Public Health Ontario | Santé publique Ontario

SYNOPSIS

Review of "Safety and Efficacy of Single-Dose of Ad26.COV2.S Vaccine against COVID-19"

05/03/2021

Article citation: Sadoff J, Gray G, Vandebosch A, Cárdenas V, Shukarev G, Grinsztejn B, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against covid-19. N Engl J Med. 2021 Apr 21 [Epub ahead of print]. Available from: https://doi.org/10.1056/nejmoa2101544

Supplementary Appendix available from:
https://www.nejm.org/doi/suppl/10.1056/NEJMoa2101544/suppl_file/nejmoa2101544_appendix.pdf

One-minute summary

- The authors report findings of ENSEMBLE, a phase 3 international, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of a **single dose of the Janssen pharmaceutical (Johnson & Johnson) Ad26.COV2.S COVID-19 vaccine.** This vaccine is a recombinant, replication-incompetent, human adenovirus 26 vector encoding a full-length Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) spike protein in the pre-fusion stabilized confirmation.
- The trial was conducted in Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and the United States. Data for this analysis were collected from the period of September 21, 2020 to January 22, 2021. **Eligible patients were non-pregnant adults aged ≥ 18 years** who were clinically stable and not receiving immunosuppressive or anti-neoplastic medications.
- Participants were randomly assigned 1:1 to receive a single intramuscular dose of Ad26.COV2.S (n=19,630) or saline placebo (n=19,691). Randomization was stratified by trial site, age group, and the presence of co-existing conditions associated with risk of severe Coronavirus Disease 2019 (COVID-19). The primary outcomes were the occurrence of **moderate to severe-critical COVID-19, 1) at least 14 days after vaccination, and 2) at least 28 days after vaccination.** All cases of COVID-19 were laboratory-confirmed via reverse transcriptase polymerase chain reaction (RT-PCR). Patients with positive RT-PCR for SARS-CoV-2 at days 1 to 14 and days 1 to 28 after administration were excluded from the ≥ 14 day and ≥ 28 day vaccine efficacy estimates, respectively.
- **Overall vaccine efficacy against moderate to severe-critical COVID-19** was 66.9% (adjusted 95% confidence interval [CI]: 59.0 to 73.4) at least 14 days after administration and 66.1% (adjusted 95% CI: 55.0 to 74.8) at least 28 days after administration. Confidence intervals were adjusted for multiple testing to account for the possibility of type 1 error.
- The **vaccine displayed similar efficacy across population subgroups,** including race, ethnicity, age, and sex, with overall numerically higher efficacy against more severe disease.
  Vaccine efficacy at **≥ 14 days** and **≥ 28 days**, respectively:
  - Age 18-59 years: 63.7% (95% CI: 53.9 to 71.6%); 66.1% (95% CI: 53.3 to 75.8%)
  - Age ≥ 60 years: 76.3% (95% CI: 61.6 to 86.0%); 66.2% (95% CI: 36.7 to 83.0%)

    - Moderate COVID-19: 64.8% (adjusted 95% CI: 55.8 to 72.2%); 62.0% (adjusted 95% CI: 48.7 to 72.2%)
    - Severe-Critical COVID-19: 76.7% (adjusted 95% CI: 54.6 to 89.1%); 85.4% (adjusted 95% CI: 54.2 to 96.9%)
- A subgroup of participants assessed serologically at day 71 (n=2,650) for new seropositivity found **vaccine efficacy for asymptomatic infection** to be 65.5% (95% CI: 39.9 to 81.1%).
- Local reaction, such as injection-site pain (48.6%), headache (38.9%), fatigue (38.2%), myalgia (33.2%), and nausea (14.2%) were the **most common side effects** reported in participants receiving the vaccine. Most symptoms were mild to moderate in severity and lasted 1 to 2 days. Reactogenicity was transient and lower in older participants than younger participants.
- The proportion of participants reporting **serious adverse events**, excluding those related to COVID-19, were similar between recipients of the vaccine (0.4%) and placebo (0.4%). However, there were numerically more patients in the vaccine group than the placebo group that experienced venous thromboembolism (11 vaccinated vs. 3 placebo), seizure (4 vs. 1), tinnitus (6 vs. 0), transverse sinus thrombosis with cerebral hemorrhage (1 vs. 0) and Guillain–Barré syndrome (1 vs. 0).

Additional information

- Each dose of the Janssen Ad26.COV2.S vaccine was 5×10^{10} viral particles administered as a single intramuscular injection (0.5 mL).
- Primary and secondary efficacy evaluations were to be based on centrally confirmed COVID-19, but not all cases had been centrally confirmed at the time of this analysis.
- Median follow-up was 58 days (range 1 to 124 days).
- Study population included the following:
    - Baseline seropositivity for SARS-CoV-2: 9.6% (9.8% in vaccine group, 9.4% in placebo group). Seropositive patients were not included in the per-protocol efficacy analysis.
    - Median age: 52 years (range 18-100 years).
    - Age 18-59: 66.5%; Age ≥ 60: 33.5%.
    - Female 45%, Male 54.9%.
    - Ethnicity or race: White 58.7%; Black 19.4%; Indigenous South American 9.0%; multiracial 5.6%; Asian 3.3%.
    - Regions represented: United States 44.1%; Latin America 40.9%; South Africa 15.0%.
- For participants over 60 years, vaccine efficacy appeared lower among those with co-existing conditions, which the authors attribute to imprecision and shorter follow-up in this subgroup. However the Kaplan-Meier curves suggest similar vaccine efficacy among those with and without co-existing conditions. Additionally vaccine efficacy against hospitalization of 82% in patients over 60 years with co-existing conditions suggests adequate efficacy in this subgroup.
- Participants who experienced COVID-19 at least 28 days after administration reported lower symptom-severity score if they were vaccinated. Symptom scores were 24% (95% CI: −1 to 46) lower among vaccine recipients at day 1 after symptom-onset and 53% (95%CI: 0 to 81) lower at day 14 after symptom-onset among participants who received vaccine compared to placebo.
- Vaccine efficacy was consistently high across all countries despite the range in prevalence of variants of concern (VOC). For example, in South Africa the B.1.351 variant represented 94.5% of all sequences but the vaccine displayed an efficacy of 64.0% (adjusted 95%CI: 41.2% to 78.7%) against moderate to severe-critical COVID-19 and 81.7% (adjusted 95%CI: 46.2% to 95.4%) against severe-critical disease at ≥ 28 days after administration. In Brazil, the P.2 variant of interest was predominant at 69.4% and the vaccine efficacy against moderate to severe-critical

and severe-critical at ≥ 28 days was 68.1% (adjusted 95%CI: 48.8% to 80.7%) and 87.6% (adjusted 95%CI: 7.8% to 99.7%), respectively.

- Vaccine efficacy appeared to diverge between vaccinated and unvaccinated participants at approximately 14 days after administration, with continued accrual of cases in the placebo group, leading to increased vaccine efficacy over time. Efficacy was maintained for up to 15 weeks, suggesting no waning of protection.
- Moderate COVID-19 was defined as a positive RT-PCR for SARS-CoV-2 and two or more of: fever or chills; cough; heart rate ≥ 90 beats/minute; myalgia; headache; new loss of taste or smell; sore throat; red or bruised-looking feet or toes; nausea; vomiting; or diarrhea, with one or more of: shortness of breath; respiratory rate >20/minute; clinical or radiological evidence of pneumonia; deep vein thrombosis; or abnormal oxygen saturation (above 93%).
- Severe-Critical COVID-19 was defined as a positive RT-PCR for SARS-CoV-2 and one or more of: respiratory failure; shock (systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg or requiring vasopressors); respiratory rate >30 /minute; heart rate ≥125 beats/minute; oxygen saturation of 93% or less (ambient air), or a ratio of the partial pressure of oxygen to the fraction of inspired oxygen <300 mmHg; intensive care admission; significant acute kidney, liver, or nerve dysfunction; or death.

PHO reviewer's comments

- The follow-up period for this analysis was relatively short given the urgent need for COVID-19-related vaccine efficacy data. Despite the lack of evidence of waning efficacy over the median 58 day follow-up, more longitudinal data are needed to assess longer-term efficacy.
- Close post-marketing safety monitoring will be needed to evaluate for the risk of Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT) given the signal in this trial for increased risk of thromboembolism, recent cases of VITT reported with this vaccine in the United States, and concern for VITT with another adenovirus vector vaccine developed by AstraZeneca/Oxford University.
- In contrast to earlier clinical trial data for other vaccines, prospective efficacy data for the Janssen vaccine in regions where certain variants of concern are predominant (i.e., B.1.351 in South Africa and P.2 in Brazil) provides reassurance that this vaccine maintains efficacy against these variants.
- In contrast to mRNA vaccines that require ultra-cold storage and other vaccines currently available in Canada that require a 2-dose schedule, the Janssen vaccine can be stored for 2 years in a freezer and 3 months at refrigerator temperatures and is a single dose regimen. This may lead to additional vaccine uptake and compliance from a health care system and public health perspective with added acceptability for patients wishing to receive a single vaccine dose.

Citation

Ontario Agency for Health Protection and Promotion (Public Health Ontario). Review of "Safety and efficacy of single-dose Ad26.COV2.S vaccine against COVID-19". Toronto, ON: Queen's Printer for Ontario; 2021.

Disclaimer

This document was developed by Public Health Ontario (PHO). PHO provides scientific and technical advice to Ontario's government, public health organizations and health care providers. PHO's work is guided by the current best available evidence at the time of publication. The application and use of this document is the responsibility of the user. PHO assumes no liability resulting from any such application or use. This document may be reproduced without permission for non-commercial purposes only and provided that appropriate credit is given to PHO. No changes and/or modifications may be made to this document without express written permission from PHO.

Public Health Ontario

Public Health Ontario is an agency of the Government of Ontario dedicated to protecting and promoting the health of all Ontarians and reducing inequities in health. Public Health Ontario links public health practitioners, front-line health workers and researchers to the best scientific intelligence and knowledge from around the world.

For more information about PHO, visit publichealthontario.ca.

Ontario