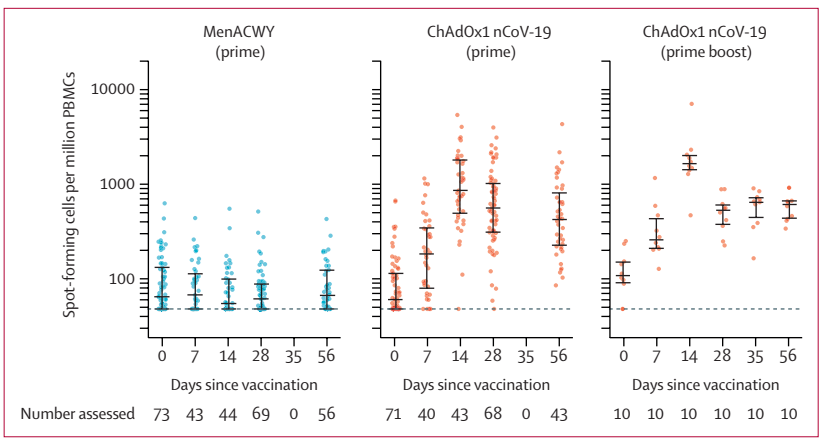


Figure 6: **Interferon-γ ELISpot response to peptides spanning the SARS-CoV-2 spike vaccine insert**
Error bars show median (IQR). The lower limit of detection, indicated with the dotted line, is 48 spot-forming cells per million PBMCs. PBMC=peripheral blood mononuclear cell. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. ELISpot=enzyme linked immunospot. MenACWY=meningococcal group A, C, W-135, and Y conjugate vaccine.

similar to that seen among those who were not advised to use it prophylactically (data not shown).

In the PHE $PRNT_{50}$ assay, which determined the extent to which serum can be diluted and still reduce SARS-CoV-2 plaque formation by 50%, 35 (100%) of 35 participants achieved neutralising titres with a median titre of 218 (IQR 122–395) at day 28 and similar results were obtained with the PHE MNA_{80} assay, with titres inducing 80% virus neutralisation achieved in 32 (91%) of 35 participants after one dose (median titre 51, 32–103), and in nine (100%) of nine participants after the booster dose (median titre 136, 115–241; figure 4; appendix 1 pp 17–19). In the Marburg VN assay, 23 (62%) of 37 recipients had neutralising antibodies that induced complete inhibition of the cytopathic effect caused by SARS-CoV-2 by day 56 after one dose, as did ten (100%) of ten participants after a booster dose, with a median titre of 29 (24–32; figure 4).

Titres from the PseudoNA assay and the Marburg VN assay correlated positively with other live virus neutralisation assay titres and with ELISA (PseudoNA R^2=0·53 and Marburg VN R^2=0·67; both p<0·001; figure 4, 5; appendix 1 pp 20–21). We included responses following natural exposure as a point of reference for vaccine response data, and found that vaccine-induced responses were in a similar range (figure 5). Interferon-γ ELISpot responses against SARS-CoV-2 spike peptides peaked at 856 spot-forming cells per million peripheral blood mononuclear cells (IQR 493–1802; n=43) at day 14, declining to 424 (221–799; n=43) by day 56 after vaccination (figure 6).

A small number (four [4%] of 98) participants had neutralising antibody titres greater than 8 against SARS-CoV-2 spike protein before vaccination (Marburg VN) and 11 (4%) of 270 participants had high ELISA titres at baseline, representing possible prior asymptomatic infection.

Before vaccination, only one (1%) of 98 participants who were tested had high titre (>200) neutralising antibodies against ChAdOx1. Antibodies were detectable at a lower level in a further 18 (18%) participants, and in 79 (81%) participants there were no detectable anti-ChAdOx1 antibodies. We found no relationship between presence of low-level antibodies to ChAdOx1 on the day of vaccination and the ELISA titre to SARS-CoV-2 spike protein in those randomly assigned to receive ChAdOx1 nCoV-19 (appendix 1 p 22).

Discussion

Our preliminary findings show that the candidate ChAdOx1 nCoV-19 vaccine given as a single dose was safe and tolerated, despite a higher reactogenicity profile than the control vaccine, MenACWY. No serious adverse reactions to ChAdOx1 nCoV-19 occurred. The majority of adverse events reported were mild or moderate in severity, and all were self-limiting. The profile of adverse events reported here is similar to that for other ChAdOx1-vectored vaccines and other closely related simian adenoviruses, such as ChAdOx2, ChAd3, and ChAd63, expressing multiple different antigens[8,12–14] at this dose level, as well as to some licensed vaccines.[15] A dose of 5×10^{10} viral particles was chosen on the basis of our previous experience with ChAdOx1 MERS, where despite increased reactogenicity, a dose–response relationship with neutralising antibodies was observed.[8] The protocol was written when the pandemic was accelerating in the UK and a single higher dose was chosen to provide the highest chance of rapid induction of neutralising antibody. In the context of a pandemic wave where a single higher, but more reactogenic, dose might be more likely to rapidly induce protective immunity, the use of prophylactic paracetamol appears to increase tolerability and would reduce confusion with COVID-19 symptoms that might be caused by short-lived vaccine-related symptoms without compromising immunogenicity.

We show that a single dose of ChAdOx1 nCoV-19 elicits an increase in spike-specific antibodies by day 28 and neutralising antibody in all participants after a booster dose. High levels of neutralising antibody at baseline seen in a small number of participants probably indicates prior asymptomatic infection, as potential participants with recent COVID-19-like symptoms or with a history of positive PCR test for SARS-CoV-2 were excluded from the study. Individuals with high titres on the day of vaccination who received ChAdOx1 nCoV-19 were boosted by vaccination.

Neutralising antibodies targeting different epitopes of the spike glycoprotein have been associated with protection from COVID-19 in early preclinical rhesus macaque studies.[16] Although a correlate of protection has not been defined for COVID-19, high levels of neutralising antibodies have been shown in convalescent individuals, with a wide range, as confirmed in our study.[17,18]

Antibodies capable of neutralising live SARS-CoV-2 were induced by day 28 with titres of 51 (PHE MNA_{80}) and 218 (PHE $PRNT_{50}$), and with titres of 29 (Marburg VN) or

136 (PHE MNA_{80}) after a booster dose, as measured using different assays. In a non-human primate study where primary SARS-CoV-2 infection elicited at least short-term protection against reinfection, neutralising antibody titres of the magnitude found in our study after boosting appeared sufficient to confer protection using the Marburg VN assay methodology.[19] Neutralising antibody titres were increased by a two-dose regimen, and further investigation of this approach is underway. The correlation of neutralisation assays with IgG quantitation indicates that, if confirmed, a standardised ELISA might be sufficient to predict protection, should neutralising antibody also be shown to be protective in humans. We have presented data from three different live neutralising antibody assays and a pseudo-neutralisation assay, which show tight correlation with each other but give very different neutralising antibody titres. This issue highlights the urgent need for centralised laboratory infrastructure to allow bridging between vaccine candidates and accelerate the availability of multiple products to provide the global capacity to end the pandemic. If any one candidate demonstrates efficacy, bridging this result to other candidate vaccines through rigorously conducted laboratory assays will become a crucial issue for global health.

Importantly, there are accumulating data to suggest T-cell responses play an important role in COVID-19 mitigation; individuals who were exposed but asymptomatic developed a robust memory T-cell response without symptomatic disease in the absence of a measurable humoral response.[20–22] Adenovirus-vectored vaccines are known to induce strong cellular immunity and ChAdOx1 nCoV-19 vaccination resulted in marked increases in SARS-CoV-2 spike-specific effector T-cell responses as early as day 7, peaking at day 14 and maintained up to day 56 as expected with adenoviral vectors. However, a boost in cellular responses was not observed following the second ChAdOx1 nCoV-19 dose. This is consistent with previous findings on viral vectored vaccines given as part of a homologous prime-boost regimen.[12]

Severe and fatal cases of COVID-19 disproportionally affect older individuals. Therefore, it is important that vaccines developed to reduce or prevent COVID-19 are suitable for administration in older age groups. Immunogenicity of a ChAdOx1-vectored vaccine against influenza has been shown in older adults (50–78 years of age).[6] As previously reported,[10] anti-vector immunity was low before vaccination in UK adults aged 18–55 years, with no relationship between the presence of antibodies to ChAdOx1 and immune response to the vaccine antigen. Future studies will address the potential effect of anti-vector antibodies on homologous boosting, although in the subgroup reported on here, who received two vaccinations 28 days apart, there was clear evidence of boosting of antibody response to SARS-CoV-2 spike protein.

Limitations of this study include the short follow-up reported to date, the small number of participants in the prime-boost group, and single-blinded design, although staff undertaking clinical evaluation and laboratory staff all remained blinded. Additionally, the study findings are not easily generalisable, as this is a first-in-human study of fairly young and healthy volunteers, the majority of whom were white. Further studies are required to assess the vaccine in various population groups including older age groups, those with comorbidities, and in ethnically and geographically diverse populations. The participants recruited in this study will be followed up for at least 1 year and further safety, tolerability, and immunogenicity (in addition to efficacy) results will be reported when data are available.[23–25]

In conclusion, ChAdOx1 nCoV-19 was safe, tolerated, and immunogenic, while reactogenicity was reduced with paracetamol. A single dose elicited both humoral and cellular responses against SARS-CoV-2, with a booster immunisation augmenting neutralising antibody titres. The preliminary results of this first-in-human clinical trial supported clinical development progression into ongoing phase 2 and 3 trials. Older age groups with comorbidities, health-care workers, and those with higher risk for SARS-CoV-2 exposure are being recruited and assessed for efficacy, safety, and immunogenicity of ChAdOx1 nCoV-19 given as a single-dose or two-dose administration regimen in further trials conducted in the UK and overseas. We will also evaluate the vaccine in children, once sufficient safety data have been accumulated in adult studies. Phase 3 trials are now underway in Brazil, South Africa, and the UK and will evaluate vaccine efficacy in diverse populations.

Contributors

SCG and AJP conceived and designed the trial and AJP is the chief investigator. AJP, PMF, DJ, HR, and MV contributed to the protocol and design of the study. AF, PH, RL, KMP, SNF, BA, and AVSH were the study site principal investigators. DB, MB, CD, SBi, SBe, EAC, TL, KJE, ALF, BH, RM, and SB-R were responsible for laboratory testing and assay development. PKA, DJ, HR, PMF, AMM, MR, and MS contributed to the implementation of the study. MV conducted the statistical analysis. CG, ADD, and RT were responsible for vaccine manufacturing. TL and SCG were responsible for vaccine development. AVSH and SCG developed the ChAdOx1 vector. TL, KJE, MV, SCG, AVSH, PMF, and AJP contributed to the preparation of the report. 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

SCG is co-founder and board member 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 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. AF is a member of JCVI, Chair of the WHO European Technical Advisory Group of Experts on Immunisation, an ex-officio member of WHO SAGE working group on COVID-19 vaccines, and acting director of National Institute for Health Research West of England Local Clinical Research Network. KMP reports grants from the NIHR Imperial Biomedical Research Centre and Gilead Sciences, and personal fees from Sanofi Pasteur, outside of the submitted work. 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.

Data sharing

The study protocol is provided in the appendix 1 (pp 49–130). Individual 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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Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial

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Summary

Background Older adults (aged ≥70 years) are at increased 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 worse in older adults as a result of immunosenescence. We have reported the immunogenicity of a novel chimpanzee adenovirus-vectored vaccine, ChAdOx1 nCoV-19, in young adults, and now describe the safety and immunogenicity of this vaccine in a wider range of participants, including adults aged 70 years and older.

Methods In this report of the phase 2 component of a single-blind, randomised, controlled, phase 2/3 trial (COV002), healthy adults aged 18 years and older were enrolled at two UK clinical research facilities, in an age-escalation manner, into 18–55 years, 56–69 years, and 70 years and older immunogenicity subgroups. Participants were eligible if they did not have severe or uncontrolled medical comorbidities or a high frailty score (if aged ≥65 years). First, participants were recruited to a low-dose cohort, and within each age group, participants were randomly assigned to receive either intramuscular ChAdOx1 nCoV-19 ($2·2\times10^{10}$ virus particles) or a control vaccine, MenACWY, using block randomisation and stratified by age and dose group and study site, using the following ratios: in the 18–55 years group, 1:1 to either two doses of ChAdOx1 nCoV-19 or two doses of MenACWY; in the 56–69 years group, 3:1:3:1 to one dose of ChAdOx1 nCoV-19, one dose of MenACWY, two doses of ChAdOx1 nCoV-19, or two doses of MenACWY; and in the 70 years and older, 5:1:5:1 to one dose of ChAdOx1 nCoV-19, one dose of MenACWY, two doses of ChAdOx1 nCoV-19, or two doses of MenACWY. Prime-booster regimens were given 28 days apart. Participants were then recruited to the standard-dose cohort ($3·5–6·5\times10^{10}$ virus particles of ChAdOx1 nCoV-19) and the same randomisation procedures were followed, except the 18–55 years group was assigned in a 5:1 ratio to two doses of ChAdOx1 nCoV-19 or two doses of MenACWY. Participants and investigators, but not staff administering the vaccine, were masked to vaccine allocation. The specific objectives of this report were to assess the safety and humoral and cellular immunogenicity of a single-dose and two-dose schedule in adults older than 55 years. Humoral responses at baseline and after each vaccination until 1 year after the booster were assessed using an in-house standardised ELISA, a multiplex immunoassay, and a live severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) microneutralisation assay (MNA_{80}). Cellular responses were assessed using an ex-vivo IFN-γ enzyme-linked immunospot assay. The coprimary outcomes of the trial were efficacy, as measured by the number of cases of symptomatic, virologically confirmed COVID-19, and safety, as measured by the occurrence of serious adverse events. Analyses were by group allocation in participants who received the vaccine. Here, we report the preliminary findings on safety, reactogenicity, and cellular and humoral immune responses. This study is ongoing and is registered with ClinicalTrials.gov, NCT04400838, and ISRCTN, 15281137.

Findings Between May 30 and Aug 8, 2020, 560 participants were enrolled: 160 aged 18–55 years (100 assigned to ChAdOx1 nCoV-19, 60 assigned to MenACWY), 160 aged 56–69 years (120 assigned to ChAdOx1 nCoV-19: 40 assigned to MenACWY), and 240 aged 70 years and older (200 assigned to ChAdOx1 nCoV-19: 40 assigned to MenACWY). Seven participants did not receive the boost dose of their assigned two-dose regimen, one participant received the incorrect vaccine, and three were excluded from immunogenicity analyses due to incorrectly labelled samples. 280 (50%) of 552 analysable participants were female. Local and systemic reactions were more common in participants given ChAdOx1 nCoV-19 than in those given the control vaccine, and similar in nature to those previously reported

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(injection-site pain, feeling feverish, muscle ache, headache), but were less common in older adults (aged ≥56 years) than younger adults. In those receiving two standard doses of ChAdOx1 nCoV-19, after the prime vaccination local reactions were reported in 43 (88%) of 49 participants in the 18–55 years group, 22 (73%) of 30 in the 56–69 years group, and 30 (61%) of 49 in the 70 years and older group, and systemic reactions in 42 (86%) participants in the 18–55 years group, 23 (77%) in the 56–69 years group, and 32 (65%) in the 70 years and older group. As of Oct 26, 2020, 13 serious adverse events occurred during the study period, none of which were considered to be related to either study vaccine. In participants who received two doses of vaccine, median anti-spike SARS-CoV-2 IgG responses 28 days after the boost dose were similar across the three age cohorts (standard-dose groups: 18–55 years, 20 713 arbitrary units [AU]/mL [IQR 13 898–33 550], n=39; 56–69 years, 16 170 AU/mL [10 233–40 353], n=26; and ≥70 years 17 561 AU/mL [9705–37 796], n=47; p=0·68). Neutralising antibody titres after a boost dose were similar across all age groups (median MNA_{80} at day 42 in the standard-dose groups: 18–55 years, 193 [IQR 113–238], n=39; 56–69 years, 144 [119–347], n=20; and ≥70 years, 161 [73–323], n=47; p=0·40). By 14 days after the boost dose, 208 (>99%) of 209 boosted participants had neutralising antibody responses. T-cell responses peaked at day 14 after a single standard dose of ChAdOx1 nCoV-19 (18–55 years: median 1187 spot-forming cells [SFCs] per million peripheral blood mononuclear cells [IQR 841–2428], n=24; 56–69 years: 797 SFCs [383–1817], n=29; and ≥70 years: 977 SFCs [458–1914], n=48).

Interpretation **ChAdOx1 nCoV-19 appears to be better tolerated in older adults than in younger adults and has similar immunogenicity across all age groups after a boost dose. Further assessment of the efficacy of this vaccine is warranted in all age groups and individuals with comorbidities.**

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Introduction

As of Nov 13, 2020, over 52 million people have been diagnosed with COVID-19 worldwide, with over 1·2 million confirmed deaths.[1] Severe COVID-19 is more common in adults aged 70 years and older and in individuals with comorbidities such as hypertension, diabetes, cardiovascular disease, and chronic respiratory disease.[2] A safe and effective vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) will be an important tool in controlling the global COVID-19 pandemic. Although there are no licensed vaccines against COVID-19, 48 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 in clinical trials (of which 11 candidates are in phase 3 trials) and a further 164 candidates are in preclinical testing.[3]

The WHO global target product profile of critical characteristics for prequalification of a COVID-19 vaccine requires candidates to be targeted at the most at-risk groups, including older adults; have a favourable safety profile; provide efficacy as measured by prevention of virologically confirmed disease or transmission, or both; and to provide at least 6 months of protection for individuals at ongoing risk of exposure to SARS-CoV-2.[4] On Sept 25, 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: first, older adults living in residential care homes and residential care home workers; second, all adults aged 80 years or older and health-care and social-care workers; and third, all adults aged 75 years and older. However, the JCVI acknowledged that this priority ranking could change substantially if the first available vaccines were not considered safe or effective in older adults. Similar recommendations have also been made by the US Advisory Committee on Immunization Practices.[6]

Immunosenescence refers to the gradual deterioration and decline of the immune system brought on by ageing. Age-dependent differences in the functionality and availability of T-cell and B-cell populations are thought to have a key role in the decrease of immune response.[7] There has been a drive to develop vaccines and adjuvant formulations tailored for older adults to overcome this diminished immune response after vaccination. Assessment of immune responses in older adults is therefore essential in the development of COVID-19 vaccines that could protect this susceptible 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.[8] Most COVID-19 candidate vaccines have been developed to induce anti-spike protein immune responses. Clinical trials using several different vaccine platforms including mRNA,[9,10] adenoviral vectored vaccines,[11,12] inactivated virus,[13,14] and adjuvanted

Research in context

Evidence before this study

We searched PubMed for research articles published from database inception until Nov 13, 2020, with no language restrictions, using the terms "SARS-CoV-2", "vaccine", AND "clinical trial". We identified published clinical trial data on eight other vaccine candidates. Two recombinant viral vectored vaccines have been tested in clinical trials. A single dose adenovirus (Ad) 5 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 older than 55 years. A heterologous prime-boost Ad5/Ad26-vectored vaccine schedule (Gamaleya Research Institute, Russia) generated neutralising antibody and cellular responses in adults younger than 60 years. Two nucleoside-modified mRNA vaccine candidates using a two-dose regimen were tested in adults aged 18–55 years and 65–85 years, and generated neutralising antibodies in both age groups in a dose-dependent manner, although immunogenicity decreased with age (Pfizer/BioNTech, USA). Another mRNA vaccine (Moderna, USA) was given to adults older than 56 years. The vaccine was tolerated, with neutralising antibodies induced in a dose-dependent manner, which increased after a second dose. Neutralising antibody responses with this mRNA vaccine appeared to be similar in adults older than 56 years to those aged 18–55 years who also received the vaccine. Two inactivated viral vaccines have also shown neutralising antibody responses in a dose-dependent manner in adults aged 18–59 years (Wuhan Institute Biological Products/SinoPharm, China) or adults aged 18–59 and 60 years and older (Beijing Institute Biological products/SinoPharm, China), with the second showing lower neutralising antibody titres in older adults after two doses. Finally, a clinical trial of a nanoparticle vaccine composed of adjuvanted trimeric severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike glycoproteins (Novavax, USA) reported results of a two-dose schedule given 3 weeks apart in healthy adults younger than 60 years. This vaccine was well tolerated and induced neutralisation responses that exceeded those measured in serum samples from convalescent symptomatic patients.

Added value of this study

This study is the fifth published clinical trial of a vaccine against SARS-CoV-2 tested in an older adult population (aged 18–55 years, 56–69 years, and ≥70 years). 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 after booster vaccination, including in the 70 years and older group. Cellular immune responses were also induced in all age and dose groups, peaking at day 14 after vaccination.

Implications of all the available evidence

The populations at greatest risk of serious COVID-19 include people with coexisting health conditions and older adults. The immune correlates of protection against SARS-CoV-2 have not yet been determined, but neutralising antibodies are thought to be associated with protection, and in a COVID-19 non-human primate challenge model, neutralising antibody responses correlated with protection. These findings have led to the use of neutralisation assays to assess immune responses in recent human COVID-19 vaccine trials. Immunisation with ChAdOx1 nCoV-19 results in development of neutralising antibodies against SARS-CoV-2 in almost 100% of participants including older adults without severe comorbidities, 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 comorbidities.

spike glycoprotein[15] have shown neutralising antibody responses after immunisation.

Replication-deficient adenovirus vectors containing a pathogen-specific transgene have been used as novel vaccines because of their ability to induce strong humoral and cellular responses.[16] However, pre-existing immunity might reduce the immunogenicity of vectors derived from human viruses; hence, use of simian adenoviruses might be preferable. ChAdOx1 nCoV-19 is a replication-defective chimpanzee adenovirus-vectored vaccine expressing the full-length SARS-CoV-2 spike 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.[17] 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 the spike glycoprotein.[18] Here we present the safety and immunogenicity results of a phase 2 component of a phase 2/3 multicentre study using ChAdOx1 nCoV-19 at two different doses, in adults including those aged 56–69 years and 70 years and older, and in a one-dose or two-dose regimen.

Methods

Study design and participants

In this continuing single-blind, multicentre, randomised, controlled, phase 2/3 trial, the safety and efficacy of the ChAdOx1 nCoV-19 vaccine is being assessed, with sequential age-escalation immunogenicity substudies being done in older age groups. The study is being run at 20 centres in the UK (listed in the appendix [pp 84–87]). Here we report selected results from the phase 2 component of the trial and for which participants were enrolled at two sites in the UK: the Oxford Vaccine Centre, Centre for Clinical Vaccinology and Tropical Medicine, University of Oxford (Oxford) and the NIHR

See Online for appendix

Southampton Clinical Research Facility, University Hospital Southampton NHS Foundation Trust (Southampton). Data on the participants from the phase 3 component will be published elsewhere.

We recruited participants in an age-escalation manner. We recruited adults aged 18–55 years, then adults aged 56–69 years, and then adults aged 70 years and older, without severe or uncontrolled medical comorbidities, as defined in the clinical study plan (appendix pp 48–54), through local advertisements. Participants aged 65 years and older with a Dalhousie Clinical Frailty Score of 4 or higher were excluded.[19]

Participants were enrolled into one of ten different groups. Recruitment was sequential with low-dose groups recruited first and standard-dose cohorts recruited after a protocol amendment was approved on June 5, 2020, that incorporated the new higher dose level. For the first stage of recruitment, participants aged 18–55 years were recruited to the low-dose group. Subsequently we recruited participants aged 56–69 years, and further extension to recruit those aged 70 years and older only occurred after safety review by the independent Data Safety Monitoring Board (DSMB). A minimum of 2 weeks of safety and immunogenicity data were reviewed by the DSMB before recruitment to each successive age cohort. The 18–55 years groups received two doses of vaccine and were randomly assigned to receive either the experimental vaccine or the control vaccine. The 56–69 years and 70 years and older groups were randomly assigned to receive either one dose or two doses of vaccine and were then randomly assigned to receive the experimental vaccine or the control vaccine. The same process was repeated with recruitment and randomisation for the standard-dose cohorts after review by the DSMB. All participants underwent a screening visit in which a full medical history, targeted examination, blood test for SARS-CoV-2 exposure, and a urinary pregnancy test in women of childbearing potential were done. Volunteers who were seropositive to SARS-CoV-2 before enrolment were excluded from participating in all groups, apart from those in the 18–55 years standard-dose cohort. Additionally, all participants included in this phase 2 component of the study, apart from those in the 18–55 years low-dose group, had additional safety tests (blood tests for HIV, hepatitis B and C serology, full blood count, and kidney and liver function tests). Full details of eligibility criteria are in the trial protocol (appendix pp 135–38).

Written informed consent was obtained from all participants, and the trial is being done in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The study was sponsored by the University of Oxford (Oxford, UK) 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 DSMB reviewed all interim safety reports. A copy of the protocol is included in the appendix (pp 83–212).

Randomisation and 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 masking of participants who had local or systemic reactions. Participants aged 18–55 years were randomly assigned (1:1) in the low-dose cohort and (5:1) in the standard-dose cohort to receive either ChAdOx1 nCoV-19 or MenACWY. For both 18–55 years cohorts, participants were given two doses of study vaccine. Participants aged 56–69 years were randomly assigned (3:1:3:1) to one dose of ChAdOx1 nCoV-19, one dose of MenACWY, two doses of ChAdOx1 nCoV-19, or two doses of MenACWY. Participants aged 70 years or older were randomly assigned (5:1:5:1) to one dose of ChAdOx1 nCoV-19, one dose of MenACWY, two doses of ChAdOx1 nCoV-19, or two doses of MenACWY.

Randomisation lists, using block randomisation stratified by age and dose group and study site, were generated by the study statistician (MV). Block sizes were chosen to align with the age group 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). 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 masking of participants. Participants, clinical investigators, and the laboratory team remained masked to group allocation for the duration of the study. However, trial staff administering the vaccine were unmasked.

Procedures

In the previous phase 1/2 study,[18] a single standard dose of 5×10^{10} virus particles of ChAdOx1 nCoV-19 was used, based on previous experience with a ChAdOx1 Middle East respiratory syndrome (MERS) construct. In this study, we assessed a lower dose of $2\cdot2\times10^{10}$ virus particles and a standard dose of $3\cdot5–6\cdot5\times10^{10}$ virus particles in adults of different age cohorts. Due to the need to rapidly produce large numbers of doses of vaccine manufactured using Good Manufacturing Practice 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 (Pomezia, Italy), and one manufactured by COBRA Biologics (Keele, UK) and vialed by Symbiosis (Sterling, UK). Both were manufactured according to Good Manufacturing Practice and approved by the regulatory agency in the UK, the Medicines and Healthcare

products Regulatory Agency. The 18–55 years standard-dose cohort received vaccine manufactured by COBRA Biologics for both first (ie, prime) and second (ie, boost) doses and all other cohorts received prime and boost doses, as randomised, manufactured by Advent. Analytical 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-dose or two-dose regimen (28 days apart) at either the low dose ($2·2\times10^{10}$ virus particles) or the standard dose ($3·5–6·5\times10^{10}$ virus particles). It was administered as a single intramuscular injection into the deltoid, according to specific study standard operating procedures. 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.[20] Depending on the batch used for vaccination, the injection volume for the low dose of ChAdOx1 nCoV-19 was either 0·22 mL or 0·5 mL. The injection volume used for the standard dose of ChAdOx1 nCoV-19 and MenACWY was 0·5 mL.

Safety data from animal studies and our previous phase 1/2 clinical trial[18] of ChAdOx1 nCoV-19 were reviewed before recruitment of participants. Volunteers were considered enrolled into the trial at the point of vaccination. Participants were observed in the clinic for a minimum of 15 min 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 after each dose. 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 (ie, 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 an emergency 24-h 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 (substantial limitation in activity and medical intervention or therapy required), or potentially life-threatening (requires assessment in emergency department or admission to hospital). All participants in the 56–69 years and 70 years and older groups and participants in the 18–55 years standard-dose group had clinical and immunogenicity assessments at 0, 7, 14, and 28 days after their prime and booster vaccinations. Participants in the 18–55 years low-dose group had clinical and immunogenicity assessments at baseline, immediately before the boost dose, and at 14 and 28 days after their booster vaccination.

Humoral responses at baseline and after vaccination were assessed using Meso Scale Discovery multiplexed immunoassay against spike and receptor binding domain [RBD], a standardised total IgG ELISA against trimeric SARS-CoV-2 spike protein, and a live SARS-CoV-2 microneutralisation assay MNA_{80}, which was done at Public Health England (Porton Down, UK), as described previously.[18] Cellular responses were assessed using an ex-vivo IFN-γ enzyme-linked immunospot (ELISpot) assay to enumerate antigen-specific T cells.[18] Neutralising antibodies to the ChAdOx1 vector were measured using a secreted embryonic alkaline phosphatase (SEAP)-reporter assay, which measures the reciprocal of the serum dilution required to reduce in-vitro expression of vector-expressed SEAP by 50%, 24 h after transduction.[21] Due 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 coprimary outcomes of the trial are to assess efficacy as measured by the number of 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 (aged 56–69 years and ≥70 years), efficacy against severe and non-severe COVID-19, death, and seroconversion against non-spike proteins. A full list of secondary and tertiary outcomes is in the protocol (pp 118–24).

Here we report preliminary results for selected secondary endpoints, 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

We present safety endpoints as frequencies (%) with 95% binomial exact CIs. We present immunological endpoints as medians and IQR. Analyses were by group allocation in participants who received the vaccine.

We did comparisons across the three age groups (aged 18–55 years, aged 56–69 years, and aged ≥70 years) using Kruskal-Wallis tests within each dose level of the vaccine (low dose or standard dose) for antibody responses or unadjusted analysis of variance applied to log-transformed values for neutralisation titres. We did comparisons between low-dose and standard-dose groups using Wilcoxon rank sum tests (antibody

response) or independent samples Student's *t* test applied to log-transformed values for neutralisation titres. We present unadjusted p values for a small number of statistical comparisons to avoid issues of multiplicity. To assess the association between responses on different assays, we used unadjusted linear regression to analyse log-transformed values after baseline.

Sample sizes were nominal for these immunogenicity subgroups and no power calculations were done.

We did all statistical analyses using SAS version 9.4 and R version 3.6.1 or later. This study is registered with ClinicalTrials.gov, NCT04400838, and with ISRCTN, 15281137.

Role of the funding source

AstraZeneca reviewed the data from the study and the final manuscript before submission, but the authors retained editorial control. All other 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 May 30 and Aug 8, 2020, 560 participants were enrolled in the study and randomly assigned to the experimental vaccine or control vaccine group: 160 participants aged 18–55 years (100 assigned to ChAdOx1 nCoV-19, 60 assigned to MenACWY), 160 aged 56–69 years (120 assigned to ChAdOx1 nCoV-19, 40 assigned to MenACWY), and 240 aged 70 years and older (200 assigned to ChAdOx1 nCoV-19, 40 assigned to MenACWY). Full details on randomisation are in figure 1. All participants randomly assigned to treatment were vaccinated. One participant (in the 18–55 years low-dose group) received the incorrect vaccine after randomisation and was excluded from analysis. Seven participants randomly assigned to receive two doses of vaccine chose not to continue with the boost dose and were excluded from further analyses. Three participants were excluded from immunology analyses due to incorrectly labelled samples (either incorrect participant identification numbers or incorrect timepoints noted on the label, or both; figure 1). The baseline characteristics of the participants eligible for inclusion in the analysis in each group are shown in the table. Participants 70 years and older were recruited from the NIHR Southampton Clinical Research Facility, University Hospital Southampton NHS Foundation Trust. All other participants were recruited at the Oxford Vaccine Centre, Centre for Clinical Vaccinology and Tropical Medicine, University of Oxford. Among the analysed population, 280 (50%) of 552 participants were female. 524 (95%) of 552 participants identified as white, and 540 (98%) were 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 18–55 years group was 43·0 years (IQR 33·6–48·0), in the 56–69 years group was 60·0 years (57·5–63·0) and in the 70 years and older group was 73·0 years (71·0–76·0). The median age in the 70 years and older groups ranged from 73 years to 74 years across dosing groups, with the oldest participants aged 83 years.

The following results for local and systemic adverse reactions are all for participants who were randomly assigned to receive two doses of vaccine. Injection-site pain and tenderness were the most common solicited local adverse reactions and occurred most frequently in the first 48 h after vaccination (data for standard-dose regimen shown in figure 2; data for the low-dose groups and control groups are shown in the appendix [pp 7, 9, 19–21]). In those aged 56 years or older, a standard dose of ChAdOx1 nCoV-19, whether the prime or boost vaccination, elicited a greater number of local or systemic reactions than did MenACWY. The difference was less clear with the low-dose vaccine in the 56–69 years and 70 years and older groups, and the number of participants in the control groups was small (appendix p 30). At least one local symptom was reported after the prime vaccination with standard-dose ChAdOx1 nCoV-19 by 43 (88%) of 49 participants in the 18–55 years group, 22 (73%) of 30 in the 56–69 years group, and 30 (61%) of 49 in the 70 years and older group (appendix p 29). Similar proportions of local symptoms were reported after the boost vaccination with the standard dose of ChAdOx1 nCoV-19, with 37 (76%) of 49 participants in the 18–55 years group, 21 (72%) of 29 in the 56–69 years group, and 27 (55%) of 49 in the 70 years and older group reporting at least one local symptom. A similar pattern was seen across the age groups in participants after their prime vaccination with low-dose ChAdOx1 nCoV-19 and after the boost vaccination with the low-dose vaccine, but with fewer total adverse reactions than in the standard-dose groups (appendix pp 7, 9, 19–21). No severe local symptoms were reported by recipients of ChAdOx1 nCoV-19. In the two-dose control groups, across both the low-dose and standard-dose cohorts, local symptoms were reported by 33 (57%) of 58 participants in the 18–55 years group, five (25%) of 20 in the 56–69 years group, and seven (35%) of 20 in the 70 years and older group after the prime vaccination with MenACWY, and by 50 (86%) of 58 in the 18–55 years group, seven (37%) of 19 in the 56–69 years group, and four (20%) of 20 in the 70 years and older group after the boost vaccination with MenACWY (appendix p 29). Data for participants randomly assigned to receive only one dose of vaccine were similar to the data after a prime dose of vaccine in the two-dose groups (data not shown).

Fatigue, headache, feverishness, and myalgia were the most commonly solicited systemic adverse reactions (data for the standard-dose groups are shown in figure 3; data for the low-dose groups and control groups are shown in the appendix [pp 8, 10, 19–21]). At least one systemic symptom was reported after the prime

vaccination with the standard dose of ChAdOx1 nCoV-19 by 42 (86%) of 49 participants in the 18–55 years group, 23 (77%) of 30 in the 56–69 years group, and 32 (65%) of 49 in the 70 years and older group (appendix p 29). The severity of symptoms reported in the standard-dose groups was reduced after the boost vaccination, with only one (1%) of 127 participants reporting a severe reaction compared with seven (5%) of 128 participants after the prime vaccination. At least one systemic adverse reaction after the boost vaccination of standard dose of ChAdOx1

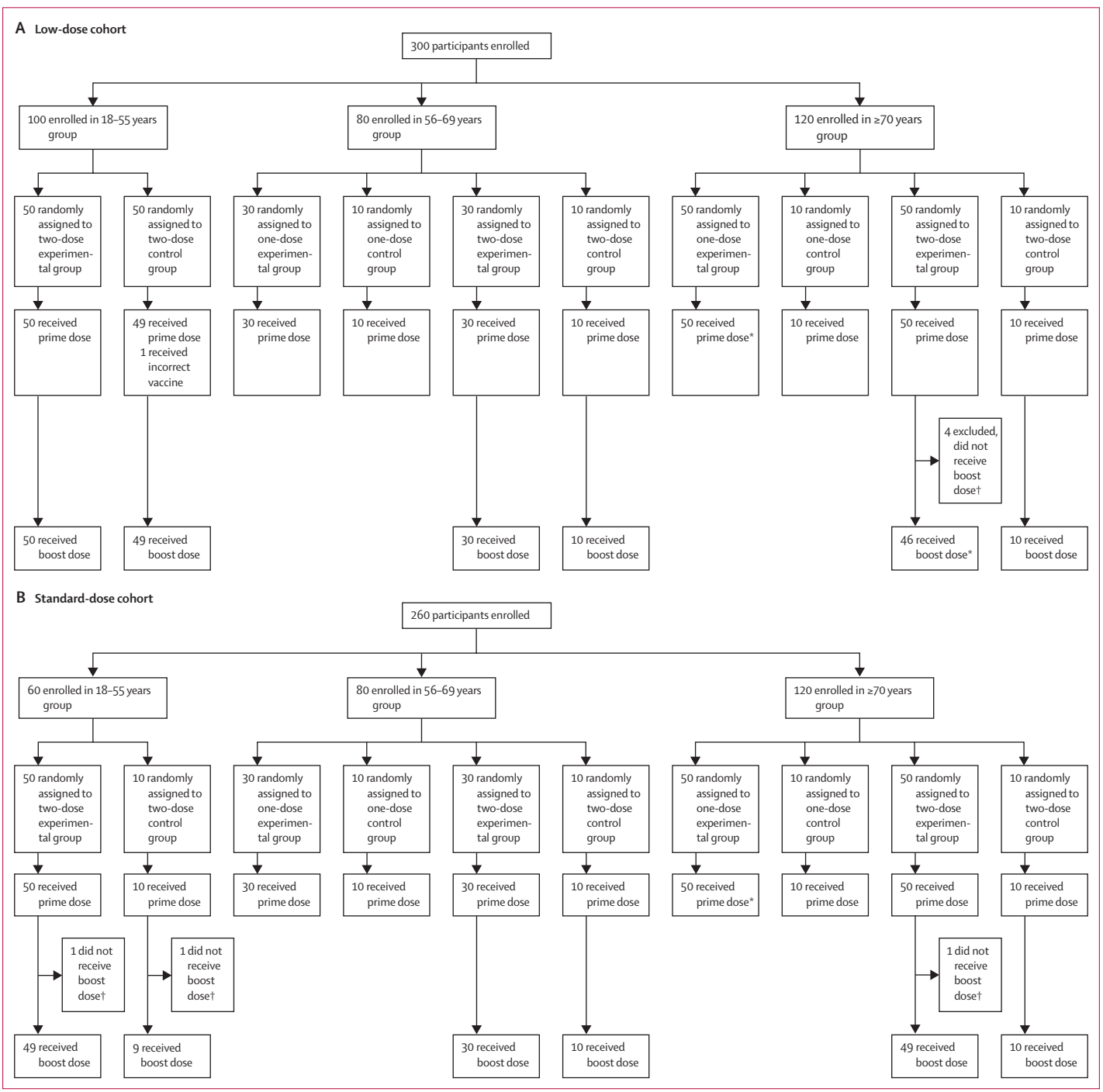

Figure 1: **Study profile for the low-dose (A) and standard-dose (B) cohorts**
*One participant excluded from immunogenicity analyses, due to mislabelling of laboratory sample. †Reasons for not receiving boost dose included that the participant moved away or was unavailable for visits, delay in receiving boost dose, or withdrawal of consent.

	Age 18–55 years		Age 56–69 years				Age ≥70 years			
	ChAdOx1 nCoV-19, two doses	MenACWY, two doses	ChAdOx1 nCoV-19, one dose	MenACWY, one dose	ChAdOx1 nCoV-19, two doses	MenACWY, two doses	ChAdOx1 nCoV-19, one dose	MenACWY, one dose	ChAdOx1 nCoV-19, two doses	MenACWY, two doses
Low dose										
Number enrolled	50	49	30	10	30	10	50	10	46	10
Sex										
Female	35 (70%)	28 (57%)	19 (63%)	4 (40%)	10 (33%)	8 (80%)	24 (48%)	6 (60%)	16 (35%)	6 (60%)
Male	15 (30%)	21 (43%)	11 (37%)	6 (60%)	20 (67%)	2 (20%)	26 (52%)	4 (40%)	30 (65%)	4 (40%)
Age, years, median (IQR, range)	44·5 (39·0–51·0, 22·0–54·0)	42·0 (32·0–48·0, 23·0–55·0)	60·0 (58·9–62·3, 56·0–69·0)	57·8 (56·3–60·8, 56·0–68·0)	60·4 (57·8–66·0, 56·0–69·4)	60·5 (58·3–63·9, 56·7–69·0)	73·5 (71·0–76·0, 69·0–83·0)	73·0 (70·0–74·0, 70·0–81·0)	73·0 (71·0–75·0, 70·0–82·0)	73·0 (71·2–74·0, 70·0–76·0)
BMI, kg/m², median (IQR, range)	24·6 (22·9–28·9, 19·4–45·1)	24·8 (21·6–27·7, 18·0–37·2)	25·0 (23·2–27·3, 20·2–37·6)	25·5 (22·5–27·3, 20·9–34·4)	25·9 (24·0–28·8, 21·3–36·6)	24·0 (23·2–26·0, 22·2–33·2)	26·0 (23·8–28·0, 20·0–36·0)	24·9 (22·3–26·9, 19·3–32·5)	26·0 (23·4–27·7, 19·4–42·1)	26·8 (24·3–29·5, 19·2–35·3)
Smoker	3 (6%)	1 (2%)	0	1 (10%)	2 (7%)	0	1 (2%)	0	1 (2%)	0
Alcohol drinker	44 (88%)	42 (86%)	28 (93%)	9 (90%)	26 (87%)	8 (80%)	43 (86%)	10 (100%)	43 (94%)	9 (90%)
Health-care worker	35 (70%)	26 (53%)	17 (57%)	7 (70%)	12 (40%)	4 (40%)	0	0	0	1 (10%)
Race or ethnicity										
White	48 (96%)	45 (92%)	30 (100%)	9 (90%)	27 (90%)	10 (100%)	50 (100%)	10 (100%)	45 (98%)	10 (100%)
Black or Black British	0	0	0	0	0	0	0	0	0	0
Asian or Asian British	2 (4%)	1 (2%)	0	0	2 (7%)	0	0	0	0	0
Mixed race or ethnicity	0	3 (6%)	0	0	0	0	0	0	1 (2%)	0
Other race or ethnicity*	0	0	0	1 (10%)	1 (3%)	0	0	0	0	0
Comorbidities										
Cardiovascular disease	4 (8%)	10 (20%)	5 (17%)	0	11 (37%)	0	14 (28%)	3 (30%)	16 (35%)	2 (20%)
Respiratory disease	12 (24%)	9 (18%)	7 (23%)	0	7 (23%)	0	6 (12%)	2 (20%)	6 (13%)	1 (10%)
Diabetes	0	0	0	0	0	1 (10%)	1 (2%)	0	2 (4%)	0
Standard dose										
Number enrolled	49	9	30	10	30	10	50	10	49	10
Sex										
Female	23 (47%)	7 (78%)	16 (53%)	3 (30%)	16 (53%)	5 (50%)	25 (50%)	1 (10%)	21 (43%)	2 (20%)
Male	26 (53%)	2 (22%)	14 (47%)	7 (70%)	14 (47%)	5 (50%)	25 (50%)	9 (90%)	28 (57%)	8 (80%)
Age, years, median (IQR, range)	39·0 (30·0–45·0, 19·0–55·0)	43·0 (35·8–50·0, 32·0–54·0)	59·0 (58·0–61·0, 56·0–69·0)	61·5 (57·5–63·8, 57·0–66·0)	59·5 (57·0–61·0, 56·0–67·0)	60·5 (57·9–61·0, 56·0–64·0)	74·0 (72·0–76·0, 70·0–80·0)	74·0 (71·0–75·5, 70·0–78·0)	73·0 (71·0–75·0, 70·0–83·0)	73·5 (72·2–74·8, 71·0–81·0)
BMI, kg/m², median (IQR, range)	26·9 (24·6–30·9, 20·2–39·7)	24·1 (23·8–25·6, 18·6–39·0)	26·7 (25·2–30·0, 18·6–36·8)	28·9 (25·6–30·2, 21·7–31·9)	24·0 (22·4–27·1, 19·9–33·5)	26·1 (23·6–27·7, 20·5–30·2)	25·1 (23·7–28·5, 17·5–32·6)	26·8 (25·8–28·5, 23·0–31·7)	27·1 (24·2–29·2, 20·3–40·2)	25·6 (24·1–29·3, 18·9–32·5)
Smoker	1 (2%)	0	0	0	0	1 (10%)	1 (2%)	0	0	0
Alcohol drinker	45 (92%)	6 (67%)	29 (97%)	10 (100%)	29 (97%)	10 (100%)	39 (78%)	9 (90%)	42 (86%)	9 (90·0%)
Health-care worker	13 (27%)	5 (56%)	10 (33%)	2 (20%)	12 (40%)	5 (50%)	2 (4%)	0	0	0
Race or ethnicity										
White	40 (82%)	7 (78%)	29 (97%)	10 (100%)	26 (87%)	9 (90%)	50 (100%)	10 (100%)	49 (100%)	10 (100%)
Black or Black British	1 (2%)	0	0	0	0	0	0	0	0	0
Asian or Asian British	7 (14%)	2 (22%)	0	0	4 (13%)	1 (10%)	0	0	0	0
Mixed race or ethnicity	0	0	0	0	0	0	0	0	0	0
Other race or ethnicity*	1 (2%)	0	1 (3%)	0	0	0	0	0	0	0
Comorbidities										
Cardiovascular disease	6 (12%)	0	4 (13%)	3 (30%)	4 (13%)	1 (10%)	20 (40%)	3 (30%)	13 (27%)	4 (40%)
Respiratory disease	10 (20%)	1 (11%)	4 (13%)	1 (10%)	3 (10%)	3 (30%)	3 (6%)	0	4 (8%)	0
Diabetes	2 (4%)	0	2 (7%)	2 (20%)	0	0	0	1 (10%)	3 (6%)	1 (10%)

Data are n (%) unless otherwise specified. BMI=body-mass index. *Included Hispanic-Columbian, Indian, Japanese, and White Irish/English.

Table: **Baseline characteristics of prime-boost participants included in the analysis**

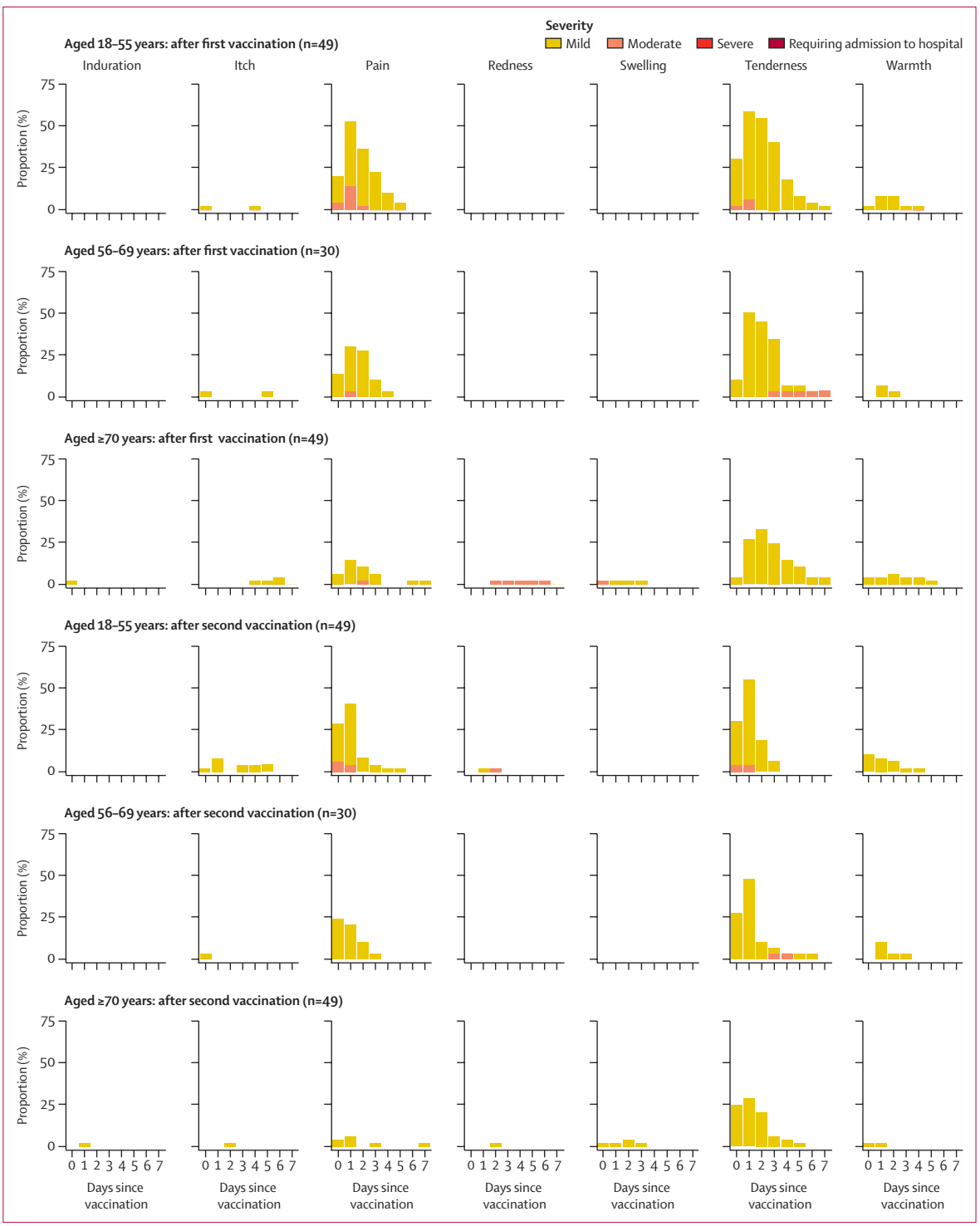

Figure 2: **Solicited local adverse reactions in the 7 days after prime and boost doses of standard-dose vaccine, by age**
Day 0 is the day of vaccination. Participants shown are those randomly assigned to receive two doses, and data are only shown for participants who received both doses of vaccine.

nCoV-19 was reported by 32 (65%) of 49 participants in the 18–55 years group, 21 (72%) of 29 in the 56–69 years group, and 21 (43%) of 49 in the 70 years and older group (appendix p 29). Within 7 days after the prime vaccination with ChAdOx1 nCoV-19, the incidence of objectively measured fever was low in the 18–55 years standard-dose

group (12 [24%] of 49), and no fevers were recorded in either the 56–69 years or 70 years and older standard-dose groups (appendix pp 16–18). No participants of any age who received the standard dose of ChAdOx1 nCoV-19 had objective fever after the boost vaccination. A similar pattern of decreasing reactogenicity with increasing age

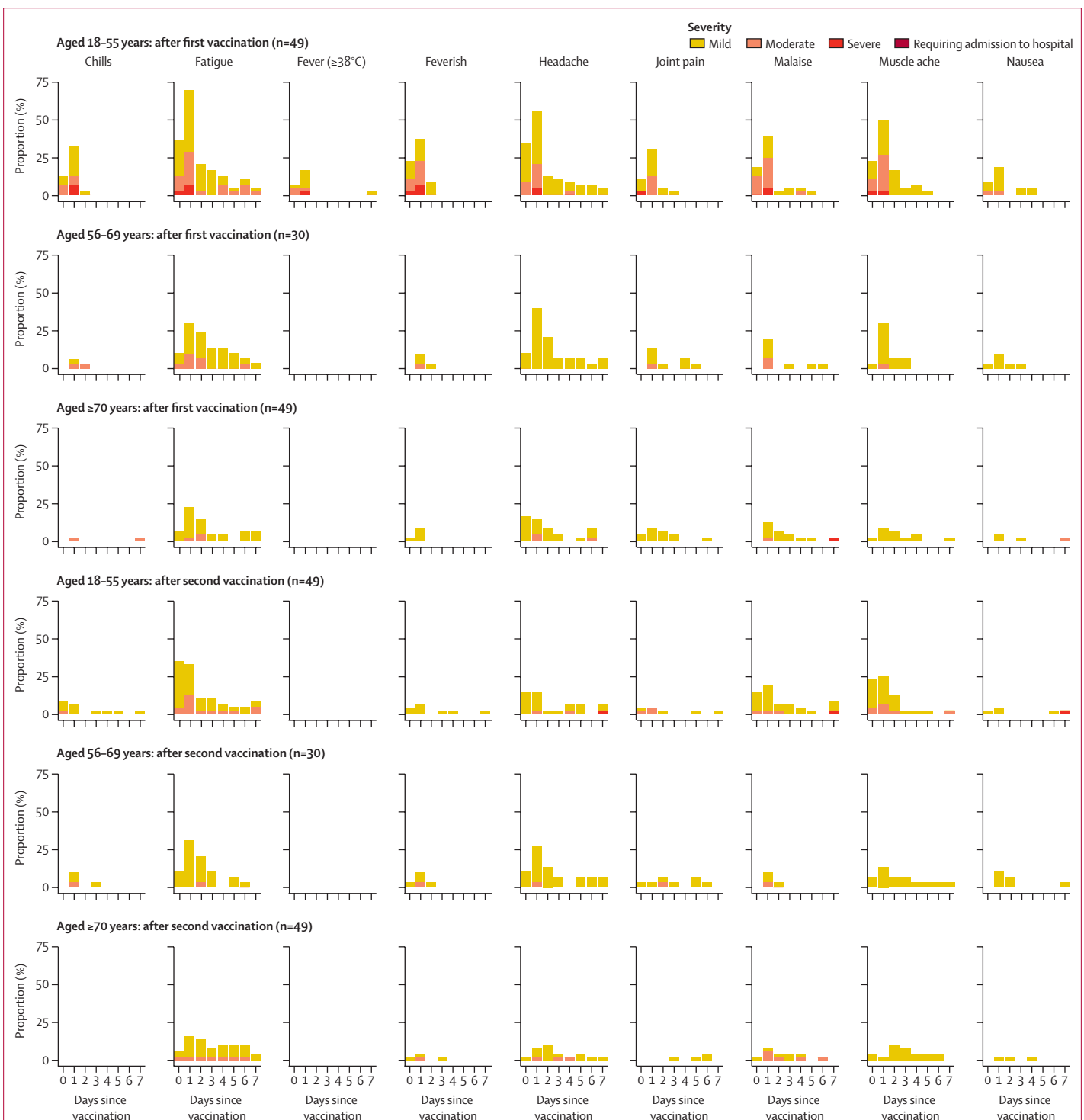

Figure 3: **Solicited systemic adverse reactions in the 7 days after prime and boost doses of standard-dose vaccine, by age**
Day 0 is the day of vaccination. Feverish is self-reported feeling of feverishness, whereas fever is an objective fever measurement (mild: 38·0 to <38·5°C, moderate: 38·5 to <39·0°C, severe: ≥39·0°C). Participants shown are those randomly assigned to receive two doses, and data are only shown for participants who received both doses of vaccine.

was seen in the low-dose groups (appendix pp 7, 8, 19–21). Similar results after the first dose were seen in those who were randomly assigned to receive only one dose of vaccine (data not shown). Data for the control groups are in the appendix (p 10).

As of Oct 26, 2020, 13 serious adverse events have occurred (across all age and vaccine groups), none of which are considered related to either study vaccine as assessed by the investigators (appendix p 31).

Using a multiplex immunoassay that detected total IgG against RBD and trimeric spike protein, we observed that participants who received the prime vaccination of standard-dose ChAdOx1 nCoV-19 had similar anti-spike antibody titres by day 28 after their prime vaccination as those who received a low dose (p=0·12 adjusted for age; figure 4; appendix p 12). At both dose levels, and for all dose groups combined, anti-spike IgG responses at day 28 decreased with increasing age (low-dose groups: 18–55 years, median 6439 arbitrary units [AU]/mL [IQR 4338–10 640], n=49; 56–69 years, 4553 AU/mL [2657–12 462], n=60; ≥70 years, 3565 AU/mL [1507–6345], n=93; p=0·0037; standard-dose groups: 18–55 years, median 9807 AU/mL [IQR 5847–17 220], n=43; 56–69 years, 5496 AU/mL [2548–12 061], n=55; ≥70 years, 4156 [2122–12 595], n=97; p=0·0044). By 28 days after the boost vaccination, similar antibody titres were seen across all two-dose groups, regardless of age or vaccine dose (eg, standard-dose groups: 18–55 years, median 20 713 AU/mL [IQR 13 898–33 550], n=39; 56–69 years, 16 170 AU/mL [10 233–40 353], n=26; and ≥70 years, 17 561 AU/mL [9705–37 796], n=47; p=0·68), and were higher than for those who did not receive a boost vaccination (appendix p 13). Similar results were seen with anti-RBD antibodies (figure 4; appendix p 12) and with an in-house standardised ELISA (appendix pp 12–13). Data for the control group are in the appendix (pp 12–13).

In a live SARS-CoV-2 microneutralisation assay (MNA_{80}), median titres peaked by day 42 in most groups that received two vaccinations (figure 5). There were no significant differences in normalised titres between age groups at day 42 (low-dose groups: 18–55 years, median 161 [IQR 99–233], n=41; 56–69 years, 143 [79–220], n=28; ≥70 years, 150 [103–255], n=34; p=0·90; standard-dose groups: 18–55 years, median 193 [IQR 113–238], n=39; 56–69 years, 144 [119–347], n=20; and ≥70 years, 161 [73–323], n=47; p=0·40). Within each age group, no significant differences were seen in neutralisation titres between low-dose and standard-dose vaccine recipients at the same timepoint (18–55 years p=0·33, 56–69 years p=0·12, ≥70 years p=0·62; figure 5; appendix p 14). Neutralising titres were achieved by 14 days after the boost vaccination in 208 (>99%) of 209 recipients of a boost vaccination. The one participant with a non-neutralising level was in the 70 years and older two-dose low-dose group.

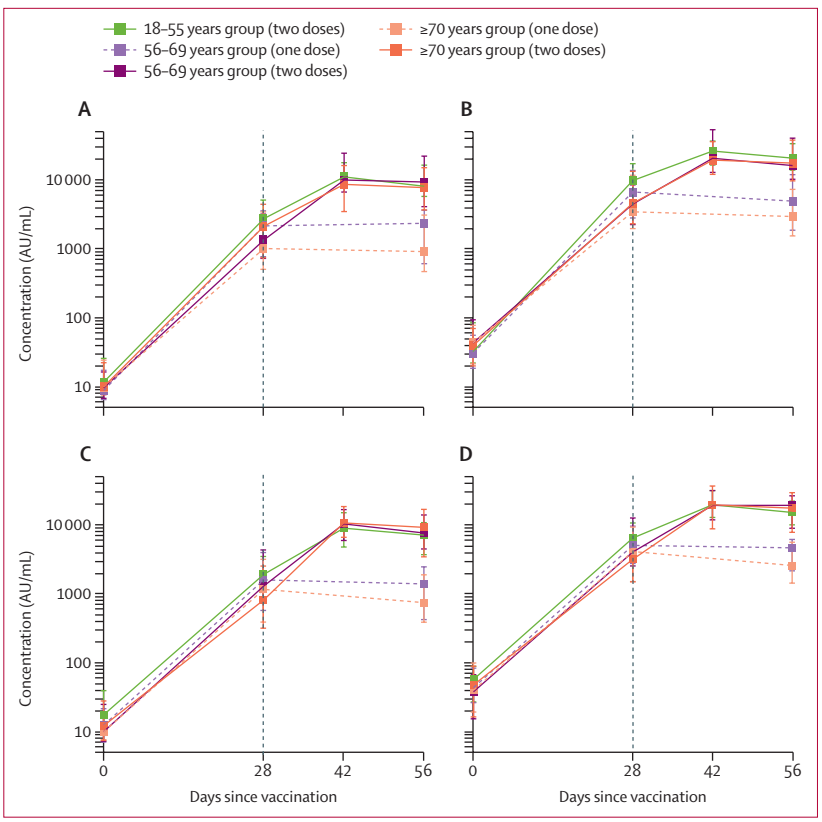

Figure 4: **SARS-CoV-2 IgG response to the receptor binding domain in the standard-dose groups (A) and low-dose groups (C) and the spike protein in the standard-dose groups (B) and the low-dose groups (D), by age**

Datapoints are medians, with whiskers showing the IQRs. Solid lines show participants who were randomly assigned to and received two doses of vaccine and dashed lines indicate participants who were randomly assigned to receive one dose. The vertical black line indicates when participants who received two doses received their boost dose. Data for the control groups are shown in the appendix (p 12). AU=arbitrary units. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Anti-spike IgG levels after vaccination across all timepoints in those who received two doses of vaccine were highly correlated with neutralising titres in all age groups and for both low-dose and standard-dose vaccines (r^2 from linear regression 0·42–0·75, all p<0·0001; appendix p 32).

IFN-γ ELISpot responses against SARS-CoV-2 spike protein peaked 14 days after the prime vaccination (standard-dose groups: 18–55 years, median 1187 spot-forming cells [SFCs] per million peripheral blood mononuclear cells [PBMCs; IQR 841–2428], n=24; 56–69 years, 797 SFCs [383–1817], n=29; and ≥70 years, 977 SFCs [458–1914], n=48; appendix p 16) and did not increase significantly after the boost vaccination (p=0·46 from paired Student's *t* test of day 28 *vs* day 42; figure 6). ELISpot data were unavailable for the 18–55 years low-dose group because PBMCs were not collected in this group. In those who received two standard doses of vaccine, a significant difference was seen across age groups with those aged 56–69 years having higher responses at day 42 than other age groups receiving the

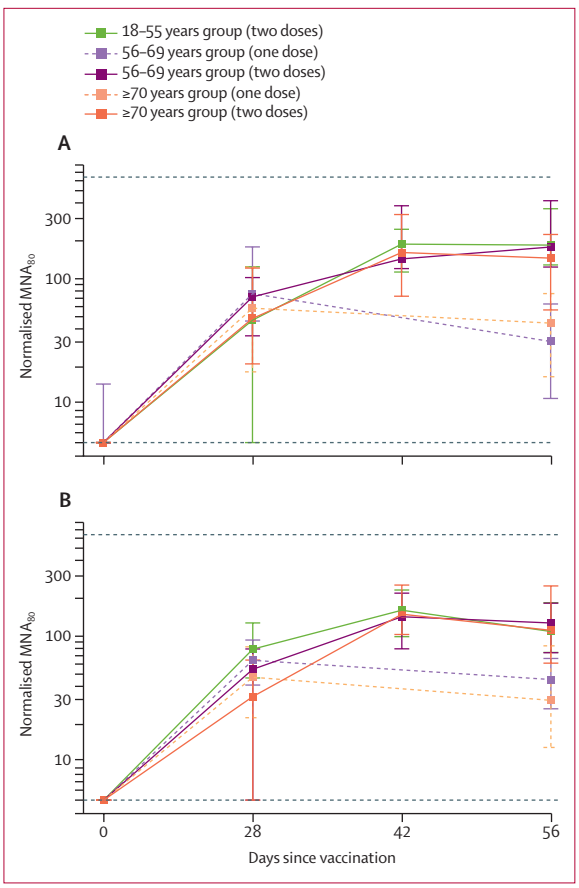

Figure 5: **Neutralising antibody titres measured using a live SARS-CoV-2 microneutralisation assay (MNA_{80}) after prime and boost doses of vaccine in standard-dose groups (A) and low-dose groups (B), by age**
Datapoints are medians, with whiskers showing the IQR. Solid lines show participants who were randomly assigned to and received two doses of vaccine and dashed lines indicate participants who were randomly assigned to receive one dose. Horizontal dotted lines show upper and lower limits of assay (values outside this range set to 640 beyond the upper limit and 5 beyond the lower limit). Data for the control groups are shown in the appendix (p 14).
To normalise data across assay runs, a reference sample was included in all assay runs and test samples normalised to this value by generating log_{10} ratios.
SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

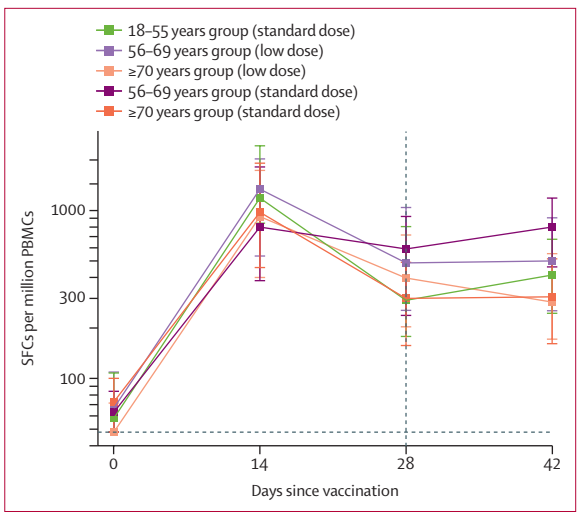

Figure 6: **IFN-γ ELISpot response to peptides spanning the SARS-CoV-2 spike insert after prime and boost doses of vaccine for all participants who were given two doses of vaccine, by age group and vaccine dose**
ELISpot data were unavailable for the 18–55 years low-dose group because PBMCs were not collected in this group. Datapoints are medians, with whiskers showing the IQR. The lower limit of detection is 48 SFCs per million PBMCs (horizontal dotted line). Day 42 samples are from participants who received the boost dose at day 28 (vertical dotted line). Data for both one-dose and two-dose groups, with numbers analysed at each timepoint, are in the appendix (p 15).
ELISpot=enzyme-linked immunospot. PBMC=peripheral blood mononuclear cells. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. SFC=spot-forming cells.

same vaccine regimen (18–55 years, median 413 SFCs per million PBMCs [IQR 245–675], n=23; 56–69 years, 798 SFCs [462–1186], n=28; and ≥70 years, 307 SFCs [161–516], n=47; p<0·0001; appendix p 15).

Anti-ChAdOx1 neutralising antibody titres across different age and dose groups are shown in figure 7. Titres increased with the prime vaccination with ChAdOx1 nCoV-19 in all groups to similar levels, but were not increased further after a boost dose of vaccine at day 28. This observation was in contrast with the anti-SARS-CoV-2 spike protein antibody levels, which were increased 28 days after the boost vaccination (figure 4). Anti-ChAdOx1 neutralising titres immediately before the boost vaccination were negatively correlated with standardised ELISA values 28 days after the boost vaccination (p=0·037; figure 7), but no significant correlation was seen between anti-ChAdOx1 neutralising titres immediately before the boost vaccination and ELISpot responses 14 days after the boost vaccination (p=0·22; figure 7).

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 a boost vaccination. If these responses correlate with protection in humans, these findings are encouraging because older individuals are at disproportionate risk of severe COVID-19 and so any vaccine adopted for use against SARS-CoV-2 must be effective in older adults.

Most 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[18] and previously reported studies of ChAdOx1-vectored vaccines.[22–24] Fewer adverse events were reported after the boost vaccination than after the prime vaccination and reactogenicity reduced with increasing age. The lower dose of vaccine was less reactogenic than the standard dose of vaccine across all age groups.

The serious adverse events observed during the trial in these study groups were judged to be unrelated to the study vaccines and occurred at frequencies expected for these conditions in the general population. None of the participants included in this report had any suspected

unexpected serious adverse reactions. In the phase 3 component of the trial, suspected unexpected serious adverse reactions occurred in other groups, and will be reported in detail in a subsequent publication. We carefully monitored suspected unexpected serious adverse reactions and other adverse events to ensure that no pattern of unexplained illnesses emerged that could indicate a safety concern. Independent assessments have led to the recommendation that the trial is safe to continue.

The ChAdOx1 nCoV-19 vaccine induced a specific antibody response to the SARS-CoV-2 spike glycoprotein and RBD at 28 days after a single dose across all age groups, including adults aged 70 years and older. A clear effect of a boost vaccination on antibody titres at day 56 was seen that was unrelated to dose regimen or age group. Similar patterns were observed with neutralising antibody responses, with no difference in the magnitude of the response at day 28 after the prime vaccine regardless of age or vaccine dose, but a booster effect was observed in individuals who received a second dose of vaccine.

Other clinical trials have also assessed safety, tolerability, and immunogenicity of SARS-CoV-2 vaccines in older adults. An adenovirus 5 vector-based vaccine also had reduced reactogenicity in adults aged 55 years and older compared with adults aged 18–54 years after a single dose of vaccine, although immunogenicity was concurrently reduced in this older age group.[11] A two-dose mRNA vaccine has also been shown to be immunogenic in adults older than 56 years with dose-dependent immune responses and similar neutralising antibody titres and cellular immune responses to younger adults.[9] Another two-dose mRNA vaccine has shown immunogenicity in older adults, but absolute neutralising antibody responses in adults aged 65–85 years were lower than in those aged 18–55 years.[10] By contrast with our observations, in both these studies, reactogenicity was more common after the second dose of an mRNA vaccine. A two-dose inactivated virus vaccine has also shown lower absolute neutralising antibody titres in adults aged 60 years and older than in adults aged 18–59 years, but reactogenicity was not formally compared between the first and second doses in this study.[13]

T-cell responses are important in controlling disease in natural infection[8] and therefore generation of a robust cellular immune response is a desirable attribute for a vaccine against SARS-CoV-2. Here, we found that spike-specific T-cell responses measured with ELISpot peaked at 14 days after the prime vaccination, consistent with previous studies of simian adenovirus-vectored vaccines,[25] and were similar in all groups regardless of age and vaccine dose. Spike protein T-cell responses measured with ELISpot have also been reported in studies with other adenovirus-vectored vaccines against SARS-CoV-2,[12] including in adults older than 55 years.[11] Theoretical concerns about vaccine-enhanced disease have led to a

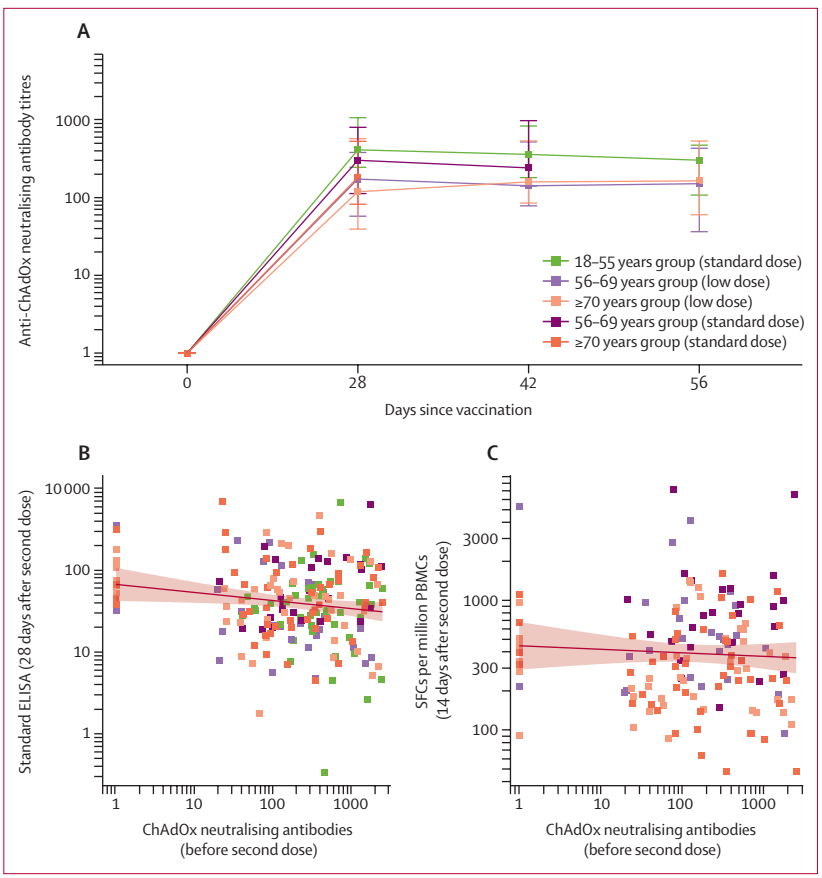

Figure 7: **Anti-ChAdOx1 vector neutralising titres after prime and boost doses of vaccine, by age and vaccine dose, and the correlation between pre-boost dose anti-ChAdOx1 neutralising antibodies and 28 days after boost dose antibody and T-cell responses**

(A) Anti-ChAdOx1 neutralising antibody titres in participants who received ChAdOx1 nCoV-19 vaccine by age and dose: datapoints are medians, with whiskers showing the IQR. Values below the limit of detection were assigned a value of 1. (B) Anti-ChAdOx1 neutralising antibody titre immediately before boost dose of vaccine versus standardised IgG ELISA against SARS-CoV-2 spike 28 days after the boost dose of vaccine with linear regression of logged values (p=0·037). (C) Anti-ChAdOx1 neutralising antibody titres immediately before boost dose of vaccine versus SARS-CoV-2 spike specific T cells measured by IFN-γ ELISpot on day 14 after the boost dose of vaccine with linear regression of logged values (p=0·22). In B and C, each datapoint is one participant and the solid line shows the linear regression, with the shaded area showing the 95% CI from an unadjusted linear regression of anti-vector neutralisation titres against logged ELISA (in B) or ELISpot (in C) response. Data were unavailable at day 56 for the 56–69 years standard-dose group. ELISpot=enzyme-linked immunospot. PBMC=peripheral blood mononuclear cells. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. SFC=spot-forming cells.

view that a type 1 T-helper (Th1)-biased CD4 response is a preferred coronavirus vaccine characteristic.[26] An adjuvanted nanoparticle vaccine has been shown to induce spike-specific CD4 T-cell cytokine responses with a predominantly Th1 profile,[15] as has an mRNA vaccine in small numbers of adults aged 56–70 years and 71 years and older.[9] 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 shown that decreasing immune function with age leads to decreased immune responses to vaccines. This fact holds true for vaccines such as for influenza, for which pre-existing

immune memory exists,[27] and vaccines that induce primary immune responses, such as hepatitis B.[28] Other adenovirus-vector platforms against SARS-CoV-2 have either shown reduced immunogenicity in an older age group[11] (although this study was of a single-dose regimen and so not directly comparable with our prime-boost regimen) or have not yet been tested in an older population.[12]

However, our results are consistent with previous studies of adenovirus-vector-based vaccines against respiratory pathogens that evoke humoral and T-cell responses in older adults, including a human adenovirus-vectored respiratory syncytial virus (RSV) vaccine[29] and a simian adenovirus-vectored RSV vaccine.[30] Our results with ChAdOx1 nCoV-19 are also consistent with those of a ChAdOx1-vectored vaccine against influenza that showed good immunogenicity in adults older than 50 years.[22]

Notably, the anti-spike antibody responses in our study increased after a boost 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. We observed a small negative correlation between anti-vector antibody titres and anti-spike total IgG, but not T-cell ELISpot responses. Further work is needed to investigate if homologous boosting with adenovirus-vectored vaccines can be done 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 focused on measuring neutralising antibodies because these have been shown to confer protection from challenge in animal models.[9–15] Live virus neutralisation assays are labour intensive and can only be done in specialist laboratories under category 3 biological safety conditions. We found here that anti-spike IgG levels correlate with neutralising antibody titres for all age groups. This finding suggests that, should neutralising antibodies 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 its single-blind design. However, all laboratory analyses and clinical assessments reported in this manuscript were done in a blinded fashion. A further limitation is possible variation of severity of local reactions due to the difference in injection volumes between different batches of vaccine in the low-dose group. Ongoing studies in larger groups will investigate the reactogenicity of a booster dose in more detail. Finally, the selection of participants aged 70 years and older, with a median age of 73–74 years between dose groups and with few comorbidities, might not be representative of the general older population, including those living in residential care settings or older than 80 years. Early phase studies in older adults require healthy volunteers to be enrolled for safety assessments, and recruitment to the study occurred during a period of national lockdown when more susceptible individuals were advised by Public Health England to self-isolate. Therefore, we excluded volunteers with substantial comorbidities or clinical frailty. Larger studies are now underway to assess 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 and safety. Phase 3 studies with ChAdOx1 nCoV-19 are ongoing in the UK, Brazil, and the USA to assess vaccine efficacy and safety. Here we found similar safety and immunogenicity of ChAdOx1 nCoV-19 in older adults compared with younger adults, which could support the use of this vaccine in this older age group, if it is shown to be protective in phase 3 trials.

Contributors

AJP and SCG 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. AVSH and SNF were the study site principal investigators. ALF, CD, EAC, KJE, RM, and TL were responsible for laboratory testing and assay development. MV and NGM did the statistical analysis. SCG and TL were responsible for vaccine development. ADD, CG, and RT were responsible for vaccine manufacture. AJP, AMM, MNR, MV, NGM, and TL contributed to the preparation of the report. AMM, DRO, 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 AstraZeneca for further development of ChAdOx1 nCoV-19 (AZD1222). AstraZeneca reviewed the data from the study and the final manuscript before submission, but the authors retained editorial control. SCG is cofounder of Vaccitech (a collaborator in the early development of this vaccine candidate) and named as an inventor on a patent covering use of ChAdOx1-vectored vaccines (PCT/GB2012/000467) 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 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 cofounder of and consultant to Vaccitech and is named as an inventor on a patent covering design and use of ChAdOx1-vectored vaccines (PCT/GB2012/000467). MDS reports grants from Janssen, GlaxoSmithKline, MedImmune, Novavax, and MCM Vaccine 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. All other authors declare no competing interests.

Data sharing

The study protocol and clinical study plan are provided in the appendix (pp 45–212). Anonymised participant data will be made available when the trial is complete, upon requests directed to the corresponding author. Proposals will be reviewed and approved by the sponsor, investigator, and collaborators on the basis of scientific merit. After approval of a proposal, data can be shared through a secure online platform after signing a data access agreement. All data will be made available for a minimum of 5 years from the end of the trial.

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Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK

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Summary

Background A safe and efficacious vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), if deployed with high coverage, could contribute to the control of the COVID-19 pandemic. We evaluated the safety and efficacy of the ChAdOx1 nCoV-19 vaccine in a pooled interim analysis of four trials.

Methods This analysis includes data from four ongoing blinded, randomised, controlled trials done across the UK, Brazil, and South Africa. Participants aged 18 years and older were randomly assigned (1:1) to ChAdOx1 nCoV-19 vaccine or control (meningococcal group A, C, W, and Y conjugate vaccine or saline). Participants in the ChAdOx1 nCoV-19 group received two doses containing 5×10^{10} viral particles (standard dose; SD/SD cohort); a subset in the UK trial received a half dose as their first dose (low dose) and a standard dose as their second dose (LD/SD cohort). The primary efficacy analysis included symptomatic COVID-19 in seronegative participants with a nucleic acid amplification test-positive swab more than 14 days after a second dose of vaccine. Participants were analysed according to treatment received, with data cutoff on Nov 4, 2020. Vaccine efficacy was calculated as 1 – relative risk derived from a robust Poisson regression model adjusted for age. Studies are registered at ISRCTN89951424 and ClinicalTrials.gov, NCT04324606, NCT04400838, and NCT04444674.

Findings Between April 23 and Nov 4, 2020, 23 848 participants were enrolled and 11 636 participants (7548 in the UK, 4088 in Brazil) were included in the interim primary efficacy analysis. In participants who received two standard doses, vaccine efficacy was 62·1% (95% CI 41·0–75·7; 27 [0·6%] of 4440 in the ChAdOx1 nCoV-19 group *vs* 71 [1·6%] of 4455 in the control group) and in participants who received a low dose followed by a standard dose, efficacy was 90·0% (67·4–97·0; three [0·2%] of 1367 *vs* 30 [2·2%] of 1374; $p_{interaction}$=0·010). Overall vaccine efficacy across both groups was 70·4% (95·8% CI 54·8–80·6; 30 [0·5%] of 5807 *vs* 101 [1·7%] of 5829). From 21 days after the first dose, there were ten cases hospitalised for COVID-19, all in the control arm; two were classified as severe COVID-19, including one death. There were 74 341 person-months of safety follow-up (median 3·4 months, IQR 1·3–4·8): 175 severe adverse events occurred in 168 participants, 84 events in the ChAdOx1 nCoV-19 group and 91 in the control group. Three events were classified as possibly related to a vaccine: one in the ChAdOx1 nCoV-19 group, one in the control group, and one in a participant who remains masked to group allocation.

Interpretation ChAdOx1 nCoV-19 has an acceptable safety profile and has been found to be efficacious against symptomatic COVID-19 in this interim analysis of ongoing clinical trials.

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Research in context

Evidence before this study

We searched PubMed for research articles published from database inception until Nov 23, 2020, with no language restrictions, using the terms "SARS-CoV-2", "vaccine", "clinical trial", and "efficacy". There were no peer-reviewed publications available on efficacy of any severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines in development and, at the time of the search, there were no licensed vaccines against SARS-CoV-2. Three vaccine developers recently reported initial efficacy results from phase 3 trials in the media (Pfizer/BioNTech, Moderna, and the Gamaleya National Research Center). Pfizer/BioNTech and Moderna, both developing mRNA vaccines, have reported initial efficacy results of 95% in their primary analysis (Pfizer/BioNTech) and 94·5% in an interim analysis (Moderna). We have previously published safety and immunogenicity results of ChAdOx1 nCoV-19 (AZD1222) for different age groups in phase 1/2 and 2/3 trials.

Added value of this study

We report on the first clinical efficacy results of ChAdOx1 nCoV-19 in a pooled analysis of phase 2/3 trials in the UK and Brazil, and safety data from more than 20 000 participants enrolled across four clinical trials in the UK, Brazil, and South Africa. ChAdOx1 nCoV-19 has an acceptable safety profile and is efficacious against symptomatic COVID-19, with no hospital admissions or severe cases reported in the ChAdOx1 nCoV-19 arm. The vaccine can be stored and distributed at 2–8°C, making it particularly suitable for global distribution.

Implications of all the available evidence

The development of safe, effective, affordable, and deployable vaccines against COVID-19 remains paramount in solving the pandemic crisis and re-establishing normality. The positive results presented here support regulatory submissions for conditional or emergency use of ChAdOx1 nCoV-19.

Introduction

As the COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to unfold, there has been widespread impact on health, including substantial mortality among older adults and those with pre-existing health conditions,[1,2] and repercussions for the global economy, caused by physical distancing measures, with the greatest consequences for the most vulnerable in society.

Despite global spread of the virus, a large proportion of the population in many countries is thought to have thus far escaped infection and remains non-immune to SARS-CoV-2.[3] Vaccines could play an important role in increasing population immunity, preventing severe disease, and reducing the ongoing health crisis. In response, rapid global efforts to develop and test vaccines against SARS-CoV-2 have led to an unprecedented number of candidate vaccines starting clinical trials during 2020. Currently, 48 vaccines are under clinical evaluation.[4] Several of these have shown good safety and immunogenicity, and 11 of these are currently being evaluated in phase 3 clinical efficacy studies.

The ChAdOx1 nCoV-19 vaccine (AZD1222) was developed at Oxford University and consists of a replication-deficient chimpanzee adenoviral vector ChAdOx1, containing the SARS-CoV-2 structural surface glycoprotein antigen (spike protein; nCoV-19) gene.

Following initiation of a phase 1 clinical trial in the UK (COV001) on April 23, 2020, three further randomised controlled trials of the candidate vaccine were initiated across the UK (COV002), Brazil (COV003), and South Africa (COV005). A further phase 1/2 trial has recently been initiated in Kenya and is not reported here. The immunogenicity results from the phase 1/2 UK study, COV001, in 1077 healthy adults aged 18–55 years,[5] and a phase 2 cohort in COV002 in older adults (≥56 years)[6] have been published and show an acceptable safety profile for the vaccine with induction of binding and neutralising antibodies as well as generation of interferon-γ enzyme-linked immunospot responses, with higher antibody titres after a second dose of vaccine.[5–7]

The phase 1 study (COV001) included an efficacy cohort and the phase 2 and 3 studies (COV002, COV003, and COV005) expanded enrolment to a wider population of participants with higher likelihood of exposure to the virus, such as health-care workers. Exclusion criteria were reduced for phase 3 trials, so that older adults and individuals with a range of comorbidities were also enrolled.

All studies have completed enrolment of their respective efficacy cohorts and are in the follow-up phase. Paediatric studies have not yet been initiated.

Here, we present the combined interim analysis of efficacy and safety from randomised controlled trials of ChAdOx1 nCoV-19.

Methods

Overview

This interim analysis of the efficacy and safety of the ChAdOx1 nCoV-19 vaccine includes data from four ongoing blinded, randomised, controlled trials done across three countries: COV001 (phase 1/2; UK), COV002 (phase 2/3; UK), COV003 (phase 3; Brazil), and COV005 (phase 1/2; South Africa). The interim efficacy is being assessed by a prespecified global pooled analysis combining data from COV002 and COV003. The safety of the vaccine is being assessed using data from all four studies (appendix 1 pp 3–4). Three of the studies are single blind and one is double blind (COV005). Primary efficacy was assessed in participants who received

two doses of the vaccine. All four studies included participants who received two doses, with a booster dose incorporated into the three trials[6] that were initially designed to assess a single-dose of ChAdOx1 nCoV-19 compared with control (COV001, COV002, and COV003) after review of the antibody response data from COV001.

Despite minor differences across the studies, there is sufficient consistency to justify the proposal for pooled analysis of data, which will provide greater precision for both efficacy and safety outcomes than can be achieved in individual studies and provides a broader understanding of the use of the vaccine in different populations. Once the studies were underway, a statistical analysis plan for the global pooled analysis of these studies was developed before data lock on Nov 4, 2020, and analysis, and was finalised with extensive feedback from national and international regulators (including the Medicines and Healthcare Products Regulatory Agency [UK] and the European Medicines Agency [EU]), including justification for including groups receiving different vaccine doses in the analysis (see statistical analysis plan for further details; appendix 2 pp 2–73). All participants in the four trials provided written informed consent.

Details of amendments to the four trial protocols and the statistical analysis plan are included in appendix 2 (pp 9, 178–182, 327–335, 438–441, 548–550).

Study design and participants

COV001 (UK)

COV001 is a continuing single-blind phase 1/2 clinical trial in five sites in the UK, which began on April 23, 2020, and enrolled 1077 healthy volunteers aged 18–55 years, as previously described.[5] Briefly, healthy adult participants were enrolled after screening to exclude those with pre-existing health conditions. Participants were randomly assigned 1:1 to receive ChAdOx1 nCoV-19 at a dose of 5×10^{10} viral particles (standard dose), measured using spectrophotometry, or meningococcal group A, C, W, and Y conjugate vaccine (MenACWY) as control. An open-label non-randomised subgroup of ten participants were given two doses of ChAdOx1 nCoV-19 28 days apart, as previously reported.[5] This study was originally planned as a single-dose study and 88 participants in the phase 1 part of the study remain recipients of a single dose. However, the protocol was modified to a two-dose regime, following an amendment on July 30, 2020 (version 9.0; appendix 2 pp 180–181), for the remaining phase 2 cohorts as a result of robust booster responses identified in the evaluation of the early immunogenicity cohorts, with the booster dose given at the earliest possible time.[5]

COV002 (UK)

COV002 is a continuing single-blind phase 2/3 study in the UK that began on May 28, 2020, and enrolled participants in 19 study sites in England, Wales, and Scotland. Enrolment particularly targeted individuals working in professions with high possible exposure to SARS-CoV-2, such as health and social care settings.

Two dosage groups were included in COV002: participants who received a low dose of the vaccine ($2\cdot2\times10^{10}$ viral particles) as their first dose and were boosted with a standard dose (in the LD/SD group), and subsequent cohorts who were vaccinated with two standard-dose vaccines (SD/SD group). Initial dosing in COV002 was with a batch manufactured at a contract manufacturing organisation using chromatographic purification. During quality control of this second batch, differences were observed between the quantification methods (spectrophotometry and quantitative PCR [qPCR]) prioritised by different manufacturing sites. In consultation with the national regulator (Medicines and Healthcare products Regulatory Agency), we selected a dose of 5×10^{10} viral particles by spectrophotometer ($2\cdot2\times10^{10}$ viral particles by qPCR), in order to be consistent with the use of spectrophotometry in the phase 1 study (COV001),[5] and to ensure the dose was within a safe and immunogenic range according to measurements by both methods. A lower-than-anticipated reactogenicity profile was noted in the trial, and unexpected interference of an excipient with the spectrophotometry assay was identified. After review and approval by the regulator, it was concluded that the qPCR (low-dose) reading was more accurate and further doses were adjusted to the standard dose (5×10^{10} viral particles) using a qPCR assay. The protocol was amended on June 5, 2020, resulting in enrolment of two distinct groups with different dosing regimens with no pause in enrolment (version 6.0; appendix 2 p 330). A suite of assays has now been developed for characterisation of concentration (which confirmed the low and standard dosing), and future batches are all released with a specification dose of $3\cdot5–6\cdot5\times10^{10}$ viral particles, and this was used for the booster doses in the efficacy analysis presented here.

The LD/SD cohort (aged 18–55 years) was enrolled over 11 days between May 31 and June 10, 2020. The SD/SD cohort (aged 18–55 years) was enrolled from June 9 to July 20, 2020. Subsequently, enrolment of older age cohorts began (from Aug 8, 2020, for participants aged 56–69 years and from Aug 13, 2020, for participants aged ≥70 years), all of whom were assigned to two standard doses (SD/SD cohort). Each site implemented the protocol amendment before changing from low-dose administration to standard-dose administration, and therefore there was no overlap in enrolment of participants in these cohorts.

The 18–55-year-old cohorts were originally planned as single-dose efficacy cohorts. However, the protocol was modified on July 20, 2020, to offer a second dose to the participants in these cohorts as a result of robust booster responses identified in the evaluation of the early immunogenicity cohorts (version 9.0; appendix 2 pp 331–332).[5] Boosting began on Aug 3, 2020, resulting

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See **Online** for appendix 1

See **Online** for appendix 2

in a longer gap between prime and booster vaccines in these cohorts than for those aged 55–69 years and those aged 70 years or older, as these participants were enrolled into two-dose groups from the start.

Results for participants enrolled into immunogenicity subgroups have been previously published, including a small subset who received a low-dose boost.[6] Full details are available in the study protocol (appendix 2 pp 184–342) and the procedures have been previously described.[6]

COV003 (Brazil)

COV003 is a continuing single-blind phase 3 study in Brazil that began on June 23, 2020. The focus of recruitment was targeted at those at high risk of exposure to the virus, including health-care workers at six sites across Brazil. Participants were aged 18 years or older, and this trial included individuals with stable pre-existing health conditions. All participants were offered two doses of the vaccine at a dose of $3 \cdot 5–6 \cdot 5 \times 10^{10}$ viral particles with administration up to 12 weeks apart (target 4 weeks), following a protocol amendment on July 28, 2020, to include booster groups (version 4.0; appendix 2 pp 438–439). Full details are available in the study protocol (appendix 2 pp 343–441).

COV005 (South Africa)

COV005 is a continuing double-blind phase 1/2 study in South Africa in healthy adults aged 18–65 years living without HIV that began on June 28, 2020. An additional immunogenicity cohort of those living with HIV was also enrolled but are not included in this interim analysis. All participants were offered two doses of the vaccine at a dose of $3 \cdot 5–6 \cdot 5 \times 10^{10}$ viral particles, with doses administered 4 weeks apart. A small subgroup of 44 participants received a half-dose vaccine (21 as their first dose and 23 as their second dose) as a result of variability in the release assay, before the adoption of new methods for characterisation of concentration. Adjustment in dose was discussed with and approved by the national regulator. Full details are available in the study protocol (appendix 2 pp 442–559).

A combined independent data safety monitoring board reviews safety data from all four trials on a regular basis.

Randomisation and masking

In efficacy cohorts for all studies, participants were randomised 1:1 to receive ChAdOx1 nCoV-19 or a control product. In COV002, MenACWY was chosen as the control group vaccine to minimise the chance of accidental participant unmasking due to local or systemic reactions to the vaccine. COV003 used MenACWY as the control for the first dose and saline for the second dose. In COV005, participants randomly assigned to the control group were administered saline solution. Randomisation lists were prepared by the study statistician (MV) using block randomisation, stratified by study site and study group, and uploaded into to the secure web platform used for the study electronic case report form (REDCap version 9.5.22) for COV001, COV002, and COV003. In COV005, the randomisation list was held by the unmasked study pharmacist who prepared the vaccines for administration, with all other trial staff masked to group allocation. 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 masking of participants.

Procedures

The recombinant adenovirus for ChAdOx1 nCoV-19 was manufactured and vialed by Advent (Pomezia, Italy), and additional batches produced by COBRA Biologics (Keele, UK) and vialed by Symbiosis (Sterling, UK). Both were manufactured according to Good Manufacturing Practice and approved by the regulatory agency in the UK, the Medicines and Healthcare products Regulatory Agency.

Baseline assessments included review of inclusion and exclusion criteria, medical history, vital signs measurement, history-directed clinical examination, and collection of serum for SARS-CoV-2 serology.

Participants across all four trials were asked to contact the study site if they experienced specific symptoms associated with COVID-19 and received regular reminders to do so. Those who met symptomatic criteria had a clinical assessment, a swab taken for a nucleic acid amplification test (NAAT), and blood samples taken for safety and immunogenicity. In the UK and Brazil, the list of qualifying symptoms for swabbing included any one of the following: fever of at least 37·8°C, cough, shortness of breath, and anosmia or ageusia. In South Africa, the list of qualifying symptoms for swabbing was broader, and additionally included myalgia, chills, sore throat, headache, nasal congestion, diarrhoea, runny nose, fatigue, nausea, vomiting, and loss of appetite.

In all studies, if participants were tested outside of the trial, either in their workplace if a health-care worker or by private providers, these results were recorded and assessed by a masked independent endpoint review committee. The source of each swab was recorded plus the details of the test kit where available.

To test for asymptomatic infections, participants in COV002 in the UK were asked to provide a weekly self-administered nose and throat swab for NAAT testing from 1 week after first vaccination using kits provided by the UK Department of Health and Social Care (DHSC). Participants were given home test kits provided by the DHSC that included step-by-step instructions on how to do a self-swab and a link to a demonstration video. The site trial team provided support with logistics of packaging and returning test kits and tracking swab results to participants if required. Swabs were taken by participants in their homes and posted to dedicated DHSC testing laboratories for processing. Participants were directly informed of their results by text or email from the National Health Service (NHS). Swab results

from participants in England and Wales were provided to the trial statistician on a daily basis by the NHS and matched to individuals based on personal identification data (name, date of birth, NHS number, and postcode). Swab results from participants in Scotland were unavailable to the study team at the time of the data cutoff for this analysis, but will be included in future analyses. Any swab results that were not able to be matched to a study participant using at least two pieces of personal data were not added to the study database.

In Brazil, there was no testing plan for asymptomatic infections. In South Africa, asymptomatic infections were detected from swabs obtained at study visits attended, but are not summarised here as there were only a small number of timepoints for detection of these cases.

All cases of COVID-19 were reviewed by two members of a masked independent clinical review team who assessed clinical details, including medical history, symptoms, adverse events, and swab results, and assigned severity scores according to the WHO clinical progression scale.[8]

For symptomatic participants in COV002 in the UK, weekly swabbing continued both before and after participants reported symptoms to the study site. Thus, a participant who reported symptoms and was clinically assessed might also have had additional swabs return positive results through the asymptomatic testing process for several weeks. In addition, due to the large number of health-care workers enrolled in these studies, some participants were tested according to their workplace testing policies and these results were also entered into the database for review by the masked endpoint evaluation committee. Further exploratory assessment of the length of time participants remained NAAT-positive, and the sources of information used for case detection will be done in future analyses.

Outcomes

The primary objective was to evaluate the efficacy of ChAdOx1 nCoV-19 vaccine against NAAT-confirmed COVID-19. The primary outcome was virologically confirmed, symptomatic COVID-19, defined as a NAAT-positive swab combined with at least one qualifying symptom (fever ≥37·8°C, cough, shortness of breath, or anosmia or ageusia).

All participants were given an emergency 24-h telephone number to contact the on-call study physician for the duration of the study to report any illnesses. Serious adverse events were recorded throughout the study and reviewed at each study visit, with causality assigned by the site investigator. Events were clinically coded according to the Medical Dictionary for Regulatory Activities.

Statistical analysis

The plan for assessing efficacy and safety for the ChAdOx1 nCoV-19 vaccine is based on global analyses using all available data from four studies with analysis pooled across the studies. A global statistical analysis plan for pooling study data was developed, after extensive advice from regulators, to prespecify the analyses that would contribute to the assessment of efficacy and this was signed off before any data analysis was conducted.

Randomised participants who received at least one dose in all studies are included in the safety analysis. However, each study had to meet prespecified criteria of having at least five cases eligible for inclusion in the primary outcome before a study was included in efficacy analyses. Neither COV001 or COV005 met these criteria and so are not included in the efficacy assessment for this interim analysis. It is expected that they will be included in efficacy assessments in future analyses once more cases have accrued. Additionally, only efficacy groups for COV002 (ie, groups 4, 6, 9, and 10) were included.

Vaccine efficacy was calculated as 1– adjusted relative risk (ChAdOx1 nCoV-19 *vs* control groups) computed using a Poisson regression model with robust variance.[9] The model contained terms for study, treatment group, and age group (18–55, 56–69, and ≥70 years) at randomisation. A reduced model that did not contain a term for age was used for models affected by convergence issues due to having few cases in the older age groups. The logarithm of the period at risk for the primary endpoint for pooled analysis was used as an offset variable in the model to adjust for volunteers having different follow-up times during which the events occurred. Cumulative incidence is presented using the Kaplan-Meier method.

The global pooled analysis plan allowed for an interim and a final efficacy analysis with α adjusted between the two analyses using a flexible gamma α-spending function, with significance being declared if the lower bound of the (1–α)% CI is greater than 20%. Evidence of efficacy at the time of the interim analysis was not considered reason to stop the trials and all trials are continuing to accrue further data that will be included in future analyses.

The first interim analysis was planned to be triggered when at least 53 cases in participants who had received two standard-dose vaccines (SD/SD) had accrued that met the primary outcome definition more than 14 days after the second dose. This analysis provides 77% power for the 20% threshold to assume a true vaccine efficacy of 70%. Although the number of cases in the SD/SD cohort was used as the trigger for the interim analysis, the prespecified primary analysis included both SD/SD and LD/SD recipients. Due to the rapid increase in incidence of COVID-19 in the UK in October, more than 53 cases had accrued by the time of data lock for this interim analysis. There were 98 cases available for inclusion in the SD/SD cohorts. Based on these numbers, the α level calculated using the gamma α-spending function for this analysis is 4·16%.

Participants were excluded from the primary efficacy analysis if they were seropositive at baseline or had no baseline result. Other exclusions included those with NAAT-positive swabs within 14 days after the second vaccination, or those who discontinued from the study before having met the primary efficacy endpoint with a follow-up time of less than 15 days after the second vaccination. All reasons for exclusion are shown in appendix 1 (pp 5–8).

An analysis of efficacy after the first standard-dose vaccine in those who only received standard-dose vaccines was undertaken as a secondary analysis. Individuals were excluded if they had a NAAT-positive swab within 21 days after their first standard-dose vaccine.

Participants were analysed according to the vaccines they received. Sensitivity analyses included those who were seropositive at baseline and an intention-to-treat analysis. Safety analyses include all randomised participants who received at least one dose of any vaccine in any study.

Prespecified subgroup analyses are not included in this report but will be presented in future analyses when a larger dataset is available. However, in response to reviewer and editorial comments, a small number of exploratory subgroup comparisons has been included to explore differences in efficacy in the LD/SD and SD/SD groups and potential confounder variables. The LD/SD cohort in the UK comprised participants aged 18–55 years who received their second dose after a substantial gap. Age and the time difference between vaccines were therefore potential confounders and were explored further in subgroup analyses, restricted to those aged 18–55 years, those with more than 8 weeks' interval between vaccine doses, and a comparison of those in the SD/SD cohort receiving vaccines at short (<6 weeks) or long (≥6 weeks) intervals. Subgroup comparisons were done by incorporating the treatment-by-subgroup interaction term in the model and reporting the p value for the interaction term.

Data analysis was done using R (version 3.6.1 or later). Robust Poisson models were fitted using the PROC GENMOD function in SAS (version 9.4). The α level for the analysis was calculated using the gsDesign function in R. The cutoff date for inclusion in the analysis was Nov 4, 2020, and the data lock date was Nov 21, 2020.

The four trials are registered at ISRCTN89951424 (COV003) and ClinicalTrials.gov, NCT04324606 (COV001), NCT04400838 (COV002), and NCT04444674 (COV005).

Role of the funding source

AstraZeneca reviewed the data from the study and the final manuscript before submission, but the academic authors

	COV002 (UK; LD/SD; N=2741)		COV002 (UK; SD/SD; N=4807)		COV003 (Brazil; all SD/SD; N=4088)	
	ChAdOx1 nCoV-19 (n=1367)	MenACWY (n=1374)	ChAdOx1 nCoV-19 (n=2377)	MenACWY (n=2430)	ChAdOx1 nCoV-19 (n=2063)	MenACWY plus saline (n=2025)
Age, years						
18–55	1367 (100·0%)	1374 (100·0%)	1879 (79·0%)	1922 (79·1%)	1843 (89·3%)	1833 (90·5%)
56–69	0	0	285 (12·0%)	293 (12·1%)	209 (10·1%)	187 (9·2%)
≥70	0	0	213 (9·0%)	215 (8·8%)	11 (0·5%)	5 (0·2%)
Sex						
Female	886 (64·8%)	927 (67·5%)	1378 (58·0%)	1437 (59·1%)	1261 (61·1%)	1156 (57·1%)
Male	481 (35·2%)	447 (32·5%)	999 (42·0%)	993 (40·9%)	802 (38·9%)	869 (42·9%)
BMI, kg/m²	25·2 (22·8–28·7)	25·3 (22·7–28·8)	25·4 (22·9–28·7)	25·5 (22·9–29·1)	25·6 (22·8–29·1)	25·6 (23·1–29·0)
Ethnicity						
White	1257 (92·0%)	1278 (93·0%)	2153 (90·6%)	2214 (91·1%)	1357 (65·8%)	1366 (67·5%)
Black	6 (0·4%)	2 (0·1%)	17 (0·7%)	14 (0·6%)	230 (11·1%)	210 (10·4%)
Asian	76 (5·6%)	59 (4·3%)	137 (5·8%)	138 (5·7%)	54 (2·6%)	53 (2·6%)
Mixed	19 (1·4%)	22 (1·6%)	48 (2·0%)	42 (1·7%)	410 (19·9%)	386 (19·1%)
Other	9 (0·7%)	13 (0·9%)	22 (0·9%)	22 (0·9%)	12 (0·6%)	10 (0·5%)
Health and social care setting workers	1236 (90·4%)	1253 (91·2%)	1441 (60·6%)	1513 (62·3%)	1833 (88·9%)	1775 (87·7%)
Comorbidities						
Cardiovascular disease	104 (7·6%)	92 (6·7%)	264 (11·1%)	266 (10·9%)	271 (13·1%)	244 (12·0%)
Respiratory disease	158 (11·6%)	176 (12·8%)	285 (12·0%)	316 (13·0%)	215 (10·4%)	210 (10·4%)
Diabetes	18 (1·3%)	15 (1·1%)	58 (2·4%)	60 (2·5%)	59 (2·9%)	60 (3·0%)

Data are n (%) or median (IQR). The primary efficacy population (LD/SD and SD/SD) includes randomly assigned participants who were seronegative at baseline and received LD/SD or SD/SD or were in the corresponding control group, and remained on study more than 14 days after their second dose without having had a previous virologically confirmed severe acute respiratory syndrome coronavirus 2 infection. In addition, for groups in COV002, only efficacy groups (ie, groups 4, 6, 9, and 10) are included. LD/SD=low-dose prime plus standard-dose boost. SD/SD=two standard-dose vaccines given. MenACWY=meningococcal group A, C, W, and Y conjugate vaccine. BMI=body-mass index.

Table 1: **Baseline characteristics of participants included in the primary efficacy population, by study and dosing strategy**

	Total number of cases	ChAdOx1 nCoV-19		Control		Vaccine efficacy (CI*)
		n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	
All LD/SD and SD/SD recipients	131	30/5807 (0·5%)	44·1 (248 299)	101/5829 (1·7%)	149·2 (247 228)	70·4% (54·8 to 80·6)†
COV002 (UK)	86	18/3744 (0·5%)	38·6 (170 369)	68/3804 (1·8%)	145·7 (170 448)	73·5% (55·5 to 84·2)
LD/SD recipients	33	3/1367 (0·2%)	14·9 (73 313)	30/1374 (2·2%)	150·2 (72 949)	90·0% (67·4 to 97·0)‡§
SD/SD recipients	53	15/2377 (0·6%)	56·4 (97 056)	38/2430 (1·6%)	142·4 (97 499)	60·3% (28·0 to 78·2)
COV003 (Brazil; all SD/SD)	45	12/2063 (0·6%)	56·2 (77 930)	33/2025 (1·6%)	157·0 (76 780)	64·2% (30·7 to 81·5)‡
All SD/SD recipients	98	27/4440 (0·6%)	56·4 (174 986)	71/4455 (1·6%)	148·8 (174 279)	62·1% (41·0 to 75·7)
Other non-primary symptomatic COVID-19 disease¶	18	7/5807 (0·1%)	10·3 (248 299)	11/5829 (0·2%)	16·3 (247 228)	36·4% (−63·8 to 75·3)‡
Any symptomatic COVID-19 disease	149	37/5807 (0·6%)	54·4 (248 299)	112/5829 (1·9%)	165·5 (247 228)	67·1% (52·3 to 77·3)
Asymptomatic or symptoms unknown (COV002)	69	29/3288 (0·9%)	69·8 (151 673)	40/3350 (1·2%)	96·0 (152 138)	27·3% (−17·2 to 54·9)
LD/SD recipients	24	7/1120 (0·6%)	41·4 (61 782)	17/1127 (1·5%)	100·6 (61 730)	58·9% (1·0 to 82·9)‡
SD/SD recipients	45	22/2168 (1·0%)	89·4 (89 891)	23/2223 (1·0%)	92·9 (90 408)	3·8% (−72·4 to 46·3)
Any NAAT-positive swab	221	68/5807 (1·2%)	100·0 (248 299)	153/5829 (2·6%)	226·0 (247 228)	55·7% (41·1 to 66·7)

Vaccine efficacy was calculated from the robust Poisson model. The primary efficacy population (LD/SD and SD/SD) includes randomly assigned participants who were seronegative at baseline and received LD/SD or SD/SD or were in a corresponding control group, and remained on study more than 14 days after their second dose without having had a previous virologically confirmed SARS-CoV-2 infection. In addition, for groups in COV002, only efficacy groups (ie, groups 4, 6, 9, and 10) are included. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. LD/SD=low-dose prime plus standard-dose boost. SD/SD=two standard-dose vaccines given. NAAT=nucleic acid amplification test. *CIs are 95% unless indicated otherwise. †95·8% CI used for primary analysis. ‡Vaccine efficacy calculated from a reduced robust Poisson model that was not adjusted for age. All other models included an adjustment for age. §p value for interaction term comparing LD/SD with SD/SD is p=0·010. ¶Other non-primary symptomatic COVID-19 disease includes cases who have symptoms other than the five main symptoms that are required for inclusion in the primary analysis (eg, a participant who has diarrhoea and malaise but no fever, cough, shortness of breath, anosmia, or ageusia).

Table 2: **Efficacy against SARS-CoV-2 more than 14 days after a second dose of ChAdOx1 nCoV-19 vaccine in the primary efficacy population**

retained editorial control. All other 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 April 23 and Nov 4, 2020, 23 848 participants were recruited and vaccinated across the four studies: 1077 in COV001 (UK), 10 673 in COV002 (UK), 10 002 in COV003 (Brazil), and 2096 in COV005 (South Africa). 11 636 participants in COV002 and COV003 met the inclusion criteria for the primary analysis, 5807 of whom received two doses of ChAdOx1 nCoV-19 and 5829 of whom received two doses of control product. A trial profile and reasons for exclusion from the primary analysis are shown in appendix 1 (pp 5–7). Here, we provide safety data on 74 341 person-months of follow-up after first dose (median 3·4 months, IQR 1·3–4·8) and 29 060 person-months of follow-up after two doses (median 2·0, 1·3–2·3).

Of the participants in COV002 and COV003 included in the primary efficacy analyses, the majority were aged 18–55 years (6542 [86·7%] of 7548 in the UK and 3676 [89·9%] of 4088 in Brazil; table 1). Those aged 56 years or older were recruited later and contributed 12·2% of the total cohort in the current analysis (1006 [13·3%] in the UK and 412 [10·1%] in Brazil). 7045 (60·5%) participants were female. 6902 (91·4%) participants in the UK and 2723 (66·6%) participants in Brazil were white (table 1). Baseline participants of the safety population are shown in appendix 1 (pp 9–10).

The timing of priming and booster vaccine administration varied between studies. As protocol amendments to add a booster dose took place when the trials were underway, and owing to the time taken to manufacture and release a new batch of vaccine, doses could not be administered at a 4-week interval. 1459 (53·2%) of 2741 participants in COV002 in the LD/SD group received a second dose at least 12 weeks after the first (median 84 days, IQR 77—91) and only 22 (0·8%) received a second dose within 8 weeks of the first. The median interval between doses for the SD/SD group in COV002 was 69 days (50–86). Conversely, the majority of participants in COV003 in the SD/SD group (2493 [61·0%] of 4088) received a second dose within 6 weeks of the first (median 36 days, 32–58; appendix 1 p 11).

A small proportion of participants were seropositive at baseline (138 [1·3%] of 10 673 in the UK and 235 [2·3%] of 10 002 in Brazil). Three participants seropositive at baseline had subsequent NAAT-positive swabs. One participant had an asymptomatic infection 3 weeks after a first dose of ChAdOx1 nCoV-19. Two other participants in the control group had symptomatic infections 8 weeks and 21 weeks after their baseline sample was taken.

There were 131 cases of symptomatic COVID-19 in LD/SD or SD/SD recipients who were eligible for inclusion in the primary efficacy analysis more than 14 days after the second dose of vaccine (table 2). There were 30 (0·5%) cases among 5807 participants in the vaccine arm and 101 (1·7%) cases among 5829 participants in the control group, resulting in vaccine efficacy of 70·4% (95·8% CI 54·8–80·6; table 2; figure). In participants who received two standard-dose vaccines, vaccine efficacy was 62·1% (95% CI 41·0–75·7), whereas in those who received a low dose as their first dose of vaccine, efficacy was higher at 90·0% (67·4–97·0; $p_{interaction}$=0·010; table 2; appendix 1 pp 12–13).

In England and Wales, 129 529 weekly self-swabs were processed by the DHSC, of which 126 324 (97·5%) were matched to study participants. There were 435 positive swabs, of which 354 (81·4%) were matched. Symptoms in these participants were not routinely assessed as swabs were done at home and sent for testing through the post. Asymptomatic infections or those with unreported symptoms were detected in 69 participants (table 2). Vaccine efficacy in the 24 LD/SD recipients was 58·9% (95% CI 1·0 to 82·9), whereas it was 3·8% (–72·4 to 46·3) in the 45 participants receiving SD/SD (table 2).

Results from sensitivity analyses, including participants who were seropositive at baseline and by intention to treat, were very similar to main results (data not shown).

Results from the subgroup comparisons presented in this analysis were similar to overall results (table 3). In the SD/SD UK cohort who were aged 18–55 years, 49 cases were available for inclusion in the analysis and vaccine efficacy was 59·3% (95% CI 25·1 to 77·9; $p_{interaction}$=0·019; table 3). When further restricted to those who received their vaccines more than 8 weeks apart, 33 cases were included in the SD/SD analysis and vaccine efficacy was 65·6% (24·5 to 84·4; $p_{interaction}$=0·082; table 3; appendix 1 pp 12–13). In the SD/SD cohorts in the UK and Brazil, vaccine efficacy was similar when analysed in subgroups according to time between

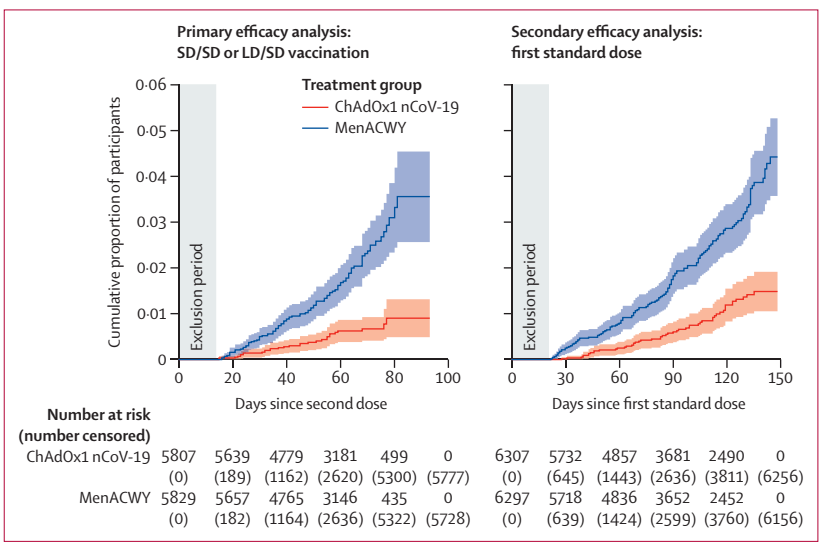

Figure: **Kaplan-Meier cumulative incidence of primary symptomatic, NAAT-positive COVID-19**
Cumulative incidence of symptomatic COVID-19 after two doses (left) or after first standard dose in participants receiving only standard-dose vaccines (right). Grey shaded areas show the exclusion period after each dose in which cases were excluded from the analysis. Blue and red shaded areas show 95% CIs. LD/SD=low-dose prime plus standard-dose boost. MenACWY=meningococcal group A, C, W, and Y conjugate vaccine. NAAT=nucleic acid amplification test. SD/SD=two standard-dose vaccines given.

	Total number of cases	ChAdOx1 nCoV-19	Control	Vaccine efficacy (95% CI)	p value for interaction
COV002 (UK), age 18–55 years*	..	..	..	..	0·019
LD/SD recipients	33	3/1367 (0·2%)	30/1374 (2·2%)	90·0% (67·3 to 97·0)	..
SD/SD recipients	49	14/1879 (0·7%)	35/1922 (1·8%)	59·3% (25·1 to 77·9)	..
COV002 (UK), age 18–55 years with >8 weeks' interval between vaccine doses*	..	..	..	..	0·082
LD/SD recipients	33	3/1357 (0·2%)	30/1362 (2·2%)	90·0% (67·3 to 97·0)	..
SD/SD recipients	34	8/1407 (0·6%)	26/1512 (1·7%)	65·6% (24·5 to 84·4)	..
All SD/SD (UK and Brazil)†	..	..	..	..	0·557
<6 weeks' interval between vaccine doses	28	9/1702 (0·5%)	19/1698 (1·1%)	53·4% (–2·5 to 78·8)	..
≥6 weeks' interval between vaccine doses	70	18/2738 (0·7%)	52/2757 (1·9%)	65·4% (41·1 to 79·6)	..

Cohorts are all subsets of the primary efficacy population. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. LD/SD=low-dose prime plus standard-dose boost. SD/SD=two standard-dose vaccines given. BMI=body-mass index. *Models adjusted for BMI (<30 *vs* ≥30 kg/m^2), health-care worker status (yes *vs* no), and ethnicity (white *vs* non-white). †Model adjusted for BMI (<30 *vs* ≥30 kg/m^2), health-care worker status (yes *vs* no), ethnicity (white *vs* non-white), age (<56 years *vs* ≥56 years), and study (COV002 *vs* COV003).

Table 3: **Subgroup comparisons of efficacy against SARS-CoV-2 more than 14 days after a second dose of ChAdOx1 nCoV-19 vaccine in the primary efficacy population**

	Total number of cases	ChAdOx1 nCoV-19		Control		Vaccine efficacy (95% CI)
		n/N (%)	Incidence per 1000 person-years (person-days of follow-up)	n/N (%)	Incidence per 1000 person-years (person-days of follow-up)	
COV002 (UK)	90	28/3060 (0·9%)	35·4 (288 955)	62/3064 (2·0%)	78·5 (288 395)	55·0% (29·7 to 71·1)
COV003 (Brazil)	102	23/3247 (0·7%)	46·7 (179 743)	79/3233 (2·4%)	162·4 (177 693)	71·2% (54·2 to 81·9)
Primary symptomatic COVID-19*	192	51/6307 (0·8%)	39·7 (468 698)	141/6297 (2·2%)	110·5 (466 088)	64·1% (50·5 to 73·9)
Other non-primary symptomatic COVID-19†	21	12/6307 (0·2%)	9·4 (468 698)	9/6297 (0·1%)	7·1 (466 088)	−32·8% (−214·8 to 44·0)‡
Any symptomatic COVID-19	213	63/6307 (1·0%)	49·1 (468 698)	150/6297 (2·4%)	117·5 (466 088)	58·3% (44·0 to 68·9)
Asymptomatic or symptoms unknown (COV002)	71	34/2751 (1·2%)	46·8 (265 142)	37/2760 (1·3%)	51·0 (264 994)	7·8% (−46·7 to 42·1)
Any NAAT-positive swab	291	102/6307 (1·6%)	79·5 (468 698)	189/6297 (3·0%)	148·1 (466 088)	46·3% (31·8 to 57·8)

Vaccine efficacy was calculated from the robust Poisson model. The first-standard-dose efficacy population includes participants seronegative at baseline who received only standard dose vaccines or were in the corresponding control group, and remained on study 22 days after their first dose without having had a previous virologically confirmed SARS-CoV-2 infection. In addition, for groups in COV002, only efficacy groups (ie, groups 4, 6, 9, and 10) are included. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. NAAT=nucleic acid amplification test. *NAAT-positive swab plus at least one of cough, shortness of breath, fever higher than 37·8°C, anosmia, or ageusia. †Other non-primary symptomatic COVID-19 disease includes cases that have symptoms other than the five main symptoms required for inclusion in the primary analysis (eg, a participant who has diarrhoea and malaise but no fever, cough, shortness of breath, anosmia, or ageusia). ‡Vaccine efficacy was calculated from a reduced robust Poisson model (excluding the age group category due to the full model failing to converge). Participants with a low-dose prime were excluded.

Table 4: **Efficacy against SARS-CoV-2 more than 21 days after the first standard dose in seronegative participants who received only standard doses**

vaccines, at 53·4% (−2·5 to 78·8) in participants with less than 6 weeks' interval between doses and 65·4% (41·1 to 79·6) in participants with at least 6 weeks' interval ($p_{interaction}$=0·56; table 3).

For our secondary analysis of cases occurring more than 21 days after the first standard dose in participants who received only standard doses, there were 192 included cases with a vaccine efficacy of 64·1% (95% CI 50·5–73·9; table 4; figure)

More than 21 days after their first dose, ten participants were hospitalised due to COVID-19 (defined as WHO clinical progression score ≥4), two of whom were assessed as having severe COVID-19 (WHO score ≥6), including one fatal case. All ten cases were in the control group (table 5).

Five cases included in the primary analysis occurred in those participants older than 55 years of age. Vaccine efficacy in older age groups could not be assessed but will be determined, if sufficient data are available, in a future analysis after more cases have accrued.

Across all four studies, the vaccine had a good safety profile with serious adverse events and adverse events of special interest balanced across the study arms. Serious adverse events occurred in 168 participants, 79 of whom received ChAdOx1 nCoV-19 and 89 of whom received MenACWY or saline control (appendix 1 pp 15–18). There were 175 events (84 in the ChAdOx1 nCoV-19 group and 91 in the control group), three of which were considered possibly related to either the experimental or a control vaccine. A case of haemolytic anaemia in the control group in the UK phase 1/2 study occurring 10 days after MenACWY vaccine was considered possibly related to the intervention and has been previously described.[5] A case of transverse myelitis was reported

	ChAdOx1 nCoV-19 (n=12 021)	MenACWY or saline control (n=11 724)
Hospitalisation (WHO clinical progression score ≥4)		
≤21 days after the first dose	2*	6
>21 days after the first dose and ≤14 days after the second dose	0	5
>14 days after the second dose	0	5
Severe COVID-19 (WHO clinical progression score ≥6)		
≤21 days after the first dose	0	0
>21 days after the first dose and ≤14 days after the second dose	0	1
>14 days after the second dose	0	1

The safety population includes all randomisation participants who received at least one dose of vaccine. Severe COVID-19 (WHO score ≥6) is a subset of hospitalisations (WHO score ≥4). Cases were eligible for inclusion in efficacy if the first symptom or first NAAT-positive result was on or before the data cutoff date (Nov 4, 2020). Two cases appear in this table that do not appear in the table for serious adverse events in appendix 1 (pp 15–20) as the adverse event reporting date was after the data cutoff date. MenACWY=meningococcal group A, C, W, and Y conjugate vaccine. NAAT=nucleic acid amplification test. *One case on the day of the first vaccination and one case 10 days after the first dose.

Table 5: **Hospitalisation for COVID-19 and severe COVID-19 in the safety population**

14 days after ChAdOx1 nCoV-19 booster vaccination as being possibly related to vaccination, with the independent neurological committee considering the most likely diagnosis to be of an idiopathic, short segment, spinal cord demyelination. A potentially vaccine-related serious adverse event was reported 2 days after vaccination in South Africa in an individual who recorded fever higher than 40°C, but who recovered

rapidly without an alternative diagnosis and was not admitted to hospital. The participant remains masked to group allocation, continues in the trial, and received a second dose of the allocated vaccine without a similar reaction.

There were two additional cases of transverse myelitis that were originally reported as potentially related but later determined to be unlikely to be related to vaccination by an independent committee of neurological experts. One case that occurred 10 days after a first vaccination with ChAdOx1 nCoV-19 was initially assessed as possibly related, but later considered unlikely to be related by the site investigator when further investigation revealed pre-existing, but previously unrecognised, multiple sclerosis. The second case was reported 68 days after MenACWY vaccination. While considered possibly related by the site investigator at the time of reporting, an independent panel of neurological experts considered this to be unlikely. All trial participants have recovered, or are in a stable or improving condition.

There were four non-COVID-19 deaths reported across the studies (three in the control arm and one in the ChAdOx1 nCoV-19 arm) that were all considered unrelated to the vaccine, with cause of death assessed as road traffic accident, blunt force trauma, homicide, and fungal pneumonia.

Discussion

Here, we present the first interim safety and efficacy data for a viral vector coronavirus vaccine, ChAdOx1 nCoV-19, evaluated in four trials across three continents, showing significant vaccine efficacy of 70·4% after two doses and protection of 64·1% after at least one standard dose, against symptomatic disease, with no safety concerns.

The prespecified analysis population, which was determined following feedback from national and international regulators before unblinding of the study, included a pooled analysis from several countries to improve generalisability, and inclusion of two dose subgroups within the UK trial. This pooling strategy was authorised by the chief investigator (AJP) and study statistician (MV), with no concerns about pooling different control groups, and was accepted by regulators involved in the discussions. There had been initial concern that the LD/SD regimen might have lower efficacy than SD/SD, and the regulatory authority acceptance of the inclusion of the two trial regimens (LD/SD and SD/SD) in analysis was based on the observation that these regimens generated similar levels of binding antibody, and would therefore increase the sample size available for analysis without compromising efficacy. The discussion about pooling and inclusion of LD/SD was made at a time when disease rates were low in the UK and, in the face of the pandemic, it was agreed that pooling could provide the earliest possible read on efficacy that could contribute to public health.

No previous trials have been published on the efficacy of a viral-vectored coronavirus vaccine and so this study provides the first peer-reviewed evidence that induction of immune responses against spike protein using viral vectors provides protection against the disease in humans, as has been seen in animal models.

In participants who received two standard doses, efficacy against primary symptomatic COVID-19 was consistent in both the UK (60·3% efficacy) and Brazil (64·2% efficacy), indicating these results are generalisable across two diverse settings with different timings for the booster dose (with most participants in the UK receiving the booster dose more than 12 weeks after the first dose and most participants in Brazil receiving their second dose within 6 weeks of the first). Exploratory subgroup analyses included at the request of reviewers and editors also showed no significant difference in efficacy estimates when comparing those with a short time window between doses (<6 weeks) and those with longer (≥6 weeks), although further detailed exploration of the timing of doses might be warranted.

Efficacy of 90·0% seen in those who received a low dose as prime in the UK was intriguingly high compared with the other findings in the study. Although there is a possibility that chance might play a part in such divergent results, a similar contrast in efficacy between the LD/SD and SD/SD recipients with asymptomatic infections provides support for the observation (58·9% [95% CI 1·0 to 82·9] *vs* 3·8% [–72·4 to 46·3]). Exploratory subgroup analyses, included at the request of reviewers and editors, that were restricted to participants aged 18–55 years, or aligned (>8 weeks) intervals between doses, showed similar findings. Use of a low dose for priming could provide substantially more vaccine for distribution at a time of constrained supply, and these data imply that this would not compromise protection. While a vaccine that could prevent COVID-19 would have a substantial public health benefit, prevention of asymptomatic infection could reduce viral transmission and protect those with underlying health conditions who do not respond to vaccination, those who cannot be vaccinated for health reasons, and those who will not or cannot access a vaccine, providing wider benefit for society. However, the wide CIs around our estimates show that further data are needed to confirm these preliminary findings, which will be done in future analyses of the data accruing in these ongoing trials.

Similar results have been seen for other vaccines where a reduced number or type of priming dose in infancy can lead to higher responses to a booster vaccine.[10] Further work is needed to determine the mechanism of the increased efficacy with a LD/SD regimen, which might be due to higher levels of neutralising antibody, lower levels of anti-vector immunity with lower vector-derived antigen content of the first dose, or differential antibody functionality or cellular immunity, including altered avidity or immunodominance.

Other coronavirus vaccine developers have released preliminary high-level results in public statements, including more than 90% efficacy reported for the lipid nanoparticle mRNA vaccine BNT162b2,[11] 92% efficacy for the Sputnik V vaccine (developed at the National Research Centre for Epidemiology and Microbiology),[12] and 94·5% for the Moderna lipid nanoparticle mRNA-1273 vaccine.[13] The possibility that more than one efficacious vaccine against COVID-19 might be approved for use in the near future is encouraging. However, control of pandemic coronavirus will only be achieved if the licensure, manufacturing, and distribution of these vaccines can be achieved at an unprecedented scale and vaccination is rolled out to all those who are vulnerable.

The US Food and Drug Administration's guidelines indicate that they would license a vaccine against the pandemic virus that showed at least 50% efficacy[14] and WHO have indicated a minimum efficacy of 50% in its target product profile.[15] A modelling study found that a vaccine with efficacy of 60–80% could allow reduction in physical distancing measures, but this would still require high coverage.[16] The findings here indicate that the efficacy of ChAdOx1 nCoV-19 exceeds these thresholds and has the potential to have a public health impact.

Much consideration has been given to the statistical confidence in vaccine efficacy estimates, given the size of the global population who might be vaccinated. To ensure that point estimates of efficacy in clinical trials are sufficiently robust, some regulatory authorities consider that the lower bound of the CI for efficacy should be higher than 20% (personal communication), with other authorities more stringent and anticipating a lower bound of 30% for licensure.[14] Here, we present data that exceed both these thresholds in the pooled analysis, which we had agreed with regulators before unblinding of the study, and also meet the thresholds set in the individual analyses of trials by country and by study arm.

We designed our studies early in the pandemic and fixed our primary symptomatic disease endpoint on the basis of expert analysis and guidelines from Public Health England and WHO as the first wave of disease spread around the world, although these have now been substantially updated.[17,18] We have used a restricted definition of symptomatic disease, since many other symptoms that are associated with COVID-19 disease are non-specific. Since endpoints in protocols for different vaccines are not well aligned, we recognise that it will be difficult to compare efficacy across programmes. However, we have also included hospital admissions and severe disease as an endpoint in the current study, which might be easier to assess in comparison with other vaccines, and found that in the ten cases available for analysis more than 21 days after the first dose, there was complete protection against hospitalisation for COVID-19.

While the data presented here show that ChAdOx1 nCov-19 is efficacious against symptomatic disease, with most cases accruing in adults younger than 55 years of age so far, an important public health consideration is the morbidity and mortality of the disease in an older adult population and thus the potential efficacy in this age group. We have reported immunogenicity data showing similar immune responses following vaccination with two doses of ChAdOx1 nCov-19 in older adults, including those older than 70 years of age, when compared with those younger than 55 years.[6] As older age groups were recruited later than younger age groups, there has been less time for cases to accrue and as a result, efficacy data in these cohorts are currently limited by the small number of cases, but additional data will be available in future analyses.

These trials, conducted on three different continents, enrolled geographically and ethnically diverse populations. Severe COVID-19 has been seen to disproportionately affect people of non-white ethnicity, as well as those who are male, overweight, and the elderly.[19,20]

In our studies, the demographic characteristics of those enrolled varied between countries. In the UK, the enrolled population was predominantly white and, in younger age groups, included more female participants due to the focus on enrolment of health-care workers. This is a typically lower risk population for severe COVID-19. The demographic profile combined with the weekly self-swabbing for asymptomatic infection in the UK results in a milder case-severity profile. In Brazil, there was a larger proportion of non-white ethnicities, and again the majority of those enrolled were health-care workers.

We have previously reported on the local and systemic reactogenicity of ChAdOx1 nCoV-19 and shown that it is tolerated and that the side-effects are less both in intensity and number in older adults, with lower doses, and after the second dose. Although there were many serious adverse events reported in the study in view of the size and health status of the population included, there was no pattern of these events that provided a safety signal in the study. Three cases of transverse myelitis were initially reported as suspected unexpected serious adverse reactions, with two in the ChAdOx1 nCoV-19 vaccine study arm, triggering a study pause for careful review in each case. Independent clinical review of these cases has indicated that one in the experimental group and one in the control group are unlikely to be related to study interventions, but a relationship remained possible in the third case. Careful monitoring of safety, including neurological events, continues in the trials. All safety data will be provided to regulators for review.

In this interim analysis, we have not been able to assess duration of protection, since the first trials were initiated in April, 2020, such that all disease episodes have accrued within 6 months of the first dose being administered. Further evidence will be required to determine duration of protection and the need for additional booster doses of vaccine.

The results presented in this Article constitute the key findings from the first interim analysis, which are

provided for rapid review by the public and policy makers. In future analyses with additional data included as they accrue, we will investigate differences in key subgroups such as older cohorts, ethnicity, dose regimen, and timing of booster vaccines, and we will search for correlates of protection.

Until widespread immunity halts the spread of SARS-CoV-2, physical distancing measures and novel therapies are needed to control COVID-19. In the meantime, an efficacious vaccine has the potential to have a major impact on the pandemic if used in populations at risk of severe disease. Here, we have shown for the first time that a viral vector vaccine, ChAdOx1 nCoV-19, is efficacious and could contribute to control of the disease in this pandemic.

Contributors

AJP and SCG conceived the trial and AJP is the chief investigator. AJP, PMF, DJ, MV, and TL 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, PTH, HH, DMF, VL, AM, AI, AF, CB, GK, MET, AP, EPM, AVS, AVAM, CLC, ALG, AN, SDP, KMP, ES, RKS, RT, and DPJT are study site principal investigators. PKA, EP, DJ, PMF, SB, AMM, AML, KRWE, MNR, BA, PC, SK, KJE, AL, AF, SR, PJO, SHCH, SJ, HM, JV, IH, RM, YFM, NS, RS, MDS, MEEW, TLV, RC-J, and CH contributed to the implementation of the study or data collection. MV and SF did the statistical analysis. CMG, ADD, CCDJ and RT were responsible for vaccine manufacturing. MV and AJP contributed to the preparation of the report. All authors critically reviewed and approved the final version.

Declaration of interests

Oxford University has entered into a partnership with AstraZeneca for further development of ChAdOx1 nCoV-19. 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 (PCT/GB2012/000467). 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, during the conduct of the study. PMF is a consultant to Vaccitech during the conduct of the study. AJP is chair of the UK Department of 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 WHO's SAGE. AJP is a National Institute for Health Research (NIHR) Senior Investigator. The views expressed in this Article do not necessarily represent the views of the DHSC, JCVI, NIHR, or WHO. AVSH reports personal fees from Vaccitech, outside of the submitted work, and has a patent on ChAdOx1 licensed to Vaccitech (PCT/GB2012/000467), and might benefit from royalty income to the University of Oxford from sales of this vaccine by AstraZeneca and sublicensees. MS reports grants from NIHR and non-financial support from AstraZeneca, during the conduct of the study; and 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. AF is a member of the JCVI and chair of the WHO European Technical Advisory Group of Experts. AF declares research grants from Pfizer, GlaxoSmithKline, Sanofi, Merck Sharp & Dohme, and Valneva, outside of the submitted work. JV, TLV, and IH are employees of AstraZeneca. The other authors declare no competing interests.

Data sharing

Anonymised participant data will be made available when the trials are complete, upon requests directed to the corresponding author. Proposals will be reviewed and approved by the sponsor, investigator, and collaborators on the basis of scientific merit. After approval of a proposal, data can be shared through a secure online platform after signing a data access agreement. All data will be made available for a minimum of 5 years from the end of the trial.

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AstraZeneca and Oxford University announce landmark agreement for COVID-19 vaccine

PUBLISHED 30 April 2020

Collaboration will enable global development, manufacturing and distribution of the vaccine

AstraZeneca and the University of Oxford today announced an agreement for the global development and distribution of the University's potential recombinant adenovirus vaccine aimed at preventing COVID-19 infection from SARS-CoV-2.

The collaboration aims to bring to patients the potential vaccine known as ChAdOx1 nCoV-19, being developed by the Jenner Institute and Oxford Vaccine Group, at the University of Oxford. Under the agreement, AstraZeneca would be responsible for development and worldwide manufacturing and distribution of the vaccine.

Pascal Soriot, Chief Executive Officer, AstraZeneca, said: "As COVID-19 continues its grip on the world, the need for a vaccine to defeat the virus is urgent. This collaboration brings together the University of Oxford's world-class expertise in vaccinology and AstraZeneca's global development, manufacturing and distribution capabilities. Our hope is that, by joining forces, we can accelerate the globalisation of a vaccine to combat the virus and protect people from the deadliest pandemic in a generation."

Mene Pangalos, Executive Vice President, BioPharmaceuticals R&D, AstraZeneca, said: "The University of Oxford and AstraZeneca have a longstanding relationship to advance basic research and we are hugely excited to be working with them on advancing a vaccine to prevent COVID-19 around the world. We are looking forward to working with the University of Oxford and innovative companies such as Vaccitech, as part of our new partnership."

Alok Sharma, UK Business Secretary, said: "This collaboration between Oxford University and AstraZeneca is a vital step that could help rapidly advance the manufacture of a coronavirus vaccine. It will also ensure that, should the vaccine being developed by Oxford University's Jenner Institute work, it will be available as early as possible, helping to protect thousands of lives from this disease."

Professor Sir John Bell, Regius Professor of Medicine at Oxford University, said: "Our partnership with AstraZeneca will be a major force in the struggle against pandemics for many years to come. We believe that together we will be in a strong position to start immunising against coronavirus once we have an effective approved vaccine. Sadly, the risk of new pandemics will always be with us and the new research centre will enhance the world's preparedness and our speed of reaction the next time we face such a challenge."

Professor Louise Richardson, Vice-Chancellor of Oxford University, said: “Like my colleagues all across Oxford, I am deeply proud of the work of our extraordinarily talented team of academics in the Jenner Institute and the Oxford Vaccine Group. They represent the best tradition of research, teaching and contributing to the world around us, that has been the driving mission of the University of Oxford for centuries. Like people all across the country, we are wishing them success in developing an effective vaccine. If they are successful, our partnership with AstraZeneca will ensure that the British people and people across the world, especially in low and middle income countries, will be protected from this terrible virus as quickly as possible.”

The potential vaccine entered Phase I clinical trials last week to study safety and efficacy in healthy volunteers aged 18 to 55 years, across five trial centres in Southern England. Data from the Phase I trial could be available next month. Advancement to late-stage trials should take place by the middle of this year.

ChAdOx1 nCoV-19

Developed at the University of Oxford’s Jenner Institute, and working with the Oxford Vaccine Group, ChAdOx1 nCoV-19 uses a viral vector based on a weakened version of the common cold (adenovirus) containing the genetic material of SARS-CoV-2 spike protein. After vaccination, the surface spike protein is produced, which primes the immune system to attack COVID-19 if it later infects the body.

The recombinant adenovirus vector (ChAdOx1) was chosen to generate a strong immune response from a single dose and it is not replicating, so cannot cause an ongoing infection in the vaccinated individual. Vaccines made from the ChAdOx1 virus have been given to more than 320 people to date and have been shown to be safe and well tolerated, although they can cause temporary side effects such as a temperature, flu-like symptoms, headache or sore arm.

AstraZeneca

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Adrian Kemp
Company Secretary
AstraZeneca PLC

AstraZeneca advances response to global COVID-19 challenge as it receives first commitments for Oxford's potential new vaccine

PUBLISHED 21 May 2020

This announcement contains inside information

21 May 2020 07:00 BST

Company working on a number of agreements in parallel to ensure broad and equitable supply of the vaccine throughout the world at no profit during the pandemic

First agreements to supply at least 400 million doses; Company has total capacity sourced for one billion doses through 2020 and into 2021; continues to increase capacity further

More than $1bn US BARDA investment to support development and production of the vaccine

AstraZeneca is advancing its ongoing response to address the unprecedented challenges of COVID-19, collaborating with a number of countries and multilateral organisations to make the University of Oxford's vaccine widely accessible around the world in an equitable manner.

The Company has concluded the first agreements for at least 400 million doses and has secured total manufacturing capacity for one billion doses so far and will begin first deliveries in September 2020. AstraZeneca aims to conclude further agreements supported by several parallel supply chains, which will expand capacity further over the next months to ensure the delivery of a globally accessible vaccine.

AstraZeneca today received support of more than $1bn from the US Biomedical Advanced Research and Development Authority (BARDA) for the development, production and delivery of the vaccine, starting in the fall. The development programme includes a Phase III clinical trial with 30,000 participants and a paediatric trial.

In addition, the Company is engaging with international organisations such as the Coalition for Epidemic Preparedness Innovations (CEPI), Gavi the Vaccine Alliance and the World Health Organisation (WHO), for the fair allocation and distribution of the vaccine around the world. AstraZeneca is also in discussions with governments around the world to increase access. Furthermore, AstraZeneca is in discussions with the Serum Institute of India and other potential partners to increase production and distribution.

AstraZeneca recently joined forces with the UK Government to support Oxford University's vaccine and has progressed rapidly in its efforts to expand access around the world. The Company will supply the UK starting in September and is thankful for the Government's commitment and overall work on vaccines.

Pascal Soriot, Chief Executive Officer, said: "This pandemic is a global tragedy and it is a challenge for all of humanity. We need to defeat the virus together or it will continue to inflict huge personal suffering and leave long-lasting economic and social scars in every country around the world. We are so proud to be collaborating with Oxford University to turn their ground-breaking work into a medicine that can be produced on a global scale. We would like to thank the US and UK governments for their substantial support to accelerate the development and production of the vaccine. We will do everything in our power to make this vaccine quickly and widely available."

AstraZeneca has now finalised its licence agreement with Oxford University for the recombinant adenovirus vaccine. The licensing of the vaccine, formerly ChAdOx1 nCoV-19 and now known as AZD1222, follows the recent global development and distribution agreement with the University's Jenner Institute and the Oxford Vaccine Group. AstraZeneca has also agreed to support the establishment of a joint research centre at Oxford University for pandemic preparedness research.

A Phase I/II clinical trial of AZD1222 began last month to assess safety, immunogenicity and efficacy in over 1,000 healthy volunteers aged 18 to 55 years across several trial centres in southern England. Data from the trial is expected shortly which, if positive, would lead to late-stage trials in a number of countries. AstraZeneca recognises that the vaccine may not work but is committed to progressing the clinical program with speed and scaling up manufacturing at risk.

The Company's comprehensive pandemic response also includes rapid mobilisation of AstraZeneca's global research efforts to discover novel coronavirus-neutralising antibodies to prevent and treat progression of the COVID-19 disease, with the aim of reaching clinical trials in the next three to five months. Additionally, the Company has quickly moved into testing of new and existing medicines to treat the infection, including CALAVI and ACCORD trials underway for *Calquence* (acalabrutinib) and DARE-19 trial for *Farxiga* (dapagliflozin) in COVID-19 patients.

Financial considerations

Today's announcement is not anticipated to have any significant impact on the Company's financial guidance for 2020; expenses to progress the vaccine are anticipated to be offset by funding by governments.

AZD1222

ChAdOx1 nCoV-19, now known as AZD1222, was developed by Oxford University's Jenner Institute, working with the Oxford Vaccine Group. It uses a replication-deficient chimpanzee viral vector based on a weakened version of a common cold (adenovirus) virus that causes infections in chimpanzees and contains the genetic material of SARS-CoV-2 spike protein. After vaccination, the surface spike protein is produced, priming the immune system to attack COVID-19 if it later infects the body.

The recombinant adenovirus vector (ChAdOx1) was chosen to generate a strong immune response from a single dose and it is not replicating, so cannot cause an ongoing infection in the vaccinated individual. Vaccines made from the ChAdOx1 virus have been given to more than 320 people to date and have been shown to be safe and well tolerated, although they can cause temporary side effects such as a temperature, influenza-like symptoms, headache or a sore arm.

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Adrian Kemp
Company Secretary
AstraZeneca PLC

AstraZeneca takes next steps towards broad and equitable access to Oxford University's COVID-19 vaccine

PUBLISHED 4 June 2020

4 June 2020 16:00 BST

Agreements with CEPI and Gavi and the Serum Institute of India will bring vaccine to low and middle-income countries and beyond

Global supply capacity to exceed two billion doses

AstraZeneca has taken the next steps in its commitment to broad and equitable global access to the University of Oxford's COVID-19 vaccine, following landmark agreements with the Coalition for Epidemic Preparedness Innovations (CEPI), Gavi the Vaccine Alliance, and the Serum Institute of India (SII).

The Company today reached a $750m agreement with CEPI and Gavi to support the manufacturing, procurement and distribution of 300 million doses of the vaccine, with delivery starting by the end of the year. In addition, AstraZeneca reached a licensing agreement with SII to supply one billion doses for low and middle-income countries, with a commitment to provide 400 million before the end of 2020.

Together, the agreements mark the latest commitments to enable global access to the vaccine, including to low and middle-income countries, beyond AstraZeneca's recent partnerships with the UK and US. The Company is building a number of supply chains in parallel across the world to support global access at no profit during the pandemic and has so far secured manufacturing capacity for two billion doses of the vaccine.

The agreement with CEPI and Gavi also represents the first advanced market commitment through the Access to COVID-19 Tools (ACT) Accelerator, a global collaboration of philanthropic, multilateral, private sector and civil society partners. The mechanism will work to accelerate the development, production and equitable access to the new COVID-19 tools across the world including in low and middle-income nations. CEPI will lead vaccine development and manufacturing and Gavi will lead the procurement within the global mechanism.

Pascal Soriot, Chief Executive Officer, AstraZeneca, said: "We are working tirelessly to honour our commitment to ensure broad and equitable access to Oxford's vaccine across the globe and at no profit. Today marks an important step in helping us supply hundreds of millions of people around the world, including to those in countries with the lowest means. I am deeply grateful for everyone's commitment to this cause and for their work in bringing this together in such a short time."

Dr Richard Hatchett, Chief Executive Officer, CEPI, said: “AstraZeneca and our other industry partners have a critical role to play in rapidly developing safe and effective vaccines and manufacturing the billions of doses needed to put a permanent end to the COVID-19 pandemic. AstraZeneca is admirably committed to equitable global access for this vaccine, and this partnership demonstrates how the COVID-19 Vaccine Global Access Facility will bring the private, public and third sectors together to make COVID-19 vaccines available to those who need them most, for the benefit of all.”

Dr Seth Berkley, Chief Executive Officer, Gavi, said: “Today we have seen tremendous willingness from donor governments to support equitable access, particularly to developing countries – and it is incredibly heartening to see the private sector join in this effort. We encourage other vaccine manufacturers to work with us towards the shared global goal of finding solutions for this unprecedented pandemic.”

Adar Poonawalla, Chief Executive Officer, SII, said: “Serum Institute of India is delighted to partner with AstraZeneca in bringing this vaccine to India as well as low and middle-income countries. Over the past 50 years SII has built significant capability in vaccine manufacturing and supply globally. We will work closely with AstraZeneca to ensure fair and equitable distribution of the vaccine in these countries.”

AstraZeneca recently agreed to supply 400 million doses to the US and UK after reaching a licence agreement with Oxford University for its recombinant adenovirus vaccine, formerly ChAdOx1 nCoV-19 and now known as AZD1222.

Oxford University recently announced the start of a Phase II/III trial of AZD1222 in about 10,000 adult volunteers. Other late-stage trials are due to begin in a number of countries. AstraZeneca recognises that the vaccine may not work but is committed to progressing the clinical programme with speed and scaling up manufacturing at risk.

The Company’s comprehensive pandemic response also includes rapid mobilisation of AstraZeneca’s global research efforts to discover novel coronavirus-neutralising antibodies to prevent and treat progression of the COVID-19 disease, with the aim of reaching clinical trials in the next three to five months. Additionally, the Company has quickly moved into testing of new and existing medicines to treat the infection, including the CALAVI and ACCORD trials underway for *Calquence* (acalabrutinib) and the DARE-19 trial for *Farxiga* (dapagliflozin) in COVID-19 patients.

AZD1222

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tolerated, although they can cause temporary side effects such as a temperature, influenza-like symptoms, headache or a sore arm.

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COVID-19 vaccine AZD1222 showed robust immune responses in all participants in Phase I/II trial

PUBLISHED 20 July 2020

20 July 2020 14:40 BST

Interim data showed strong antibody and T-cell responses

Interim results from the ongoing Phase I/II COV001 trial, led by Oxford University, showed AZD1222 was tolerated and generated robust immune responses against the SARS-CoV-2 virus in all evaluated participants.

COV001 is a blinded, multi-centre, randomised controlled Phase I/II trial with 1,077 healthy adult participants, aged 18-55 years. It assessed a single dose of AZD1222 against a comparator meningococcal conjugate vaccine, MenACWY. Ten participants also received two doses of AZD1222 one month apart.

The results published in *The Lancet* confirmed a single dose of AZD1222 resulted in a four-fold increase in antibodies to the SARS-CoV-2 virus spike protein in 95% of participants one month after injection. In all participants, a T-cell response was induced, peaking by day 14, and maintained two months after injection.

Neutralising activity against SARS-CoV-2 (as assessed by the MNA80 assay) was seen in 91% of participants one month after vaccination and in 100% of participants who received a second dose. The levels of neutralising antibodies seen in participants receiving either one or two doses were in a similar range to those seen in convalescent COVID-19 patients. Strong correlations were observed across neutralisation assays.

The early safety responses confirmed that transient local and systemic reactions were common in the AZD1222 group and were comparable to previous trials and other adenoviral vector vaccines.[1-4] They included temporary injection site pain and tenderness, mild-to-moderate headache, fatigue, chills, feverishness, malaise and muscle ache. No serious adverse events were reported with AZD1222, and reactions were lessened with the use of prophylactic paracetamol, a pain killer, and occurred less frequently after a second dose.

Professor Andrew Pollard, Chief investigator of the Oxford Vaccine Trial at Oxford University and co-author of the trial, said: “The interim Phase I/II data for our coronavirus vaccine shows that the vaccine did not lead to any unexpected reactions and had a similar safety profile to previous vaccines of this type. The immune responses observed following vaccination are in line with what we expect will be associated with protection against the SARS-CoV-2 virus, although we must continue with our rigorous

clinical trial programme to confirm this. We saw the strongest immune response in participants who received two doses of the vaccine, indicating that this might be a good strategy for vaccination."

Mene Pangalos, Executive Vice President, BioPharmaceuticals R&D, said: "We are encouraged by the Phase I/II interim data showing AZD1222 was capable of generating a rapid antibody and T-cell response against SARS-CoV-2. While there is more work to be done, today's data increases our confidence that the vaccine will work and allows us to continue our plans to manufacture the vaccine at scale for broad and equitable access around the world."

Late-stage Phase II/III trials are currently underway in the UK, Brazil and South Africa and are due to start in the US. Trials will determine how well the vaccine will protect from the COVID-19 disease and measure safety and immune responses in different age ranges and at various doses.

In parallel, AstraZeneca continues to fulfil its commitment for broad and equitable access to the vaccine, should late-stage clinical trials prove successful. So far, commitments to supply more than two billion doses of the vaccine have been agreed with the UK, US, Europe's Inclusive Vaccines Alliance, the Coalition for Epidemic Preparedness, Gavi the Vaccine Alliance and Serum Institute of India.

Financial considerations

Today's announcement is not anticipated to impact the Company's financial guidance for 2020 as expenses to progress the vaccine are anticipated to be offset by funding by governments and international organisations.

Immune correlates of protection to COVID-19 disease[5]

Correlates of protection for a vaccine against COVID-19 have not yet been defined. High levels of neutralising antibodies have been demonstrated in individuals who have recovered from SARS-CoV-2 infection. In addition, emerging data suggest that a T-cell response could play an important role in mitigation of the disease. Some individuals who have been infected with the virus but remained asymptomatic, have developed a robust T-cell response with an absence of detectable antibodies. Rapid induction of antibodies and T-cells against the SARS-CoV-2 virus may be important in protection against COVID-19.

COV001

COV001 is a Phase I/II single-blinded randomised controlled trial to determine safety, immunogenicity and efficacy of the COVID-19 vaccine candidate AZD1222 in up to 1,077 healthy adults in five trial centres in the UK. Participants aged 18-55 years received either a single dose or two doses of AZD1222 at $5x10^{10}$ viral particles, or a single dose of a meningococcal conjugate vaccine MenACWY as control vaccine.

Participants had blood samples drawn and clinical assessments for safety as well as immunogenicity at day 0, 28 and will also be followed at day 184 and 364. In addition,

participants enrolled in the Phase I component of the study and in the two dose groups, had visits at 3, 7, 14 and 28 days after each vaccination.

AZD1222

AZD1222 was co-invented by the University of Oxford and its spin-out company, Vaccitech. It uses a replication-deficient chimpanzee viral vector based on a weakened version of a common cold virus (adenovirus) that causes infections in chimpanzees and contains the genetic material of the SARS-CoV-2 virus spike protein. After vaccination, the surface spike protein is produced, priming the immune system to attack the SARS-CoV-2 virus if it later infects the body.

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doi: https://doi.org/10.1101/2020.06.29.174888.

Adrian Kemp
Company Secretary
AstraZeneca PLC

AstraZeneca's scientific and social commitment for COVID-19 vaccine

PUBLISHED 31 August 2020

31 August 2020 21:30 BST

Company reiterates core values to "follow the science" and "put patients first"

AstraZeneca is today issuing a commitment to the highest safety standards and to broad and equitable access around the world for its COVID-19 vaccine AZD1222.

At the heart of AstraZeneca's core values is to "follow the science" and adhere to the highest scientific and clinical standards, making the safety and efficacy of the vaccine of paramount importance. The Company's submissions for market authorisation will meet the stringent requirements established by regulators everywhere around the world.

To this end, AstraZeneca is implementing a clinical development program that will enrol in excess of 50,000 volunteers, including 30,000 in the US, in Latin America, Asia, Europe, Russia and Africa that will provide data for ethnically diverse populations.

The Company also has a core value to "put patients first" and will continue to work with governments and other organisations towards broad and equitable global access to the vaccine, scaling up manufacturing with independent parallel supply chains around the world to produce billions of doses to a consistent and high standard of safety and efficacy.

Pascal Soriot, Chief Executive Officer, said: "In recent weeks we have seen an increasing number of questions around the safety and availability of vaccines to fight this terrible COVID-19 pandemic and I want to reiterate my commitment that we are putting science and the interest of society at the heart of our work. We are moving quickly but without cutting corners, and regulators have clear and stringent efficacy and safety standards for the approval of any new medicine, and that includes this potential COVD-19 vaccine. We will remain true to our values as we continue our efforts to bring this vaccine broadly and equitably to billions of people around world."

In July 2020, interim results from the ongoing Phase I/II COV001 trial were published in *The Lancet* and showed AZD1222 was tolerated and generated robust immune responses against the SARS-CoV-2 virus in all evaluated participants.

AstraZeneca continues to engage with governments, multilateral organisations and partners around the world to ensure broad and equitable access to the vaccine, should clinical trials prove successful. Recent supply announcements with Russia, South

Korea, Japan, China, Latin America and Brazil take the global supply capacity towards three billion doses of the vaccine.

AZD1222
AZD1222 was co-invented by the University of Oxford and its spin-out company, Vaccitech. It uses a replication-deficient chimpanzee viral vector based on a weakened version of a common cold virus (adenovirus) that causes infections in chimpanzees and contains the genetic material of the SARS-CoV-2 virus spike protein. After vaccination, the surface spike protein is produced, priming the immune system to attack the SARS-CoV-2 virus if it later infects the body.

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Development of COVID-19 vaccine AZD1222 expands into US Phase III clinical trial across all adult age groups

PUBLISHED 31 August 2020

31 August 2020 21:30 BST

Trial enrolling up to 30,000 adults aged 18 years or over to assess safety, efficacy and immunogenicity of AZD1222 for the prevention of COVID-19

AZD1222 supported by safety and immunogenicity across all adult age groups

AZD1222 development expanded into a Phase III clinical trial in the US to assess its safety, efficacy and immunogenicity.[1]

The US trial, called D8110C00001, is funded by the Biomedical Advanced Development Authority (BARDA), part of the office of the Assistant Secretary for Preparedness and Response (ASPR) at the U.S. Department of Health and Human Services (HHS) and the National Institute of Allergy and Infectious Diseases (NIAID), part of the U.S. National Institutes of Health, and led by AstraZeneca. The NIAID-supported COVID-19 Prevention Network (CoVPN) will participate in the trial.

Mene Pangalos, Executive Vice President, BioPharmaceuticals R&D, said: "We are pleased that AZD1222 demonstrated safety and immunogenicity across all adult age groups and are proud to be collaborating with BARDA and NIAID to accelerate the development of this vaccine. Should clinical trials demonstrate the vaccine protects against COVID-19 disease and is approved for use, we will work hard to make it globally available in a fair and equitable manner as rapidly as possible."

Trial centres across the US are recruiting up to 30,000 adults aged 18 years or over from diverse racial, ethnic and geographic groups who are healthy or have stable underlying medical conditions, including those living with HIV, and who are at increased risk of infection from the SARS-CoV-2 virus. Centres outside the US are included based on predicted transmission rates of the virus and sites in Peru and Chile are planned to initiate recruitment shortly.

Participants are being randomised to receive two doses of either AZD1222 or a saline control, four weeks apart, with twice as many participants receiving the potential vaccine than the saline control. The trial is assessing efficacy and safety of the vaccine in all participants, and local and systemic reactions and immune responses will be assessed in 3,000 participants.

Clinical development of AZD1222 is progressing globally with late-stage clinical trials ongoing in the UK, Brazil and South Africa and trials are planned to start in Japan and Russia. These trials, together with the US Phase III clinical trial will enrol up to 50,000 participants globally. Results from the late-stage trials are anticipated later this year, depending on the rate of infection within the clinical trial communities.

In July 2020, interim results from the ongoing Phase I/II COV001 trial were published in *The Lancet* and showed AZD1222 was tolerated and generated robust immune responses against the SARS-CoV-2 virus in all evaluated participants.

AstraZeneca continues to engage with governments, multilateral organisations and partners around the world to ensure broad and equitable access to the vaccine, should clinical trials prove successful. Recent supply announcements with Russia, South Korea, Japan, China, Latin America and Brazil take the global supply capacity towards three billion doses of the vaccine.

The Company today issued a commitment to the highest safety standards and to broad and equitable access, reiterating its core values to "follow the science" and "put patients first".

D8110C00001[1]

D8110C00001 is a Phase III randomised, double-blind, placebo-controlled multicentre study assessing the safety, efficacy, and immunogenicity of AZD1222 compared to placebo for the prevention of COVID-19, in up to 30,000 participants across approximately 100 trial centres in and outside the US. Trial participants aged 18 years or over who are healthy or have medically stable chronic diseases, and are at increased risk for being exposed to the SARS-CoV-2 virus and COVID-19 will be randomised in a 2:1 ratio to receive two intramuscular doses of either 5 $x10^{10}$ viral particles of AZD1222 or saline placebo four weeks apart, on day one and 29. Randomisation will be stratified by age (≥ 18 to < 65 years, and ≥ 65 years), with at least 25% of participants to be enrolled in the older age range. Individuals interested in participating in the Phase III D8110C00001 vaccine trial can visit https://www.c19vaccinestudy.com or www.CoVPN.org websites for more information.

AZD1222
AZD1222 was co-invented by the University of Oxford and its spin-out company, Vaccitech. It uses a replication-deficient chimpanzee viral vector based on a weakened version of a common cold virus (adenovirus) that causes infections in chimpanzees and contains the genetic material of the SARS-CoV-2 virus spike protein. After vaccination, the surface spike protein is produced, priming the immune system to attack the SARS-CoV-2 virus if it later infects the body.

In May 2020, AstraZeneca received support of more than $1bn from BARDA for the development, production and delivery of the vaccine. The Phase III D8110C00001 trial is part of this funding agreement.

BARDA, ASPR, HSS
HHS works to enhance and protect the health and well-being of all Americans, providing

for effective health and human services and fostering advances in medicine, public health, and social services. The mission of ASPR is to save lives and protect Americans from 21st century health security threats. Within ASPR, BARDA invests in the innovation, advanced research and development, acquisition, and manufacturing of medical countermeasures – vaccines, drugs, therapeutics, diagnostic tools, and non-pharmaceutical products needed to combat health security threats. To learn more about federal support for the nationwide COVID-19 response, visit coronavirus.gov.

NIAID and the CoVPN
The CoVPN was formed by the NIAID at the US National Institutes of Health to respond to the global pandemic. Through the CoVPN, NIAID is leveraging the infectious disease and community engagement expertise of its existing research networks and global partners to address the pressing need for vaccines and antibodies against the SARS-CoV-2 virus. CoVPN will work to develop and conduct studies to ensure rapid and thorough evaluation of vaccines and antibodies for the prevention of COVID-19.

AstraZeneca
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Contacts

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Statement on AstraZeneca Oxford SARS-CoV-2 vaccine, AZD1222, COVID-19 vaccine trials temporary pause

PUBLISHED 9 September 2020

09 September 2020 14.15 BST

As part of the ongoing randomised, controlled clinical trials of the AstraZeneca Oxford coronavirus vaccine, AZD1222, a standard review process has been triggered, leading to the voluntary pause of vaccination across all trials to allow an independent committee to review the safety data of a single event of an unexplained illness that occurred in the UK Phase III trial.

This is a routine action which has to happen whenever there is a potentially unexplained illness in one of the trials, while it is investigated, ensuring we maintain the integrity of the trials.

In large clinical trials, illnesses will happen by chance and must be independently reviewed. AstraZeneca is working to expedite the review of the single event to minimise any potential impact on the trial timeline. We are committed to the safety of our participants and the highest standards of conduct in our trials.

Pascal Soriot, Chief Executive Officer, said: “At AstraZeneca we put science, safety and the interests of society at the heart of our work. This temporary pause is living proof that we follow those principles while a single event at one of our trial sites is assessed by a committee of independent experts. We will be guided by this committee as to when the trials could restart, so that we can continue our work at the earliest opportunity to provide this vaccine broadly, equitably and at no profit during this pandemic.”

AZD1222

AZD1222 was co-invented by the University of Oxford and its spin-out company, Vaccitech. It uses a replication-deficient chimpanzee viral vector based on a weakened version of a common cold virus (adenovirus) that causes infections in chimpanzees and contains the genetic material of the SARS-CoV-2 virus spike protein. After vaccination, the surface spike protein is produced, priming the immune system to attack the SARS-CoV-2 virus if it later infects the body.

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medicines are used by millions of patients worldwide. Please visit astrazeneca.com and follow the Company on Twitter @AstraZeneca.

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COVID-19 vaccine AZD1222 clinical trials resumed in the UK

PUBLISHED 12 September 2020

12 September 2020 14:20 BST

Clinical trials for the AstraZeneca Oxford coronavirus vaccine, AZD1222, have resumed in the UK following confirmation by the Medicines Health Regulatory Authority (MHRA) that it was safe to do so.

On 6 September, the standard review process triggered a voluntary pause to vaccination across all global trials to allow review of safety data by independent committees, and international regulators. The UK committee has concluded its investigations and recommended to the MHRA that trials in the UK are safe to resume.

AstraZeneca and the University of Oxford, as the trial sponsor, cannot disclose further medical information. All trial investigators and participants will be updated with the relevant information and this will be disclosed on global clinical registries, according to the clinical trial and regulatory standards.

AstraZeneca is committed to the safety of trial participants and the highest standards of conduct in clinical trials. The Company will continue to work with health authorities across the world and be guided as to when other clinical trials can resume to provide the vaccine broadly, equitably and at no profit during this pandemic.

AZD1222
AZD1222 was co-invented by the University of Oxford and its spin-out company, Vaccitech. It uses a replication-deficient chimpanzee viral vector based on a weakened version of a common cold virus (adenovirus) that causes infections in chimpanzees and contains the genetic material of the SARS-CoV-2 virus spike protein. After vaccination, the surface spike protein is produced, priming the immune system to attack the SARS-CoV-2 virus if it later infects the body.

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COVID-19 vaccine AZD1222 clinical trial resumed in Japan, follows restart of trials in the UK, Brazil, South Africa and India

PUBLISHED 2 October 2020

2 October 2020 08:30 BST

The Phase I/II clinical trial for the COVID-19 vaccine AZD1222 has resumed in Japan after discussion with the Japanese Pharmaceuticals and Medical Devices Agency (PMDA).

A standard review process triggered a voluntary pause to vaccination across all global trials on 6 September to allow review of safety data by an independent committee. Their recommendations have been supported by international regulators in the UK, Brazil, South Africa, India and now in Japan, who have deemed that the trials are safe to resume.

AstraZeneca continues to work with the Food and Drug Administration (FDA) to facilitate review of the information needed to make a decision regarding resumption of the US trial. The safety of trial participants is of paramount importance and we are committed to upholding the highest standards of conduct in clinical trials.

AZD1222
AZD1222 was co-invented by the University of Oxford and its spin-out company, Vaccitech. It uses a replication-deficient chimpanzee viral vector based on a weakened version of a common cold virus (adenovirus) that causes infections in chimpanzees and contains the genetic material of the SARS-CoV-2 virus spike protein. After vaccination, the surface spike protein is produced, priming the immune system to attack the SARS-CoV-2 virus if it later infects the body.

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FDA authorises restart of the COVID-19 AZD1222 vaccine US Phase III trial

PUBLISHED 23 October 2020

23 October 2020 20:30 BST

AZD1222 clinical trials now resumed globally

Clinical trials for the AstraZeneca Oxford coronavirus vaccine, AZD1222, have resumed across the world with regulators in the US, UK, Brazil, South Africa and Japan confirming that it was safe to do so.

The Food and Drug Administration (FDA) today authorised the restart in the US, following the resumption of trials in other countries in recent weeks. The FDA reviewed all safety data from trials globally and concluded it was safe to resume the trial.

As part of the standard review process for trial safety events, a voluntary pause to vaccination across all global trials was triggered on 6 September to allow the examination of safety data by independent monitoring committees. The recommendations from these reviews have been supported by international regulators, who also confirmed that the trials were safe to resume.

Pascal Soriot, Chief Executive Officer, said: “The restart of clinical trials across the world is great news as it allows us to continue our efforts to develop this vaccine to help defeat this terrible pandemic. We should be reassured by the care taken by independent regulators to protect the public and ensure the vaccine is safe before it is approved for use.”

It is not unusual that in large scale vaccine trials, some participants will become unwell, and every case has to be evaluated to ensure the careful assessment of safety.

Results from the late-stage trials are anticipated later this year, depending on the rate of infection within the communities where the clinical trials are being conducted. Data readouts will be submitted to regulators and published in peer-reviewed scientific journals. Rolling reviews of the vaccine programme have already begun in countries where this regulatory pathway has been established, providing regulators access to data as soon as they become available.

While trials are ongoing, AstraZeneca and Oxford University will continue to provide information to regulators, study investigators and participants according to clinical trial and regulatory standards.[1-5]

AZD1222
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Vaccitech. It uses a replication-deficient chimpanzee viral vector based on a weakened version of a common cold virus (adenovirus) that causes infections in chimpanzees and contains the genetic material of the SARS-CoV-2 virus spike protein. After vaccination, the surface spike protein is produced, priming the immune system to attack the SARS-CoV-2 virus if it later infects the body.

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AZD1222 vaccine met primary efficacy endpoint in preventing COVID-19

PUBLISHED 23 November 2020

This announcement contains inside information

23 November 2020 07:00 GMT

Two different dosing regimens demonstrated efficacy with one showing a better profile

No hospitalisations or severe cases of COVID-19 in participants treated with AZD1222

Positive high-level results from an interim analysis of clinical trials of AZD1222 in the UK and Brazil showed the vaccine was highly effective in preventing COVID-19, the primary endpoint, and no hospitalisations or severe cases of the disease were reported in participants receiving the vaccine. There were a total of 131 COVID-19 cases in the interim analysis.

One dosing regimen (n=2,741) showed vaccine efficacy of 90% when AZD1222 was given as a half dose, followed by a full dose at least one month apart, and another dosing regimen (n=8,895) showed 62% efficacy when given as two full doses at least one month apart. The combined analysis from both dosing regimens (n=11,636) resulted in an average efficacy of 70%. All results were statistically significant ($p<=0.0001$). More data will continue to accumulate and additional analysis will be conducted, refining the efficacy reading and establishing the duration of protection.

An independent Data Safety Monitoring Board determined that the analysis met its primary endpoint showing protection from COVID-19 occurring 14 days or more after receiving two doses of the vaccine. No serious safety events related to the vaccine have been confirmed. AZD1222 was well tolerated across both dosing regimens.

AstraZeneca will now immediately prepare regulatory submission of the data to authorities around the world that have a framework in place for conditional or early approval. The Company will seek an Emergency Use Listing from the World Health Organization for an accelerated pathway to vaccine availability in low-income countries. In parallel, the full analysis of the interim results is being submitted for publication in a peer-reviewed journal.

Professor Andrew Pollard, Chief Investigator of the Oxford Vaccine Trial at Oxford, said:
“These findings show that we have an effective vaccine that will save many live

s. Excitingly, we've found that one of our dosing regimens may be around 90% effective and if this dosing regime is used, more people could be vaccinated with planned vaccine supply. Today's announcement is only possible
thanks to the many volunteers in our trial, and the hard working and talented tea m of researchers based around the world."

Pascal Soriot, Chief Executive Officer, said: "Today marks an important milestone in our fight against the pandemic. This vaccine's efficacy and safety confirm that it will be highly effective against COVID-19 and will have an immediate impact on this public health emergency. Furthermore, the vaccine's simple supply chain and our no-profit pledge and commitment to broad, equitable and timely access means it will be affordable and globally available, supplying hundreds of millions of doses on approval."

The pooled analysis included data from the COV002 Phase II/III trial in the UK and COV003 Phase III trial in Brazil. Over 23,000 participants are being assessed following two doses of either a half-dose/full-dose regimen or a regimen of two full doses of AZD1222 or a comparator, meningococcal conjugate vaccine called MenACWY or saline. The global trials are evaluating participants aged 18 years or over from diverse racial and geographic groups who are healthy or have stable underlying medical conditions.

Clinical trials are also being conducted in the US, Japan, Russia, South Africa, Kenya and Latin America with planned trials in other European and Asian countries. In total, the Company expects to enrol up to 60,000 participants globally.

The Company is making rapid progress in manufacturing with a capacity of up to 3 billion doses of the vaccine in 2021 on a rolling basis, pending regulatory approval. The vaccine can be stored, transported and handled at normal refrigerated conditions (2-8 degrees Celsius/ 36-46 degrees Fahrenheit) for at least six months and administered within existing healthcare settings.

AstraZeneca continues to engage with governments, multilateral organisations and collaborators around the world to ensure broad and equitable access to the vaccine at no profit for the duration of the pandemic.

COV002

COV002 is a single-blinded, multi-centre, randomised, controlled Phase II/III trial assessing the safety, efficacy and immunogenicity of AZD1222 in 12,390 participants in the UK. Trial participants to date are aged 18 years or over, who are healthy or have medically stable chronic diseases and are at increased risk for being exposed to the SARS-CoV-2 virus. Participants receive one or two intramuscular doses of a half dose (~2.5 $x10^{10}$ viral particles) or full dose (~$5x10^{10}$ viral particles) of AZD1222 or comparator, meningococcal vaccine MenACWY. Participants have blood samples drawn and clinical assessments for safety as well as immunogenicity at multiple timepoints up to one year post-vaccination. Suspected cases presenting with compatible symptoms were tested for virological confirmation by COVID-19 PCR. In addition, weekly swabbing are done for detection of infection and assessment of vaccine efficacy against infection.

COV003

COV003 is a single-blinded, multi-centre, randomised, controlled Phase III trial assessing the safety, efficacy, and immunogenicity of AZD1222 in 10,300 participants in Brazil. Trial participants to date are aged 18 years or over, who are healthy or have medically stable chronic diseases and are at increased risk for being exposed to the SARS-CoV-2 virus. Participants are randomised to receive two intramuscular doses of a full dose (~$5x10^{10}$ viral particles) of AZD1222 or comparator, meningococcal vaccine MenACWY as first dose and a saline placebo as second dose. Participants have blood samples drawn and clinical assessments for safety as well as immunogenicity at multiple timepoints up to one year post-vaccination. Suspected cases presenting with compatible symptoms were tested for virological confirmation by COVID-19 PCR.

AZD1222

AZD1222 was co-invented by the University of Oxford and its spin-out company, Vaccitech. It uses a replication-deficient chimpanzee viral vector based on a weakened version of a common cold virus (adenovirus) that causes infections in chimpanzees and contains the genetic material of the SARS-CoV-2 virus spike protein. After vaccination, the surface spike protein is produced, priming the immune system to attack the SARS-CoV-2 virus if it later infects the body.

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Adrian Kemp
Company Secretary
AstraZeneca PLC

Veeva ID: Z4-29105
Date of Preparation: November 2020

AZD1222 Oxford Phase III trials interim analysis results published in The Lancet

PUBLISHED 8 December 2020

8 December 2020 16:00 GMT

Interim analysis showed vaccine is effective at preventing COVID-19, with no severe cases and no hospitalisations more than 21 days after first injection

Regulatory submissions underway to support approval

Results of an interim analysis of the Phase III programme conducted by Oxford University with AZD1222, peer-reviewed and published in *The Lancet* today, demonstrated that the vaccine is safe and effective at preventing symptomatic COVID-19 and that it protects against severe disease and hospitalisation. The interim analysis for efficacy was based on 11,636 participants accruing 131 symptomatic infections from the Phase III UK and Brazil trials conducted by Oxford University.

As announced on 23 November 2020, the primary efficacy endpoint of the programme statistical plan, based on the pooling of two dosing regimens, showed that the vaccine is 70.4% (95.8% CI: 54.8% to 80.6%) effective at preventing symptomatic COVID-19 occurring more than 14 days after receiving two doses of the vaccine. A secondary efficacy endpoint of prevention of severe disease demonstrated no cases of severe infections or hospitalisations in the vaccine group.

A further analysis of the efficacy regimens showed that when the vaccine was given as two full doses, vaccine efficacy was 62.1% (n=8,895; CI 41.0% to 75.7%), and 90.0% (n=2,741; CI 67.4% to 97.0%) in participants who received a half dose followed by a full dose.

Vaccine efficacy was also assessed on the secondary endpoint of early prevention of severe disease after the first dose. There were no hospitalisations or severe cases of COVID-19 more than 21 days after the first dose of the vaccine. Ten participants in the control group were hospitalised due to COVID-19, among whom two were assessed as severe, including one fatal case.

More data will continue to accumulate as part of the upcoming primary analysis and further follow-up, refining the efficacy reading and characterising vaccine efficacy over a longer period of time.

The safety data published so far is from over 20,000 participants enrolled across four clinical trials in the UK (COV001 and COV002), Brazil (COV003) and, in addition,

from South Africa (COV005). *The Lancet* publication confirmed that AZD1222 was well tolerated and that there were no serious safety events confirmed related to the vaccine. The participants were from diverse racial and geographic groups who are healthy or have stable underlying medical conditions. This analysis provides safety data on 74,341 person-months of follow-up after first dose (median 3.4 months) and 29,060 person-months of follow-up after two doses (median 2.0). The overall reported rates of serious adverse events were 0.7% in the vaccine group and 0.8% in the control group.

Professor Andrew Pollard, Director of the Oxford Vaccine Group and Chief Investigator of the Oxford Vaccine Trial, said: "Today, we have published the interim analysis of the Phase III trial and show that this new vaccine has a good safety record and efficacy against the coronavirus. We are hugely grateful to our trial volunteers for working with us over the past eight months to bring us to this milestone."

Pascal Soriot, Chief Executive Officer, said: "Today's peer-reviewed publication enables a full disclosure of the Oxford programme interim analysis. The results show that the vaccine is effective against COVID-19, with in particular no severe infections and no hospitalisations in the vaccine group, as well as safe and well tolerated. We have begun submitting data to regulatory authorities around the world for early approval and our global supply chains are up and running, ready to quickly begin delivering hundreds of millions of doses on a global scale at no profit."

Submission of the data to regulatory authorities around the world has already begun, as part of their ongoing rolling reviews of the vaccine data for temporary use or conditional approval during this health crisis. The Company is also seeking Emergency Use Listing from the World Health Organization for an accelerated pathway to vaccine availability in low-income countries.

In addition to the Oxford led programme, AstraZeneca is conducting a large study in the US and globally. In total, Oxford University and AstraZeneca expect to enrol more than 60,000 participants globally.

The Company is also making rapid progress in manufacturing with a capacity of up to 3 billion doses of the vaccine in 2021 on a rolling basis, pending regulatory approval. The vaccine can be stored, transported and handled at normal refrigerated conditions (2-8 degrees Celsius/ 36-46 degrees Fahrenheit) for at least six months and administered within existing healthcare settings.

AstraZeneca continues to engage with governments, multilateral organisations and collaborators around the world to ensure broad and equitable access to the vaccine at no profit for the duration of the pandemic.

COV001

COV001 is a blinded, multi-centre, randomised, controlled Phase I/II trial assessing safety, immunogenicity and efficacy of AZD1222 in 1,077 healthy adults in five trial centres in the UK. Participants aged 18-55 years are randomised to receive one or two intramuscular doses of AZD1222 at $5x10^{10}$ viral particles or comparator, meningococcal vaccine MenACWY. Participants have blood samples drawn and clinical assessments for safety as well as immunogenicity at multiple timepoints up to one year post-vaccination.

Weekly COVID-19 PCR testing is performed with retest at 3-5 days post-symptoms onset if the first sample is negative and 7 days after a positive PCR test.

COV002

COV002 is a single-blinded, multi-centre, randomised, controlled Phase II/III trial assessing the safety, efficacy and immunogenicity of AZD1222 in 12,390 participants in the UK. Trial participants to date are aged 18 years or over, who are healthy or have medically stable chronic diseases and are at increased risk for being exposed to the SARS-CoV-2 virus. Participants receive one or two intramuscular doses of a half dose (~2.5 $x10^{10}$ viral particles) or full dose (~$5x10^{10}$ viral particles) of AZD1222 or comparator, meningococcal vaccine MenACWY. Participants have blood samples drawn and clinical assessments for safety as well as immunogenicity at multiple timepoints up to one year post-vaccination. Suspected cases presenting with compatible symptoms were tested for virological confirmation by COVID-19 PCR. In addition, weekly swabbing are done for detection of infection and assessment of vaccine efficacy against infection.

COV003

COV003 is a single-blinded, multi-centre, randomised, controlled Phase III trial assessing the safety, efficacy, and immunogenicity of AZD1222 in 10,300 participants in Brazil. Trial participants to date are aged 18 years or over, who are healthy or have medically stable chronic diseases and are at increased risk for being exposed to the SARS-CoV-2 virus. Participants are randomised to receive two intramuscular doses of a full dose (~$5x10^{10}$ viral particles) of AZD1222 or comparator, meningococcal vaccine MenACWY as first dose and a saline placebo as second dose. Participants have blood samples drawn and clinical assessments for safety as well as immunogenicity at multiple timepoints up to one year post-vaccination. Suspected cases presenting with compatible symptoms were tested for virological confirmation by COVID-19 PCR.

COV005

COV005 is a blinded, multi-centre, randomised, controlled Phase I/II trial assessing the safety, efficacy, and immunogenicity of AZD1222 in 2,070 participants in South Africa. Trial participants are aged 18-65 years, who are living with or without HIV, are randomised to receive two intramuscular doses of AZD1222 at 5-7.5 $x10^{10}$ viral particles or saline placebo. Participants had blood samples drawn and clinical assessments for safety as well as immunogenicity at multiple timepoints up to one year post-vaccination. Regular COVID-19 PCR testing is performed up to one year post-vaccination.

AZD1222

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