

SYNOPSIS

12/16/2020

Review of “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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One-minute summary

- The ChAdOx1 nCoV-19 vaccine was developed at Oxford University using a replication-deficient chimpanzee adenovirus vector containing the SARS-CoV-2 structural surface glycoprotein antigen (Spike protein) gene. In this interim analysis of ongoing clinical trials, the authors conclude that the vaccine has an acceptable safety profile and has been found to be efficacious against symptomatic COVID-19 in individuals **aged 18 years and older**.
- The study included data from four ongoing blinded, randomised, controlled trials done across the UK (phase 1/2, COV001; phase 2/3, COV002), Brazil (phase 3, COV003), and South Africa (COV005, phase 1/2). **Participants** were randomly assigned (1:1) to the vaccine or control (meningococcal vaccine or saline) group.
- Between April 23 and November 4, 2020, 23,848 participants were enrolled and 11,636 (7,548 in the UK, 4,088 in Brazil) were included in the interim primary efficacy analysis (assessed in participants who received two doses of the vaccine) which was a prespecified global pooled analysis combining data from two of the trials (COV002, COV003).
 - **Overall vaccine efficacy against symptomatic COVID-19 was 70.4% (95.8% CI 54.8% to 80.6%) after two doses:**
 - 62.1% (95% CI 41.0% to 75.7%) in 8,895 participants who received two standard doses (SD/SD).
 - 90.0% (95% CI 67.4% to 97.0%) in 2,741 participants who received a low dose which contained half of standard dose, followed by a standard dose (LD/SD).
 - **Overall vaccine efficacy against asymptomatic COVID-19 or symptoms unknown (n=6,638) was 27.3% (95% CI -17.2% to 54.9%)**
 - 3.8% (95% CI -72.4% to 46.3%) in 4,391 SD/SD participants.
 - 58.9% (95% CI 1.0% to 82.9%) in 2,247 LD/SD participants.

- From 21 days after the first dose, there were 10 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 in the vaccine group, 91 in the control group). **Three serious adverse events were considered possibly related to either the experimental or control vaccine (one case of haemolytic anemia in the control group, a case of transverse myelitis in the vaccine group, one high fever – allocation still masked). Two additional cases of transverse myelitis were reported but both (one in the vaccine group, one in the control group) were deemed unlikely related to the trial interventions.**

Additional information

- 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. Symptomatic was defined as at least one qualifying symptom (fever $\geq 37.8^{\circ}\text{C}$, cough, shortness of breath, or anosmia or ageusia) in the UK and Brazil, and a larger number of symptoms in South Africa. Participants were analysed according to intervention received, with data cut-off on Nov 4, 2020. Vaccine efficacy was calculated as “1 – relative risk” derived from a Poisson regression model adjusted for age.
- Participants who self-reported COVID-19-related symptoms and met the symptomatic criteria (varied across studies) were assessed clinically, and tested serologically and virologically (nucleic acid amplification test – NAAT). In addition, participants in the UK study COV002 were asked to provide a self-administered nose and throat swab weekly to test for asymptomatic infections throughout the study period.
- The interim analysis of vaccine safety includes data of participants who received at least one dose from four ongoing randomised controlled trials done across three countries:
 - COV001 (UK): single-blind, phase 1/2; n=1,067 (all aged 18-55 years, except for 2 with missing age information); median body-mass index (BMI) (ChAdOx1 nCoV-19 vs. control) = 24.2 vs. 24.4.
 - COV002 (UK): single-blind, phase 2/3; n=10,663 (77.6% aged 18-55 years, 11.3% ≥ 70 years); median BMI = 25.4 vs. 25.5.
 - COV003 (Brazil): single-blind, phase 3; n=10,002 (83.4% aged 18-55 years; 2.5% ≥ 70 years); median BMI = 26.0 vs. 25.9.
 - COV005 (South Africa): double-blind, phase 1/2; n=2,013 (95.1% aged 18-55 years; none ≥ 70 years); median BMI = 23.8 vs. 23.5.
- Adverse events of special interest reported by participants after any dose (ChAdOx1 nCoV-19 vs control groups):
 - Anaphylaxis: 1/12,021 (<0.1%) vs. 0/11,724 (0%)
 - Generalized convulsion: 1/12,021 (<0.1%) vs. 1/11,724 (<0.1%)
 - Other neurologic events: 64/12,021 (0.5%) vs. 79/11,724 (0.7%)
 - Potential immune-mediated conditions:
 - Neuroinflammatory disorders: 5/12,021 (<0.1%) vs. 4/11,724 (<0.1%)
 - Skin disorders: 3/12,021 (<0.1%) vs. 4/11,724 (<0.1%)
 - Other: 3/12,021 (<0.1%) vs. 3/11,724 (<0.1%)
 - Thrombotic, thromboembolic, and neurovascular events: 4/12,021 (<0.1%) vs. 8/11,724 (0.1%)

- The first interim vaccine efficacy analysis was planned when at least 53 cases in participants who had received two standard-dose vaccines (SD/SD) had accrued to meet the primary outcome definition. It was assessed by a prespecified global pooled analysis combining data from COV002 and COV003, which met prespecified criteria of having at least five cases. Vaccine dose, duration between doses, criteria for COVID-19 testing and other variables differed to some degree across study sites. Amongst the 11,636 participants:
 - Age distribution: 18-55 years (87.8%), 56-69 years (8.4%), ≥70 years (3.8%)
 - Duration between doses: <6 weeks (29.2%), 6-8 weeks (16.0%), 9-11 weeks (26.5%), ≥12 weeks (28.3%)
- The confidence intervals (CIs) are fairly wide. Inclusion of more data from the study's ongoing trials should narrow the CIs.
- Additional studies are needed to explore the duration of protection from COVID-19 and any reduction in transmissibility in vaccinees with asymptomatic/subclinical COVID-19.

PHO reviewer's comments

- More than half of those enrolled were lost (23,848 enrolled - 11,636 participants = 12,212 lost). The reason for this attrition is not addressed by the authors and given that more than 50% of research participants were lost to follow-up, then attrition bias is of concern in this study.
- Attempts were made by the authors to explain why the low dose had greater efficacy than the standard dose (90.0% (95% CI 67.4–97.0) versus 62.1% (41.0–75.7), respectively), but ultimately, it is not known and further work needs to be done to understand this observation.
- The vaccine efficacy is lower than that reported for other COVID-19 vaccines.
- As COVID-19 infections with onset within 14 days after the second dose (or 21 days for those vaccinated with only one dose) were excluded, vaccine efficacy might be overestimated when early-onset cases were not counted. Caution should be exercised in attempting to generalize the efficacy and safety data to other populations as the trial did not include children, adolescents, the elderly, persons with high BMI as well as those with unstable comorbidities.

Citation

Ontario Agency for Health Protection and Promotion (Public Health Ontario). Review of “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”. Toronto, ON: Queens’s Printer for Ontario; 2020.

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