

## Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19

**TO THE EDITOR:** Sadoff et al., in their article describing the ENSEMBLE trial (June 10 issue),<sup>1</sup> report that there was no evidence of waning efficacy among the approximately 3000 participants who were followed for 11 weeks or among 1000 participants who were followed for 15 weeks. This statement is true, but their statement that “the data do not suggest a waning of protection” is misleading. As Figure 2 in the article shows, no moderate to severe–critical cases of coronavirus disease 2019 (Covid-19) were noted in the placebo group beyond 91 days after administration (Fig. 2A), and no additional severe–critical cases occurred after day 84 in the placebo group through the end of the published follow-up period (day 126) (Fig. 2B). This indicates that there was apparently little risk of exposure in the study areas beyond these time points, and without sufficient exposure to severe acute respiratory syndrome coronavirus (SARS-CoV-2), waning of immunity cannot be detected clinically. More data are needed to reliably assess the duration of protection after a single dose of the Ad26.COV2.S vaccine.

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Dr. Heininger reports having received lecture fees from Pfizer, Germany, unrelated to Covid-19, and being a member of the Meta-Data and Safety Monitoring Board of the Coalition for Epidemic Preparedness Innovations, which assesses safety in vaccine studies, including studies of vaccines against Covid-19. No other potential conflict of interest relevant to this letter was reported.

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1. Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. *N Engl J Med* 2021;384:2187-201.

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**THE AUTHORS REPLY:** We would like to clarify the sentence, “No evidence of waning efficacy was noted among the approximately 3000 participants who were followed for 11 weeks or among 1000 participants who were followed for 15 weeks . . .” This was intended to contextualize that vaccine efficacy over time was driven

mainly by smaller groups of participants who were followed for long periods of time (approximately 3000 participants for 11 weeks and 1000 participants for 15 weeks), in whom no evidence of waning efficacy was observed up to day 91. All the centrally confirmed moderate to severe–critical cases of Covid-19 occurred up to day 91, as reported. In an analysis in which cases confirmed from any source were included, cases occurred up to day 105 (data on file).

Figure S4A in the Supplementary Appendix of our article, which was generated with the use of the Gilbert method,<sup>1</sup> shows projected vaccine efficacy over time against moderate to severe–critical disease and reflects the uncertainty of the estimate beyond day 56 on the basis of the width of the confidence intervals. The lack of observed cases beyond day 91 is also reflected, given that the curve stops after approximately day 91, thus illustrating data limitations. We agree that additional and longer-term data are needed to assess the durability of protection, and such analyses are planned for the ENSEMBLE trial (ClinicalTrials.gov number, NCT04505722).

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Since publication of their article, the authors report no further potential conflict of interest.

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1. Gilbert PB, Wei LJ, Kosorok MR, Clemens JD. Simultaneous inferences on the contrast of two hazard functions with censored observations. *Biometrics* 2002;58:773-80.

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