# Oxford–AstraZeneca COVID-19 vaccine efficacy

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2020 has been a difficult year for all, but has seen 58 vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) be developed and in clinical trials,[1] with some vaccines reportedly having more than 90% efficacy against COVID-19 in clinical trials. This remarkable achievement is much-needed good news as COVID-19 cases are currently at their highest daily levels globally.[2] New vaccine efficacy results are reported now in *The Lancet*: investigators of four randomised, controlled trials conducted in the UK, South Africa, and Brazil report pooled results of an interim analysis of safety and efficacy against COVID-19 of the Oxford–AstraZeneca chimpanzee adenovirus vectored vaccine ChAdOx1 nCoV-19 (AZD1222) in adults aged 18 years and older.[3] This is the first report of efficacy against COVID-19 for a non-profit vaccine aiming for global supply, equity, and commitment to low-income and middle-income countries (LMICs),[4,5] and as such its publication is very welcomed. After phase 1 results supported a two-dose regimen, the trial protocols were amended where necessary to require two standard doses (SD/SD cohort) of approximately $5 \times 10^{10}$ viral particles per dose administered 28 days apart, but a subset (LD/SD cohort) in one of the UK trials inadvertently received a half-dose of the vaccine (low dose) as the first dose before a change in dosage quantification methodology; additionally, the protocol amendments enabled other trial participants originally scheduled to receive a single dose to receive a booster more than 28 days after their first dose. Participants randomly received either the ChAdOx1 nCoV-19 vaccine or control, which was either meningococcal conjugate vaccine (MenACWY) or saline depending on the trial.


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Interim efficacy results were available and are reported for two of the four ongoing trials (from the UK and Brazil) based on cases occurring within approximately 4 months of follow-up in 11 636 participants, the majority of whom were aged 18–55 years (10 218 [87·8%] participants), white (9625 [82·7%] participants), and female (7045 [60·5%] participants). No COVID-19-related hospital admissions occurred in ChAdOx1 nCoV-19 recipients, whereas ten (two of which were severe) occurred in the control groups. Vaccine efficacy for the prespecified primary analysis (combining dose groups) against the primary endpoint of COVID-19 occurring more than 14 days after the second dose was 70·4% (95·8% CI 54·8 to 80·6; 30 [0·5%] of 5807 participants in the ChAdOx1 nCoV-19 group *vs* 101 [1·7%] of 5829 participants in the control group). Surprisingly, however, efficacy was substantially lower in the SD/SD cohort (62·1% [95% CI 41·0 to 75·7]; 27 [0·6%] of 4440 *vs* 71 [1·6%] of 4455) than in the LD/SD cohort (90·0% [67·4 to 97·0]; three [0·2%] of 1367 *vs* 30 [2·2%] of 1374), which remained after accounting for differences in age and time between doses. Efficacy was similar when evaluated starting at 21 days after the first standard dose (192 cases), suggesting there is at least short-term protection with one dose. Although efficacy was lower (58·9% [1·0 to 82·9]) against asymptomatic infection in the LD/SD cohort (and unfortunately only 3·8% [−72·4 to 46·3] in the SD/SD group), the results nonetheless provide some hope that COVID-19 vaccines might be able to interrupt some asymptomatic transmission, although fewer data (69 cases among 6638 participants) were available with this outcome and more data are needed to confirm. Only 1418 (12·1%) of those assessed for efficacy were older than 55 years (none of whom were in the LD/SD cohort), meaning that from the interim analysis of these trials, we cannot yet infer efficacy in older adults, who are the group at greatest risk of severe COVID-19 outcomes.

Serious adverse events were evaluated in 12 174 ChAdOx1 nCoV-19 recipients and 11 879 control recipients. No serious adverse events or deaths that were

treatment associated occurred in ChAdOx1 nCoV-19 recipients. There were 175 serious adverse events (84 in the ChAdOx1 nCoV-19 group and 91 in the control group), three of which were possibly related to the intervention: transverse myelitis occurring 14 days after a ChAdOx1 nCoV-19 booster vaccination, haemolytic anaemia in a control recipient, and fever higher than 40°C in a participant still masked to group allocation. Two additional transverse myelitis cases considered unlikely to be related to the intervention occurred: one 10 days after the first dose of ChAdOx1 nCoV-19 was attributed to pre-existing multiple sclerosis and one in a control group that occurred 68 days after vaccination. The transverse myelitis cases resulted in temporarily pausing the trial and all participants have recovered or are recovering.

The strengths of the study include the large sample size, randomisation to vaccine groups, inclusion of diverse sites targeting different races and ethnicities, standardisation of key elements between the trials, balance of participant characteristics between the vaccine groups, inclusion of all participants in the safety assessment, and having similar results in Brazil as in the UK for the SD/SD group, which lends credibility to the results. Three of the trials also did not restrict enrolment based on age or presence of comorbidities. Although the efficacy results reported here were from single-blind trials, which masked only the participants to the product received, the endpoints were assessed by a blinded independent review committee. The limitations include that less than 4% of participants were older than 70 years of age, no participants older than 55 years of age received the mixed-dose regimen, and those with comorbidities were a minority, with results for that subgroup not yet available. The heterogeneity in vaccine dosage was fortuitous in uncovering a potentially highly efficacious formulation but was unplanned, and needs further evaluation in older adults and to confirm the unexpected results.

The observed differences in efficacy by dose were not consistent with results from previous immunogenicity trials of this vaccine, which were similar for participants receiving two low doses and two standard doses; no immunogenicity data exist for the mixed-dose regimen.[6] If immunogenicity is also similar for this regimen, this would be an unusual finding that requires further exploration, including whether this pertains only to milder disease (as there were too few cases to assess efficacy against severe COVID-19). Disparity between immunogenicity and efficacy findings could imply that clear-cut immunological correlates of clinical protection might not exist for COVID-19 vaccines, meaning efficacy cannot be extrapolated to other unevaluated ages or populations. Furthermore, bridging trials, in which new vaccines are tested against such correlates, or immunogenicity equivalence trials, in which new vaccines are tested against licensed vaccines using such immunological surrogates (rather than disease outcomes), that are faster and easier might be infeasible, posing challenges for future vaccine development, evaluation, and regulatory approval.

Oxford–AstraZeneca's US$2–3 per dose agreement with the COVAX Facility holds good promise for equitable access for LMICs, compared with the high cost of the two mRNA vaccines that have reported more than 90% efficacy.[1,4,5,7] The ChAdOx1 nCoV-19 vaccine can also use routine refrigerated cold chain, which is important since the ultra-low temperature freezers required to store mRNA vaccines could be unaffordable and impractical in many countries and in settings such as nursing homes. However, other challenges with any two-dose regimen will exist in many LMICs where platforms to easily identify, locate, and reach—twice—adults targeted for vaccination are lacking.[8] If the two vaccine injections require different doses, this will add complexity for health workers with little formal training, but can be managed with innovative packaging and proper change management to reduce errors.

Trust and confidence in any COVID-19 vaccine will be crucial to its success. The appropriate pausing of the trial to carefully investigate for safety concerns generated much publicity despite the reassuring outcomes of the safety review and trial recommencement. Public concerns might have been raised by the unplanned administration of different doses, notwithstanding that the per-protocol primary results exceeded licensure thresholds and that the serendipitous findings for recipients of the mixed-dose regimen were of high efficacy. Further trials to substantiate the unexpected findings here and investigation of efficacy in older adults are now needed. When faced with vaccine choices, National Immunization Technical Advisory Groups will have to consider all factors and decide which vaccine is right for their setting. Efficacy is an important

consideration, but so are pragmatics of delivery, community acceptance, longevity of effect, whether a vaccine reduces infection and transmission as well as disease, efficacy in high-risk groups, and, of course, safety.

Despite the outstanding questions and challenges in delivering these vaccines, it is hard not to be excited about these findings and the existence of three safe and efficacious COVID-19 vaccines, with a further 55 already in clinical trials.[1] With a range of manufacturers, a very large global investment in production, and cooperation in procurement and distribution, it seems likely that 2021 will see COVID-19 vaccines made available to all countries in the world—at least for their priority groups.[9] Perhaps by this time next year, we can celebrate the global control of SARS-CoV-2, in person.

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# Antifibrinolytics in subarachnoid haemorrhage

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The question of whether antifibrinolytics (eg, tranexamic acid or epsilon aminocaproic acid) can improve outcomes after aneurysmal subarachnoid haemorrhage has been asked for decades. The rationale for considering antifibrinolytic therapy in aneurysmal subarachnoid haemorrhage is sound: rebleeding often has devastating consequences.[1] Early trials indicated that antifibrinolytics could reduce the rate of rebleeding, but at the expense of a greater cumulative risk of cerebral ischaemia and without an overall favourable impact on mortality or disability.[2] However, these trials were done before the practice of early aneurysm obliteration became broadly implemented, and they tested the use of the antifibrinolytic drug for up to 21 days (ie, through the course of the delayed vasospasm period, during which the risk of cerebral ischaemia is higher).[3] Subsequently, a trial by Hillman and colleagues, which evaluated faster initiation and shorter duration of tranexamic acid (<72 h) along with early aneurysm treatment, suggested that tranexamic acid might reduce the risk of rebleeding without increasing the risk of cerebral ischaemia, albeit without improving functional outcomes.[4] While the most recent aneurysmal subarachnoid haemorrhage management guidelines from various organisations,

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