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DOI: 10.1056/NEJMc2107920

ChAdOx1 nCoV-19 Vaccine Efficacy against the B.1.351 Variant

TO THE EDITOR: Madhi et al. (May 20 issue)[1] report on the efficacy of vaccination with the recombinant adenoviral vector encoding the spike protein antigen of SARS-CoV-2 (ChAdOx1 nCoV-19) against the SARS-CoV-2 B.1.351 (or beta) variant lineage. They commented that in the ENSEMBLE study evaluating the efficacy of the Ad26.COV2.S vaccine, only patients with infection that was confirmed by polymerase-chain-reaction assay who had at least three signs or symptoms of Covid-19 were approved for end-point adjudication. The authors incorrectly concluded that the vaccine efficacy analyses excluded the majority of mild Covid-19 cases. However, all patients with mild or moderate cases of Covid-19 who had one or two symptoms did not require adjudication for confirmation as a case and were included in primary or secondary efficacy analyses, as detailed in the protocol. The Clinical Severity Adjudication Committee was established to independently assess, in a blinded manner, potential severe or critical cases of Covid-19, adjudicating all cases meeting the criteria for severe–critical disease and all cases meeting the criteria for moderate disease with at least three signs or symptoms to determine whether the case was severe–critical in their judgment.[2] This focused process yielded blinded, independent confirmation of severe–critical cases by clinical infectious disease experts and pulmonologists, ensuring the robustness and clinical relevance of this important end point.

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The authors report being employees of the Janssen Pharmaceutical Companies of Johnson & Johnson and holding shares in the Johnson & Johnson group of companies. No other potential conflict of interest relevant to this letter was reported.

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1. Madhi SA, Baillie V, Cutland CL, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 vaccine against the B.1.351 variant. N Engl J Med 2021;384:1885-98.
2. Janssen Vaccines & Prevention. A randomized, double-blind, placebo-controlled phase 3 study to assess the efficacy and safety of Ad26.COV2.S for the prevention of SARS-CoV-2-mediated COVID-19 in adults aged 18 years and older. December 14, 2020 (https://www.jnj.com/coronavirus/ensemble-1-study-protocol).
DOI: 10.1056/NEJMc2110093

THE AUTHORS REPLY: We thank Struyf et al. for clarifying our interpretation of severity grading of Covid-19 end-point cases in the Ad26.COV2.S trial. Nevertheless, according to the presentation on Ad26.COV2.S at a meeting of the Vaccines and Related Biological Products Advisory Committee held by the Food and Drug Administration, only 5 mild, 526 moderate, and 99 severe Covid-19 cases were recorded in the global clinical trials.[1] In our study of AZD1222, undertaken in a younger and healthier population than that enrolled in the Ad26.COV2.S trial, 32 mild and 10 moderate Covid-19 primary end-point cases were noted. These two studies did not measure the same end point. We reported lack of efficacy of the AZD1222 vaccine against mild-to-moderate cases of infection with the beta variant in patients who were not hospitalized. Conversely, in the Ad26.COV2.S trial, 52% protection was reported in cases of moderate-to-severe disease in patients infected with the beta variant of Covid-19 in South Africa, although efficacy against a mild beta variant was not determined.[1] In a finding consistent with the observation of excellent protection provided by Ad26.COV2.S against a severe beta variant of Covid-19, AZD1222 prevented the development of gross pathological and histopathological abnormalities in the lungs in hamsters, despite viral replication in the nose.[2] In Canada, vaccine effectiveness of AZD1222 against Covid-19 hospitalization or death due to the beta or P.1 (gamma) variants, both of which share the E484K mutation, was 83% (95% confidence interval, 66 to 92).[3] These data show that the SARS-CoV-2 viral vector vaccines confer excellent protection against severe Covid-19.

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DOI: 10.1056/NEJMc2110093

Healthy Weight Loss Maintenance with Exercise, Liraglutide, or Both Combined

TO THE EDITOR: Lundgren et al. (May 6 issue)[1] showed that a combination of high-intensity exercise and treatment with liraglutide for 1 year had clinically meaningful positive effects on several health outcomes, particularly those related to metabolism, in middle-aged adults with obesity. These findings add major evidence for the treatment of obesity and may have positive public health implications. Nevertheless, can these results be maintained in the long term? A 1-year trial is a medium-to-long–term study, yet represents only a short interval from a life-course perspective. For how long should participants continue to follow a somewhat constraining treatment protocol to enjoy its benefits? Will participants adhere durably to a drug that decreases appetite and increases dizziness (and potentially causes nausea, diarrhea, and vomiting)? For how long would participants be willing to adhere to vigorous physical activity, which is very difficult to achieve in the long term? Since there is no cure for obesity and its control relies mainly on healthy behaviors, a drug-based approach without appropriate education and behavioral changes including exercise and diet plans that can be implemented as a lifelong strategy, is probably destined to fail. The input of social scientists on this topic would seem important.

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1. Lundgren JR, Janus C, Jensen SBK, et al. Healthy weight loss maintenance with exercise, liraglutide, or both combined. N Engl J Med 2021;384:1719-30.

DOI: 10.1056/NEJMc2109509

TO THE EDITOR: Lundgren et al. observed that combined therapy with exercise and liraglutide improved healthy weight loss maintenance among obese adults more than either treatment alone. However, I wonder why the investigators excluded persons with type 1 or type 2 diabetes from the trial. Most adults with diabetes mellitus are obese, with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or greater.[1] Exercise has been shown to improve glycemic control and contribute to weight loss among persons with diabetes (types 1 and 2).[2] Moreover, individualization of exercise, safety measures, and medication depends on the type of diabetes; the patient's health history, age, and cardiorespiratory fitness; and any coexisting conditions. In a trial involving obese adults with type 2 diabetes, the use of subcutaneous liraglutide (at a dose of 3.0 mg per day) in combination with a reduced-calorie diet (500 kcal per day) and increased physical activity (≥150 min per week) resulted in greater weight loss than placebo over 56 weeks.[3] Thus, it seems clear that liraglutide therapy in addition to exercise and dietary restriction is effective in reducing glucose levels and maintaining weight loss among obese adults with diabetes mellitus.[4]