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23 November 2020

**Evidence: Covid-19 vaccines – safety data**

**23 November 2020**

### You asked

The Trust’s Clinical Reference Group Vaccination Cell to be kept informed of any published safety data for the new covid vaccines. Weekly meetings.

### Published research

**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**

Author(s): Ramasamy MN; et al. IN: Lancet; Nov 2020

* **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.
* 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 × 10¹⁰ 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 × 10¹⁰ 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) icroneutralisation assay (MNA80). 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 (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 MNA80 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).

*Additional commentary around the above publication:*

Comment, The Lancet - Age and frailty in COVID-19 vaccine development

Author(s): Andrew, MK et al. The Lancet, Published online 19 Nov 2020

BMJ News - Covid-19: Moderna vaccine is nearly 95% effective, trial involving high risk and elderly people shows

Author(s): Mahase, E. BMJ 2020;371:m4471 17 Nov 2020

**SARS-CoV-2 immunity: review and applications to phase 3 vaccine candidates**

Author(s): Poland, GA. et al. IN: The Lancet, October 13, 2020 [Online First]

<https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32137-1/fulltext#%20>

*Vaccines against SARS-CoV-2*

* The front runner candidates are all administered by the intramuscular route; therefore, focus is on evaluating immune responses in the blood rather than those in the mucosal surfaces.
* The role of mucosal immunity should not be discounted, and several intranasal vaccine formulations are under investigation.

*Conclusions*

* Multiple vaccine types will probably be needed across different populations (eg, immune-immature infants, children, pregnant women, immunocompromised individuals, and immunosenescent individuals aged ≥65 years).
* In addition to the adaptive immune response, there are some data suggesting that trained innate immunity might also have a role in protection against COVID-19.
* It is crucial that research focuses on understanding the genetic drivers of infection and vaccine-induced humoral and cellular immunity to SARS-CoV-2, defining detailed targets of humoral and cellular immune responses at the epitope level, characterising the B-cell receptor and T-cell receptor repertoire elicited by infection or vaccination, and establishing the long-term durability, and maintenance, of protective immunity after infection or vaccination.
* A safe regulatory pathway leading to licensing must also be defined for use of these vaccines in children, pregnant women, immunocompromised people, and nursing home residents.
* Some have called for further shortening of the vaccine development process through the use of controlled human challenge models. As of Oct 5, 2020, no such studies have occurred, but the UK is considering initiating such trials in early 2021.

**Progress and Pitfalls in the Quest for Effective SARS-CoV-2 (COVID-19) Vaccines**

Author(s): Flanagan, KL et al. IN: Frontiers in Immunology 2020; 11: 579250

Full-text: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7566192/>

*Potential for Modest Vaccine Protection:*

* It is extremely unlikely that any of the SARS-CoV-2 vaccines will be 100% effective; while they may not prevent becoming infected, it is hoped that they will prevent progression to severe disease.
* Indeed, the seasonal influenza vaccine is generally about 50% protective against infection but does decrease disease severity and hospitalization rates.
* A recent study in which macaques were vaccinated with the Oxford University and AstraZeneca adenovirus vaccine, ChAdOx1 nCoV-19, found that the primates were protected from SARS-CoV-2-induced pneumonia. However, the macaques still had high levels of virus replicating in their upper respiratory tract.
* It is hoped that even if the vaccines do not prevent infection in the upper airways, they may reduce viral load and disease severity and in turn, the amount of virus a vaccinated person transmits to others.
* Most vaccines are tested in healthy young adult males and non-pregnant women and, if safe, they are then tested in healthy children prior to licensure. This therefore raises the issue that any vaccines may initially have less empiric data available on use in certain key vulnerable populations such as the elderly, immunocompromised groups and pregnant women.
* It is plausible that vaccines may be considerably less immunogenic in older and frail elderly who experience the most severe outcomes from COVID-19, hence the importance of adjuvants in many of the vaccine candidates, both for dose sparing and enhancing immunogenicity. Efficacy in this population is also likely to vary by the type of vaccine construct and adjuvant used

### WHO World Health Organization

Diagnostics, therapeutics, vaccine readiness, and other health products for COVID-19

Interim guidance (20 November 2020) <https://www.who.int/publications/i/item/WHO-2019-nCoV-HCF_assessment-Products-2020.1>

* This tool was developed to assess present and surge capacities for the treatment of COVID-19 in health facilities.
* The tool encompasses key components that are essential to managing COVID-19 in a hospital setting, including: COVID-19 vaccine readiness.

Guidance on developing a national deployment and vaccination Planning for COVID-19 vaccines

(16 November 2020) <https://www.who.int/publications/i/item/WHO-2019-nCoV-Vaccine_deployment-2020.1>

DRAFT landscape of COVID-19 candidate vaccines (12 pages)

WHO, R&D Blue Print 12 Nov 2020 <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>

### House of Lords Library

Covid-19 vaccine: Winter update 10 Nov 2020 <https://lordslibrary.parliament.uk/covid-19-vaccine-winter-update/>

### BBC

BBC Explainers, 19 Nov 2020 <https://www.bbc.co.uk/news/world-asia-china-51176409>

May be helpful for structuring Q&As

### Pfizer and BioNTech vaccine

**Friday 20 November 2020**

PFIZER AND BIONTECH TO SUBMIT EMERGENCY USE AUTHORIZATION REQUEST TODAY TO THE U.S. FDA FOR COVID-19 VACCINE

<https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-submit-emergency-use-authorization>

Pfizer and BioNTech announced that they have submitted a request to the U.S. Food and Drug Administration (FDA) for an Emergency Use Authorization (EUA) of their COVID-19 vaccine candidate. **If authorized by the FDA, then the investigational vaccine could be used in high-risk populations in the U.S. by the end of December 2020.**

Now that we have filed for an EUA, the FDA’s scientists will review the data on our COVID-19 vaccine candidate collected to date. Per the guidance from the FDA, this evidence also will be reviewed by an external panel of independent experts, known as the Vaccines and Related Biological Products Advisory Committee (VRBPAC). There will be a public meeting where Pfizer and BioNTech will present to the VRBPAC the safety and efficacy data that were submitted to the FDA and answer questions from the Committee members. We expect this meeting will be scheduled for December.

*What data will Pfizer and BioNTech present to VRBPAC?*

We are presenting all the data included in our EUA submission.

This includes efficacy data from the total 170 confirmed cases of COVID-19 accrued in our Phase 3 trial, and safety data from a randomized subset of at least 8,000 participants 18 years and older.

We also have data on approximately 19,000 trial participants who have been followed for a median of two months following the second and final dose of the vaccine candidate as well as data on our manufacturing processes.

*What is VRBPAC’s role in approving the EUA?*

As with any FDA advisory committee, the VRBPAC will provide a recommendation to the FDA on whether or not to authorize the vaccine candidate for emergency use. The FDA takes the VRBPAC’s recommendation into consideration, though the FDA makes the final decision.

*What happens if VRBPAC does not recommend that the FDA authorize the COVID-19 vaccine for emergency use? Does that mean the FDA won’t approve it?*

Ultimately the FDA makes the decision whether or not to approve or authorize any medical therapy, including an investigational vaccine against COVID-19. No matter the outcome of this meeting, we will continue working closely with the FDA as part of our ongoing commitment to making a potential vaccine available quickly and safely.

In addition to today’s submission to the FDA, the companies have already initiated rolling submissions across the globe including in Australia, Canada, Europe, Japan and the UK, and plan to submit applications immediately to other regulatory agencies around the world

The submission is based on a vaccine efficacy rate of 95% (p<0.0001) demonstrated in the companies’ Phase 3 clinical study in participants without prior SARS-CoV-2 infection (first primary objective) and also in participants with and without prior SARS-CoV-2 infection (second primary objective), in each case measured from 7 days after the second dose.

The first primary objective analysis was based on 170 confirmed cases of COVID-19. This submission also is supported by solicited safety data from a randomized subset of approximately 8,000 participants ≥18 years of age and unsolicited safety data from approximately 38,000 trial participants who have been followed for a median of two months following the second dose of the vaccine candidate.

The submission also includes solicited safety data on approximately 100 children 12-15 years of age. Approximately 42% of global participants and 30% of U.S. participants in the Phase 3 study have racially and ethnically diverse backgrounds, and 41% of global and 45% of U.S. participants are 56-85 years of age. To date, the Data Monitoring Committee (DMC) for the study has not reported any serious safety concerns related to the vaccine.

The companies have already initiated rolling submissions with several regulatory agencies around the world, including the EMA and the Medicines & Healthcare Products Regulatory Agency (MHRA) in the UK, and intend to submit applications to other regulatory agencies worldwide in the coming days. In some cases, governments may have regulatory pathways similar to an EUA. The companies will be ready to distribute the vaccine candidate within hours after authorization.

**Wednesday 18 November 2020**

*See:*

PFIZER AND BIONTECH CONCLUDE PHASE 3 STUDY OF COVID-19 VACCINE CANDIDATE, MEETING ALL PRIMARY EFFICACY ENDPOINTS

<https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-conclude-phase-3-study-covid-19-vaccine>

Key points:

* Primary efficacy analysis demonstrates BNT162b2 to be 95% effective against COVID-19 beginning 28 days after the first dose; 170 confirmed cases of COVID-19 were evaluated, with 162 observed in the placebo group versus 8 in the vaccine group.
* Efficacy was consistent across age, gender, race and ethnicity demographics; observed efficacy in adults over 65 years of age was over 94%.
* Safety data milestone required by U.S. Food and Drug Administration (FDA) for Emergency Use Authorization (EUA) has been achieved.
* Data demonstrate vaccine was well tolerated across all populations with over 43,000 participants enrolled; no serious safety concerns observed; the only Grade 3 adverse event greater than 2% in frequency was fatigue at 3.8% and headache at 2.0%.
* Companies plan to submit within days to the FDA for EUA and share data with other regulatory agencies around the globe.
* The companies expect to produce globally up to 50 million vaccine doses in 2020 and up to 1.3 billion doses by the end of 2021.

*More detail:*

Analysis of the data indicates a vaccine efficacy rate of 95% (p<0.0001) in participants without prior SARS-CoV-2 infection (first primary objective) and also in participants with and without prior SARS-CoV-2 infection (second primary objective), in each case measured from 7 days after the second dose.

The first primary objective analysis is based on 170 cases of COVID-19, as specified in the study protocol, of which 162 cases of COVID-19 were observed in the placebo group versus 8 cases in the BNT162b2 group. Efficacy was consistent across age, gender, race and ethnicity demographics. The observed efficacy in adults over 65 years of age was over 94%.

There were 10 severe cases of COVID-19 observed in the trial, with nine of the cases occurring in the placebo group and one in the BNT162b2 vaccinated group.

To date, the Data Monitoring Committee for the study has not reported any serious safety concerns related to the vaccine.

A review of unblinded reactogenicity data from the final analysis which consisted of a randomized subset of at least 8,000 participants 18 years and older in the phase 2/3 study demonstrates that the vaccine was well tolerated, with most solicited adverse events resolving shortly after vaccination.

The only Grade 3 (severe) solicited adverse events greater than or equal to 2% in frequency after the first or second dose was fatigue at 3.8% and headache at 2.0% following dose 2.

Consistent with earlier shared results, older adults tended to report fewer and milder solicited adverse events following vaccination.

Pfizer and BioNTech plan to submit the efficacy and safety data from the study for peer-review in a scientific journal once analysis of the data is completed.

### University of Oxford & AstraZeneca vaccine (ChAdOx1 nCoV-19)

Summary of the COVID-19 Oxford Vaccine Trial

<https://covid19vaccinetrial.co.uk/phase-ii-trial-publication>

**Monday 23rd November 2020**

*See:*

Oxford University breakthrough on global COVID-19 vaccine

* Phase 3 interim analysis including 131 Covid-19 cases indicates that the vaccine is 70.4% effective when combining data from two dosing regimens
* In the two different dose regimens vaccine efficacy was 90% in one and 62% in the other
* Higher efficacy regimen used a halved first dose and standard second dose
* Early indication that vaccine could reduce virus transmission from an observed reduction in asymptomatic infections
* There were no hospitalised or severe cases in anyone who received the vaccine
* Large safety database from over 24,000 volunteers from clinical trials in the UK, Brazil and South Africa, with follow up since April
* Crucially, vaccine can be easily administered in existing healthcare systems, stored at ‘fridge temperature’ (2-8 °C) and distributed using existing logistics
* Large scale manufacturing ongoing in over 10 countries to support equitable global access

Oxford will now support AstraZeneca in submitting both the interim Phase III efficacy data and the extensive safety data to all regulators across the world, including in the UK, Europe and Brazil for independent scrutiny and product approval, including for emergency use.

In parallel, Oxford is submitting the full analysis of the Phase III interim data for independent scientific peer review and publication.

These data also suggest that this half dose and full dose regimen could help to prevent transmission of the virus, evidenced by lower rates of asymptomatic infection in the vaccinees, with further information to become available when trial data are next evaluated.

The interim Phase III data builds on Oxford’s phase I/II peer-reviewed trial results which have shown that the vaccine induces strong antibody and T cell immune responses across all age groups, including older adults, and has a good safety profile.

The clinical trials, enrolling over 24,000 participants from diverse racial and geographical groups in the UK, Brazil and South Africa, will now continue to final analysis. Further trials are being conducted in the United States, Kenya, Japan and India and the trial team expect to have under 60,000 participants by the end of the year. These trials will provide regulators with further information about the efficacy and safety of the Oxford candidate vaccine, including its ability to both protect against and stop the transmission of COVID-19.

Astrazeneca trials:

<https://www.astrazeneca.com/media-centre/press-releases/2020/azd1222hlr.html>

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 x1010 viral particles) or full dose (~5x1010 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 (~5x1010 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.

**Reasons for not taking Covid vaccine – research to support communications messaging**



### Indicative search strategy

covid / coronavirus

vaccine(s)

phase 3 vaccine

phase III vaccine

University of Oxford / AstraZeneca /

Pfizer / BioNTech

ChAdOx1 nCoV-19

AZD1222

COV002

COV003

SARS-CoV-2 mRNA-1273 Vaccine

BNT162b1

### Sources searched

MHRA Medicines and Healthcare products Regulatory Agency <https://www.gov.uk/government/collections/mhra-guidance-on-coronavirus-covid-19>

The Oxford Vaccine Press Updates <https://covid19vaccinetrial.co.uk/press-updates>

The Oxford Vaccine <https://www.research.ox.ac.uk/Area/coronavirus-research/vaccine>

Astrazeneca Press Updates <https://www.astrazeneca.com/media-centre/press-releases.html>

Pfizer <https://www.pfizer.com/>

The Lancet Online First <https://www.thelancet.com/>

PubMed database <https://pubmed.ncbi.nlm.nih.gov/>

TRIP medical database <https://www.tripdatabase.com/>

NICE Evidence Search <https://www.evidence.nhs.uk/>

Oxford COVID-19 Evidence Service <https://www.cebm.net/oxford-covid-19-evidence-service/>

National Institute for Health Research (NIHR) <https://evidence.nihr.ac.uk/>

WHO <https://www.who.int/>

Healthcare databases: PubMed (AMED; BNI; CINAHL, Embase, Emcare, Medline)

House of Lords Library

Google

BBC

Twitter