SYNOPSIS

02/04/2021

Review of "Single dose administration, and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine".

One-minute summary

- The ChAdOx1 nCoV-19 (AZD1222) vaccine is produced in partnership between Astra Zeneca and Oxford University, England. The vaccine has been approved for emergency use by the United Kingdom (UK) regulatory authority, Medicines and Healthcare products Regulatory Agency (MHRA), as two standard doses (SD) given at an interval of between 4 and 12 weeks. The planned rollout of the vaccine in the UK involves the administration of two doses, 12 weeks apart.

- In this pre-print study, the authors' conclude "*ChAdOx1 nCoV-19 vaccination programmes aimed at vaccinating a large proportion of the population with a single dose, with a second dose given after a 3 month period is an effective strategy for reducing disease, and may be the optimal for rollout of a pandemic vaccine when supplies are limited in the short term.*"

- The study provided findings in the following three areas:

1. The study provided an update on phase I/II (UK and South Africa) and phase III (UK and Brazil) trials, with interim estimates of vaccine efficacy. This interim analysis presents data from the trial until December 7, 2020.

  - 17, 177 baseline sero-negative trial participants were eligible for inclusion in the efficacy analysis; 8948 in the UK, 6753 in Brazil and 1476 in South Africa, with 619 documented Nucleic Acid Amplification Test (NAAT) positive infections identified following vaccination, of which 332 met the primary endpoint of symptomatic COVID-19 infection >14 days after receiving the second dose.
  - The analysis of overall vaccine efficacy >14 days after the second dose, which included low dose/standard dose (LD/SD) and standard dose/standard dose (SD/SD) groups was 66.7% (95% Confidence Interval (CI) 57.4%, 74.0%). There were no hospitalisations in the

ChAdOx1 nCoV-19 vaccine group after the initial 21 day exclusion period and 15 in the control group.

2. The study explored immunogenicity and vaccine efficacy after a single SD vaccine.

- Vaccine efficacy after a single SD vaccine from day 22 to day 90 post-vaccination was 76% (95% CI 59%, 86%) and modelled analysis suggests protection did not wane in the three month period after vaccination.

3. The study explored extending the interval between the first and second dose.

- In the SD/SD group, after the second dose, efficacy was higher with a longer prime-boost interval: vaccine efficacy 82.4% (95%CI 62.7%, 91.7%) at >12 weeks, compared with vaccine efficacy 54.9% (95%CI 32.7%, 69.7%) at <6 weeks.

- These observations were supported by immunogenicity data which showed binding antibody responses more than 2-fold higher after an interval of >12 weeks compared with an interval of <6 weeks (Geometric Mean Ratio [GMR] 2.19, 95% CI 2.12, 2.26) in individuals 18-55 years of age who received 2 doses (SD/SD).

Additional information

- The ChAdOx1 nCoV-19 vaccine (AZD1222) is a replication-deficient chimpanzee adenoviral vector vaccine containing the full-length SARS-CoV-2 spike insert.

- The clinical trial studies were initially planned to evaluate single dose efficacy, but were amended to incorporate a second dose after the phase I immunogenicity data demonstrated a substantial increase in neutralizing antibodies with a second dose of vaccine.

- The authors explain that the studies were not designed to evaluate the impact of dose interval on vaccine efficacy. These data arose due to the logistics of a large-scale clinical trial (e.g., delays in administration of dose two) and, therefore, the dose interval analyses are post-hoc exploratory analyses with potential bias. Further, after initially providing consent to participate in a single dose study, some participants chose not to receive the second dose, providing a self-selected cohort of single dose recipients.

- The primary outcome was symptomatic COVID-19 disease defined as a NAAT-positive swab combined with at least one qualifying symptom (fever ≥ 37.8^{o}C, cough, shortness of breath, anosmia [loss of smell] or ageusia [loss of taste]).

- The vaccine efficacy was calculated as: 1 – the adjusted relative risk (ChAdOx1 nCoV-19 vs control groups); computed using a Poisson regression model.

- The overall vaccine efficacy against primary symptomatic COVID-19 occurring more than 14 days after the second dose was 66.7% (95% CI 57.4%, 74.0%). In the SD/SD cohort, the vaccine efficacy was 63.1%, (95% CI 51.8%, 71.7%). In the LD/SD cohort the vaccine efficacy was 80.7% (95% CI 62.1%, 90.2%). The authors suggest the higher efficacy observed in the LD/SD group may be partly driven by this group having a longer dosing interval between the two doses than the SD/SD group.

- The authors also report the vaccine efficacy against asymptomatic infection occurring more than 14 days after the second dose. In the SD/SD cohort there was no evidence of protection against asymptomatic infection with a vaccine efficacy of 2.0%, (95%CI -50.7%, 36.2%, 41 ChAdOx1 nCoV-19 versus 42 control cases). The LD/SD cohort had a vaccine efficacy of 49.3%, (95%CI 7.4%, 72.2%, 16 ChAdOx1 nCoV-19 versus 31 control cases) in preventing asymptomatic infection > 14 days after the second dose.

- The authors report a reduction in Polymerase Chain Reaction test (PCR) positivity by 67% after a single standard dose. After the second dose in the SD/SD regimen, PCR positivity was reduced to 49.5% overall. PCR positivity can be used to assess the burden of infection.

- To explore the impact of varying the timing of the second dose of vaccine, separate efficacy models were fitted using unadjusted log-binomial models for each 20-day interval starting with an interval of 20 to 40 days (midpoint for plot: 30 days) and incrementing by one day for each model.

- To explore waning after the first dose and before a second dose was received, a similar approach was taken with separate efficacy models fitted to 28-day windows of the time from vaccination.

- There were statistically significant differences in baseline characteristics of the participants who received a single dose and participants who received two doses. Statistically significant differences were found for age, sex, health or social care worker status, dose (LD/SD, SD/SD), country, ethnicity and follow up time. Participants receiving a booster dose were older (median age 40 years versus 36 years), with a higher proportion of males (44.2% versus 39.0%) and non-white individuals (24.1% versus 20.8%), and a lower proportion of health or social care workers (60.1% versus 65.7%) when compared with the group of participants who did not receive a booster dose. The potential impact of these differences in participant characteristics should be considered when interpreting the vaccine efficacy of the single SD vaccine.

- The authors were requested to conduct a post-hoc exploratory analysis of the optimal prime-boost interval in terms of: 1) impact of the interval on protection after the second dose; 2) risk of infection during the pre-boost period (as a result of lower efficacy with a single dose or rapid waning of efficacy from the first dose).

- The authors report protection with dosing intervals between 4 and 12 or more weeks and suggest that a longer prime-boost interval provides better protection post-boost without compromising protection in the three month period until the second dose is administered. A limitation of this conclusion is the limited duration of follow-up following the second dose.

PHO reviewer's comments

- The study is a pre-print and has not yet been peer reviewed. The study could benefit in communicating its various messages if it was parsed into at least three different studies.

Citation

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