ORIGINAL ARTICLE

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

J. Sadoff, G. Gray, A. Vandebosch, V. Cárdenas, G. Shukarev, B. Grinsztejn, P.A. Goepfert, C. Truyers, H. Fennema, B. Spiessens, K. Offergeld, G. Scheper, K.L. Taylor, M.L. Robb, J. Treanor, D.H. Barouch, J. Stoddard, M.F. Ryser, M.A. Marovich, K.M. Neuzil, L. Corey, N. Cauwenberghs, T. Tanner, K. Hardt, J. Ruiz-Guiñazú, M. Le Gars, H. Schuitemaker, J. Van Hoof, F. Struyf, and M. Douoguih, for the ENSEMBLE Study Group*

ABSTRACT

BACKGROUND

The Ad26.COV2.S vaccine is a recombinant, replication-incompetent human adenovirus type 26 vector encoding full-length severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein in a prefusion-stabilized conformation.

METHODS

In an international, randomized, double-blind, placebo-controlled, phase 3 trial, we randomly assigned adult participants in a 1:1 ratio to receive a single dose of Ad26.COV2.S (5×10^{10} viral particles) or placebo. The primary end points were vaccine efficacy against moderate to severe–critical coronavirus disease 2019 (Covid-19) with an onset at least 14 days and at least 28 days after administration among participants in the per-protocol population who had tested negative for SARS-CoV-2. Safety was also assessed.

RESULTS

The per-protocol population included 19,630 SARS-CoV-2–negative participants who received Ad26.COV2.S and 19,691 who received placebo. Ad26.COV2.S protected against moderate to severe–critical Covid-19 with onset at least 14 days after administration (116 cases in the vaccine group vs. 348 in the placebo group; efficacy, 66.9%; adjusted 95% confidence interval [CI], 59.0 to 73.4) and at least 28 days after administration (66 vs. 193 cases; efficacy, 66.1%; adjusted 95% CI, 55.0 to 74.8). Vaccine efficacy was higher against severe–critical Covid-19 (76.7% [adjusted 95% CI, 54.6 to 89.1] for onset at ≥14 days and 85.4% [adjusted 95% CI, 54.2 to 96.9] for onset at ≥28 days). Despite 86 of 91 cases (94.5%) in South Africa with sequenced virus having the 20H/501Y.V2 variant, vaccine efficacy was 52.0% and 64.0% against moderate to severe–critical Covid-19 with onset at least 14 days and at least 28 days after administration, respectively, and efficacy against severe–critical Covid-19 was 73.1% and 81.7%, respectively. Reactogenicity was higher with Ad26.COV2.S than with placebo but was generally mild to moderate and transient. The incidence of serious adverse events was balanced between the two groups. Three deaths occurred in the vaccine group (none were Covid-19–related), and 16 in the placebo group (5 were Covid-19–related).

CONCLUSIONS

A single dose of Ad26.COV2.S protected against symptomatic Covid-19 and asymptomatic SARS-CoV-2 infection and was effective against severe–critical disease, including hospitalization and death. Safety appeared to be similar to that in other phase 3 trials of Covid-19 vaccines. (Funded by Janssen Research and Development and others; ENSEMBLE ClinicalTrials.gov number, NCT04505722.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Douoguih at Janssen Vaccines and Prevention, Newtonweg 1, CP 2333 Leiden, the Netherlands, or at mdouogui@its.jnj.com.

*The members of the ENSEMBLE Study Group are listed in the Supplementary Appendix, available at NEJM.org.

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Since emerging in December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has caused high morbidity and mortality, with new variants rapidly spreading.[1-4] Vaccines to prevent coronavirus disease 2019 (Covid-19) have been developed with unprecedented speed.[5,6]

The Ad26.COV2.S vaccine comprises a recombinant, replication-incompetent human adenovirus type 26 (Ad26) vector[7] encoding a full-length, membrane-bound SARS-CoV-2 spike protein in a prefusion-stabilized conformation.[8,9] Other Ad26-based vaccines, including an approved Ebola vaccine, are safe and have induced durable immune responses.[8,10-13] Ad26.COV2.S induced durable protection at low doses in preclinical SARS-CoV-2 challenge studies,[8,14] and initial clinical data showed that a single dose at 5×10^{10} viral particles was safe and induced excellent humoral and cellular immune responses.[9] Ad26.COV2.S can be stored for up to 2 years in a standard freezer and up to 3 months at refrigerator temperatures, which simplifies transport, storage, and use in a pandemic.

We are conducting an ongoing phase 3 trial (ENSEMBLE) to evaluate the safety and efficacy of a single dose of Ad26.COV2.S at 5×10^{10} viral particles for the prevention of Covid-19 and SARS-CoV-2 infection in adults. Here, we report the results of the primary analyses.

Methods

Trial Design and Oversight

We are conducting this ongoing, 2-year, multicenter, randomized, double-blind, placebo-controlled, phase 3, pivotal trial in Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and the United States. All the participants provided written informed consent. The trial adheres to the principles of the Declaration of Helsinki and to the Good Clinical Practice guidelines of the International Council for Harmonisation. The protocol (available with the full text of this article at NEJM.org) and amendments were approved by institutional review boards according to local regulations. An unblinded independent data and safety monitoring board continuously monitors safety, including monitoring for vaccine-associated enhanced respiratory disease.

The trial is a collaboration between the sponsor, Janssen Research and Development, which is an affiliate of Janssen Vaccines and Prevention and part of the Janssen pharmaceutical companies of Johnson & Johnson, and the Operation Warp Speed Covid-19 Rapid Response Team (which includes the Biomedical Advanced Research and Development Authority, the National Institutes of Health, the Covid-19 Prevention Trials Network, and the Department of Defense). The trial was designed and conducted, and the data analysis and data interpretation were performed, by the sponsor and collaborators. Trial-site investigators collected and contributed to the interpretation of the data. All the data were available to the authors, who vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Medical writers who were funded by the sponsor assisted in drafting the manuscript.

Trial Participants

Stages 1a and 2a of the trial were conducted in parallel and included 2000 adults 18 to 59 years of age and 60 years of age or older, respectively, who were in good or stable health and did not have coexisting conditions that have been associated with an increased risk of severe Covid-19. After a 3-day safety review by the data and safety monitoring board, stages 1b and 2b were initiated. Those stages additionally included adults of the same respective age ranges who had stable and well-controlled coexisting conditions. The eligibility criteria are provided in the Supplementary Methods section in the Supplementary Appendix, available at NEJM.org. Participants were not excluded on the basis of SARS-CoV-2 infection or serostatus.

Procedures

Details of the trial procedures are provided in the Supplementary Methods section. Participants were randomly assigned in a 1:1 ratio, with the use of randomly permuted blocks, to receive either Ad26.COV2.S or saline placebo. Randomization was conducted with an interactive Web-response system and stratified according to trial site, age group, and the presence or absence of coexisting conditions that have been associated with an increased risk of severe Covid-19.

Vaccine or placebo was administered on day 1. Ad26.COV2.S was supplied in single-use vials at a concentration of 1×10^{11} viral particles per milliliter and was administered at a dose of 5×10^{10}

viral particles as a single intramuscular injection (0.5 ml) by a health care worker who was unaware of the group assignment.

Participants reported Covid-19 symptoms electronically using the Symptoms of Infection with Coronavirus-19 questionnaire (methods described in Fig. S1 in the Supplementary Appendix). Participants and trial staff obtained nasal swabs, which were tested with the use of a Food and Drug Administration (FDA) Emergency Use Authorization reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay for SARS-CoV-2 at a local laboratory and subsequently confirmed centrally (m-2000 SARS-CoV-2 real-time RT-PCR, Abbott). Seropositivity for SARS-CoV-2 was evaluated by means of a SARS-CoV-2 nucleocapsid (N) immunoassay (Elecsys, Roche) at trial entry and on days 29 and 71. Assays were performed according to the manufacturers' protocols.

Primary and key secondary efficacy evaluations were based on centrally confirmed cases of Covid-19. Owing to the high incidence of Covid-19 and the time taken for central confirmation, not all cases had been centrally confirmed at the time of the primary analysis. A supplementary analysis of RT-PCR–positive cases from all sources, whether centrally confirmed or not, was therefore performed for subgroups, hospitalizations, and deaths.

SAFETY ASSESSMENTS

Serious adverse events and adverse events leading to withdrawal from the trial are being recorded throughout the trial. In a safety subpopulation comprising approximately 6000 participants (see below), data on solicited local and systemic adverse events were recorded in an electronic diary for 7 days after administration and unsolicited adverse events for 28 days after administration.

EFFICACY ASSESSMENTS

The two primary end points were the efficacy of the Ad26.COV2.S vaccine against the first occurrence of centrally confirmed moderate to severe–critical Covid-19 with an onset at least 14 days after administration and at least 28 days after administration in the per-protocol population (see below). All the potential cases of severe–critical Covid-19 and cases of moderate Covid-19 with at least three signs or symptoms were classified as being severe–critical by an independent Clinical Severity Adjudication Committee whose members were unaware of the group assignments. This committee adjudicated cases on the basis of clinical judgment (e.g., a single low oxygen-saturation measurement was not classified as indicating severe Covid-19 unless other clinical findings were consistent with a severe classification). The case definitions for Covid-19 and the protocol-defined secondary and exploratory end points are described in the Supplementary Appendix.

STATISTICAL ANALYSIS

The full analysis set included all the participants who underwent randomization and received a dose of trial vaccine or placebo. The per-protocol population comprised participants who received a dose of trial vaccine or placebo, were seronegative or had an unknown serostatus at the time that the vaccine or placebo was administered, and had no protocol deviations that were likely to affect vaccine efficacy. Participants who were RT-PCR–positive between days 1 and 14 or between days 1 and 28 were excluded from the analysis of cases with an onset at least 14 days after administration and at least 28 days after administration, respectively. The per-protocol population was the main population for the efficacy analyses. Safety analyses were conducted in the full analysis set, including the safety subpopulation.

The null hypothesis was that the efficacy of Ad26.COV2.S would be no higher than 30% for each primary end point, as evaluated with a truncated sequential probability ratio test[15,16] at a one-sided significance level of 0.025. The sample size was reduced from 60,000 to approximately 40,000 on the basis of the high incidence of Covid-19 during the trial. The primary analysis was triggered on a positive recommendation from the data and safety monitoring board, after the FDA-specified median 8-week follow-up was reached and prespecified data requirements were met.

If the null hypothesis was rejected for both primary end points, secondary objectives were evaluated against a null hypothesis that used a lower limit of vaccine efficacy of more than 0% with prespecified multiplicity adjustments for familywise type I error control (Fig. S2). Exact Poisson regression[17] was used for the analysis of vaccine efficacy and the associated confidence interval calculations, with accounting for follow-up time. The cumulative incidence over time was

estimated with the use of Kaplan–Meier methods to evaluate the onset of vaccine efficacy and vaccine efficacy over time. Participants had their data censored at the end of their follow-up.

The frequency of serious adverse events was tabulated in the full analysis set. The frequency and severity of solicited and unsolicited adverse events were tabulated in the safety subpopulation.

RESULTS

PARTICIPANTS

The trial began enrollment on September 21, 2020, and the data-cutoff date for the present analysis was January 22, 2021. A total of 44,325 participants underwent randomization, of whom 43,783 received vaccine or placebo; the per-protocol population included 39,321 SARS-CoV-2–negative participants, of whom 19,630 received Ad26.COV2.S and 19,691 received placebo (Fig. S3). The demographic characteristics and coexisting conditions of the participants at baseline were balanced across the two groups (Tables 1 and S4). A total of 9.6% of the participants were SARS-CoV-2–seropositive at baseline. The median follow-up was 58 days (range, 1 to 124), and 55% of participants had at least 8 weeks of follow-up; later and slower recruitment of participants 60 years of age or older with coexisting conditions resulted in a shorter duration of follow-up in this subgroup (Table S5).

SAFETY

The safety subpopulation included 3356 participants in the vaccine group and 3380 in the placebo group. During the 7-day period after the administration of vaccine or placebo, more solicited adverse events were reported by Ad26.COV2.S recipients than by placebo recipients and by participants 18 to 59 years of age than by those 60 years of age or older (Fig. 1). In the vaccine group, injection-site pain was the most common local reaction (in 48.6% of the participants); the most common systemic reactions were headache (in 38.9%), fatigue (in 38.2%), myalgia (in 33.2%), and nausea (in 14.2%).

The adverse events of at least grade 3 that were considered by the investigators to be possibly related to Ad26.COV2.S or placebo are listed in Table S6. Serious adverse events, excluding those related to Covid-19, were reported by 83 of 21,895 vaccine recipients (0.4%) and by 96 of 21,888 placebo recipients (0.4%). Seven serious adverse events were considered by the investigators to be related to vaccination in the Ad26.COV2.S group (Table S7).

A numeric imbalance was observed for venous thromboembolic events (11 in the vaccine group vs. 3 in the placebo group). Most of these participants had underlying medical conditions and predisposing factors that might have contributed to these events (Table S8). Imbalances were also observed with regard to seizure (which occurred in 4 participants in the vaccine group vs. 1 in the placebo group) and tinnitus (in 6 vs. 0). A causal relationship between these events and Ad26.COV2.S cannot be determined. These events will be monitored in the post-marketing setting.

Three deaths were reported in the vaccine group and 16 in the placebo group, all of which were considered by the investigators to be unrelated to the trial intervention (Table S7). No deaths related to Covid-19 were reported in the vaccine group, whereas 5 deaths related to Covid-19 were reported in the placebo group. Transverse sinus thrombosis with cerebral hemorrhage and a case of the Guillain–Barré syndrome were each seen in 1 vaccine recipient.

EFFICACY

In the per-protocol at-risk population, 468 centrally confirmed cases of symptomatic Covid-19 with an onset at least 14 days after administration were observed, of which 464 were moderate to severe–critical (116 cases in the vaccine group vs. 348 in the placebo group), which indicated vaccine efficacy of 66.9% (adjusted 95% confidence interval [CI], 59.0 to 73.4) (Table 2). In terms of the primary end point of disease onset at least 28 days after administration, 66 cases of moderate to severe–critical Covid-19 in the vaccine group and 193 cases in the placebo group were observed, which indicated vaccine efficacy of 66.1% (adjusted 95% CI, 55.0 to 74.8) (Table 2).

The cumulative incidence of the first occurrence of moderate to severe–critical Covid-19 diverged between the two trial groups at approximately 14 days after the administration of vaccine or placebo, which indicates an early onset of protection with the vaccine (Fig. 2A). Fewer cases in the vaccine group were observed after day 14 while cases continued to accrue in the placebo group, which led to increasing vaccine efficacy over time (Fig. S4A). Efficacy against

Table 1. Characteristics of the Trial Participants at Baseline (Full Analysis Set).*

Characteristic	Ad26.COV2.S (N = 21,895)	Placebo (N = 21,888)	Total (N = 43,783)
Age			
Median (range) — yr	52 (18–100)	52 (18–94)	52 (18–100)
Distribution — no. (%)			
18–59 yr	14,564 (66.5)	14,547 (66.5)	29,111 (66.5)
≥60 yr	7,331 (33.5)	7,341 (33.5)	14,672 (33.5)
Sex — no. (%)			
Female	9,820 (44.9)	9,902 (45.2)	19,722 (45.0)
Male	12,071 (55.1)	11,982 (54.7)	24,053 (54.9)
Nonbinary	2 (<0.1)	4 (<0.1)	6 (<0.1)
Unknown	2 (<0.1)	0	2 (<0.1)
Race or ethnic group — no. (%)†			
American Indian or Alaskan Native	92 (0.4)	95 (0.4)	187 (0.4)
Indigenous South American	1,991 (9.1)	1,965 (9.0)	3,956 (9.0)
Asian	743 (3.4)	687 (3.1)	1,430 (3.3)
Black	4,251 (19.4)	4,264 (19.5)	8,515 (19.4)
Native Hawaiian or other Pacific Islander	58 (0.3)	48 (0.2)	106 (0.2)
White	12,858 (58.7)	12,838 (58.7)	25,696 (58.7)
Multiracial	1,204 (5.5)	1,245 (5.7)	2,449 (5.6)
Not reported, unknown, or missing	698 (3.2)	746 (3.4)	1,444 (3.3)
Hispanic ethnic group — no. (%)†			
Hispanic	9,874 (45.1)	9,963 (45.5)	19,837 (45.3)
Non-Hispanic	11,472 (52.4)	11,362 (51.9)	22,834 (52.2)
Not reported, unknown, or missing	549 (2.5)	563 (2.6)	1,112 (2.5)
Country or region — no. (%)			
Latin America	8,954 (40.9)	8,951 (40.9)	17,905 (40.9)
Argentina	1,498 (6.8)	1,498 (6.8)	2,996 (6.8)
Brazil	3,644 (16.6)	3,634 (16.6)	7,278 (16.6)
Chile	563 (2.6)	570 (2.6)	1,133 (2.6)
Colombia	2,125 (9.7)	2,123 (9.7)	4,248 (9.7)
Mexico	238 (1.1)	241 (1.1)	479 (1.1)
Peru	886 (4.0)	885 (4.0)	1,771 (4.0)
South Africa	3,286 (15.0)	3,290 (15.0)	6,576 (15.0)
United States	9,655 (44.1)	9,647 (44.1)	19,302 (44.1)
SARS-CoV-2 serostatus — no. (%)			
Positive	2,151 (9.8)	2,066 (9.4)	4,217 (9.6)
Negative	19,104 (87.3)	19,191 (87.7)	38,295 (87.5)
Missing	640 (2.9)	631 (2.9)	1,271 (2.9)
Body-mass index‡			
Median	27.0	27.0	27.0
≥30 — no./total no. (%)	6264/21,871 (28.6)	6217/21,853 (28.4)	12,481/43,724 (28.5)
≥1 Coexisting condition — no. (%)	8,936 (40.8)	8,922 (40.8)	17,858 (40.8)

* The full analysis set included all the participants who underwent randomization and received a dose of Ad26.COV2.S vaccine or placebo. Percentages may not total 100 because of rounding. SARS-CoV-2 denotes severe acute respiratory coronavirus 2.

† Race and ethnic group were reported by the participants. American Indian or Alaskan Native was reported only by participants residing in the United States.

‡ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. A BMI of 30 or higher indicates obesity.

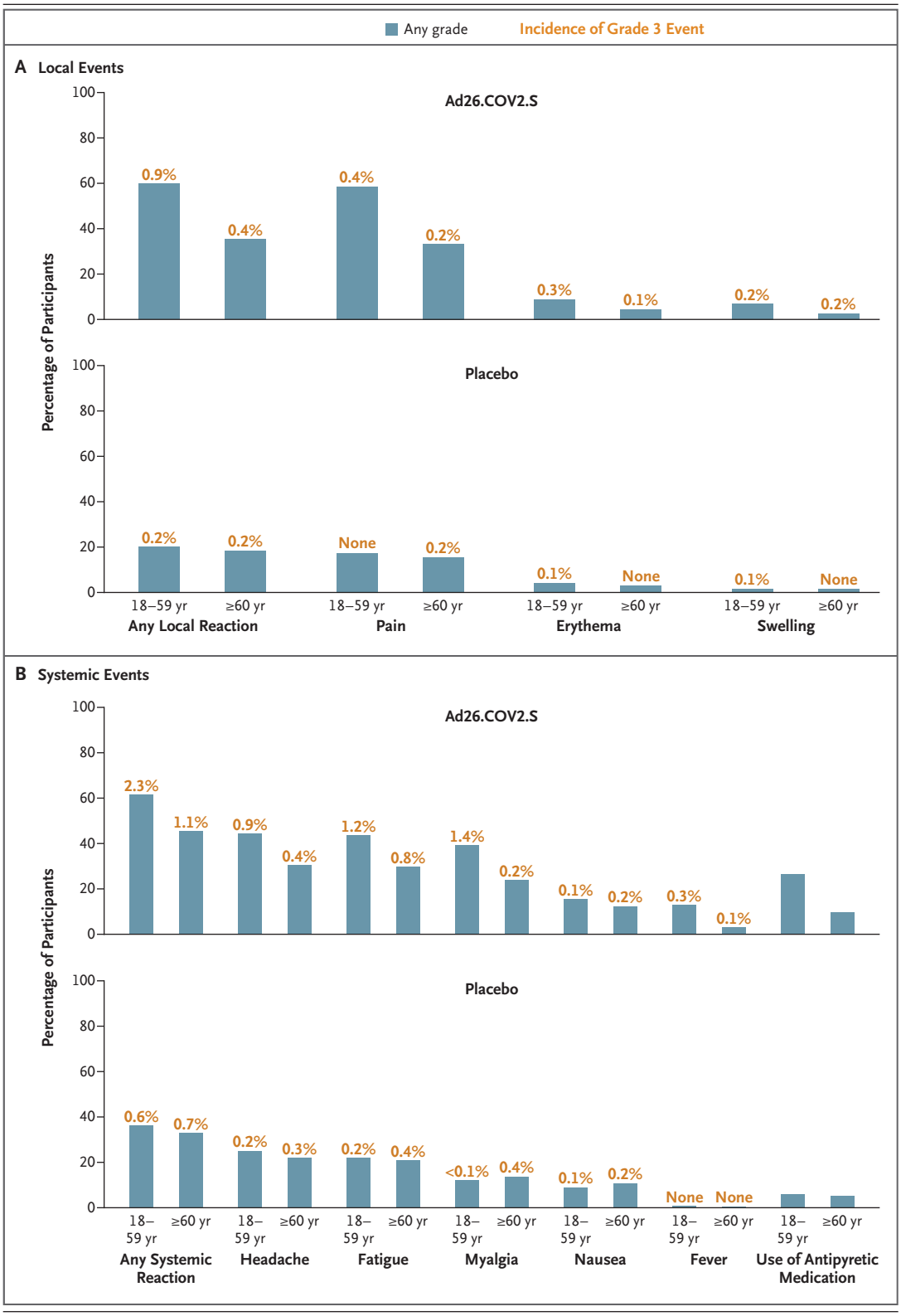


Figure 1 (facing page). Solicited Local and Systemic Adverse Events Reported within 7 days after the Administration of Vaccine or Placebo (Safety Subpopulation).

Most solicited local and systemic adverse events occurred within 1 to 2 days after the administration of vaccine or placebo and had a median duration of 1 to 2 days. No grade 4 local or systemic adverse events were reported. There were no local or systemic reactogenicity differences between participants who were seronegative at baseline and those who were seropositive (data not shown). Pain was categorized as grade 1 (mild; does not interfere with activity), grade 2 (moderate; requires modification of activity or involves discomfort with movement), grade 3 (severe; inability to perform usual activities), or grade 4 (potentially life-threatening; hospitalization or inability to perform basic self-care). Erythema and swelling were categorized as grade 1 (mild; 25 to 50 mm), grade 2 (moderate; 51 to 100 mm), grade 3 (severe; >100 mm), or grade 4 (potentially life-threatening; necrosis or leading to hospitalization). Systemic events were categorized as grade 1 (mild; minimal symptoms), grade 2 (moderate; notable symptoms not resulting in loss of work or school time), grade 3 (severe; incapacitating symptoms resulting in loss of work or school time), or grade 4 (life-threatening; hospitalization or inability to perform basic self-care). Fever was defined as grade 1 (mild; ≥38.0 to 38.4°C), grade 2 (moderate; ≥38.5 to 38.9°C), grade 3 (severe; ≥39.0 to 40.0°C), or grade 4 (potentially life-threatening; >40°C).

disease with an onset at least 28 days after administration was similar across age groups, but efficacy against disease with an onset 14 days after administration was higher among older participants than among younger participants (Table 2). This discrepancy probably resulted from differences in follow-up duration or from smaller sample sizes in subgroups. The number of primary end-point cases was similar to the number of cases of symptomatic Covid-19 as defined according to the FDA harmonized definition (Table 2); thus, the primary end-point analyses captured most of the cases of symptomatic Covid-19. Estimates of vaccine efficacy in the analyses of the two primary end points and the secondary end points of centrally confirmed cases differed by less than 2 percentage points from the estimates in analyses of positive cases from all sources, and the confidence intervals were similar (Tables 2 and 3). Vaccine-efficacy estimates in the full analysis set were generally lower than those in the per-protocol population because the estimates included cases that occurred at or after 1 day after administration, when immunity was building (Table S9).

With regard to severe–critical Covid-19, vaccine efficacy was 76.7% (adjusted 95% CI, 54.6 to 89.1) against disease with onset at least 14 days after administration and 85.4% (adjusted 95% CI, 54.2 to 96.9) against disease with onset at least 28 days after administration (Table 2). The cumulative-incidence curves began to separate approximately 7 days after administration; vaccine efficacy increased with longer follow-up and was 92.4% after day 42 (post hoc calculation) (Figs. 2B and S4B).

The analysis of vaccine efficacy against asymptomatic infection included all the participants with a newly positive N-immunoassay result at day 71 (i.e., those who had been seronegative or had no result available at day 29 and who were seropositive at day 71). Only 2650 participants had an N-immunoassay result available at day 71, and therefore only a preliminary analysis could be performed. A total of 18 asymptomatic infections were identified in the vaccine group and 50 in the placebo group (vaccine efficacy, 65.5%; 95% CI, 39.9 to 81.1).

Vaccine efficacy against Covid-19 involving medical intervention ranged from 75.0 to 100.0% (Table S10). Two cases of Covid-19 with onset at least 14 days after administration in the Ad26.COV2.S group and 29 such cases in the placebo group led to hospitalization (vaccine efficacy, 93.1%; 95% CI, 72.7 to 99.2) (Fig. S5). No hospitalizations for cases with an onset at least 28 days after administration occurred in the vaccine group, as compared with 16 hospitalizations in the placebo group (vaccine efficacy, 100%; 95% CI, 74.3 to 100.0).

Participants with moderate Covid-19 who had received Ad26.COV2.S most frequently reported 4 to 6 symptoms, as compared with 7 to 9 symptoms in participants who had received placebo (Fig. S6). The total mean symptom-severity score as reported on the Symptoms of Infection with Coronavirus-19 questionnaire was 24% (95% CI, –1 to 46) lower among vaccine recipients than among placebo recipients at day 1 after symptom onset, 47% (95% CI, 23 to 66) lower at day 7 after symptom onset, and 53% (95% CI, 0 to 81) lower at day 14 after symptom onset among partici-

Table 2. Vaccine Efficacy against Covid-19 with Onset at Least 14 Days and at Least 28 Days after the Administration of Vaccine or Placebo (Per-Protocol at-Risk Population).*

Variable	≥14 Days after Administration†					≥28 Days after Administration‡				
	Ad26.COV2.S (N=19,514)		Placebo (N=19,544)		Vaccine Efficacy (95% CI)	Ad26.COV2.S (N=19,306)		Placebo (N=19,178)		Vaccine Efficacy (95% CI)
	no. of cases	*person-yr*	*no. of cases*	*person-yr*	%	*no. of cases*	*person-yr*	*no of cases*	*person-yr*	%
Moderate to severe–critical Covid-19	116	3116.6	348	3096.1	66.9 (59.0–73.4)	66	3102.0	193	3070.7	66.1 (55.0–74.8)
18–59 yr	95	2106.8	260	2095.0	63.7 (53.9–71.6)	52	2097.6	152	2077.0	66.1 (53.3–75.8)
≥60 yr	21	1009.8	88	1001.2	76.3 (61.6–86.0)	14	1004.4	41	993.6	66.2 (36.7–83.0)
Symptomatic Covid-19 of any severity	117	3116.5	351	3095.9	66.9 (59.1–73.4)	66	3102.0	195	3070.5	66.5 (55.5–75.1)
Mild	1	3116.5	3	3095.9	NC§	0	3102.0	2	3070.5	NC§
Moderate	102	3116.6	288	3096.1	64.8 (55.8–72.2)	61	3102.0	159	3070.7	62.0 (48.7–72.2)
Severe–critical	14	3125.1	60	3122.0	76.7 (54.6–89.1)	5	3106.2	34	3082.6	85.4 (54.2–96.9)
Severity-adjusted symptomatic Covid-19¶	117	3116.5	351	3095.9	68.1 (60.3–74.3)	66	3102.0	195	3070.5	69.0 (56.7–77.6)
18–59 yr	95	2106.8	260	2095.0	65.8 (56.2–73.1)	52	2097.6	152	2077.0	69.3 (57.4–77.7)
≥60 yr	22	1009.6	91	1001.0	74.5 (57.9–84.3)	14	1004.4	43	993.5	67.9 (38.2–82.8)
Moderate to severe–critical Covid-19, including noncentrally confirmed cases	173	3113.9	509	3089.1	66.3 (59.9–71.8)	113	3100.3	324	3065.9	65.5 (57.2–72.4)
Covid-19, according to FDA harmonized definition‖	114	3116.6	345	3,096.3	67.2 (59.3–73.7)	65	3102.0	193	3070.6	66.7 (55.6–75.2)
Moderate to severe–critical Covid-19, according to Cox proportional-hazards model**	116	3116.6	348	3,096.1	66.9 (59.1–73.2)	66	3102.0	193	3070.7	66.2 (55.3–74.4)

* All cases of coronavirus disease 2019 (Covid-19) were centrally confirmed unless stated otherwise and occurred in participants who had been seronegative at baseline and negative on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) testing before 14 or 28 days after the administration of vaccine or placebo, for the respective end points, and were therefore at risk for Covid-19. The follow-up time for each participant was defined as the time from the administration of vaccine or placebo to the onset of Covid-19 or the last available trial measurement (January 22, 2021). Adjusted 95% confidence intervals are shown for moderate and severe–critical Covid-19, severe–critical Covid-19, severity-adjusted Covid-19, and moderate to severe–critical Covid-19, including non–centrally confirmed cases; unadjusted 95% confidence intervals are shown for other end points. The adjusted confidence interval was calculated with implementation of type I error control for multiple testing. Adjusted confidence intervals are presented for the end points that were prespecified for inferential evaluation at the primary analysis and on reaching the associated minimal required number of cases for that end point. Mild cases of Covid-19 were defined as a positive result on RT-PCR testing and the presence of at least one of the following symptoms: fever (body temperature, ≥38.0°C), sore throat, malaise, headache, myalgia, gastrointestinal symptoms,

cough, chest congestion, runny nose, wheezing, skin rash, eye irritation or discharge, chills, loss of taste or smell, red or bruised looking feet or toes, or shaking chills or rigors. Moderate cases were defined as a positive RT-PCR test and either the presence of at least two of the following symptoms: fever (≥38.0°C), heart rate of at least 90 beats per minute, shaking chills or rigors, sore throat, cough, malaise, headache, myalgia, gastrointestinal symptoms, loss of taste or smell, or red or bruised-looking feet or toes; or the presence at least one of the following symptoms: respiratory rate of at least 20 breaths per minute, abnormal oxygen saturation (but >93% while the patient was breathing ambient air at sea level), clinical or radiologic evidence of pneumonia, radiologic evidence of deep-vein thrombosis, or shortness of breath or difficulty breathing. Severe–critical cases were defined as a positive RT-PCR test and the presence of at least one of the following features: clinical signs at rest that were indicative of severe systemic illness (respiratory rate of ≥30 breaths per minute, heart rate of ≥125 beats per minute, oxygen saturation of ≤93% while the patient was breathing ambient air at sea level, or partial pressure of oxygen divided by the fraction of inspired oxygen, <300 mm Hg); respiratory failure (defined as the use of high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation); shock; clinically meaningful acute renal, hepatic, or neurologic dysfunction; intensive care unit admission; or death.

† The at-risk population for this analysis excluded participants who were RT-PCR–positive between days 1 and 14 after the administration of vaccine or placebo.

‡ The at-risk population for this analysis excluded participants who were RT-PCR–positive between days 1 and 28 after the administration of vaccine or placebo.

§ The vaccine efficacy was not calculated (NC) if fewer than 6 cases were observed for an end point.

¶ Shown is the weighted version of the estimates of vaccine efficacy against mild, moderate, and severe–critical Covid-19.[18]

‖ The Food and Drug Administration (FDA) harmonized definition of Covid-19 was defined as a positive RT-PCR test and the presence of Covid-19 symptoms consistent with the FDA harmonized definition at the time that the protocol was written: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, or diarrhea.

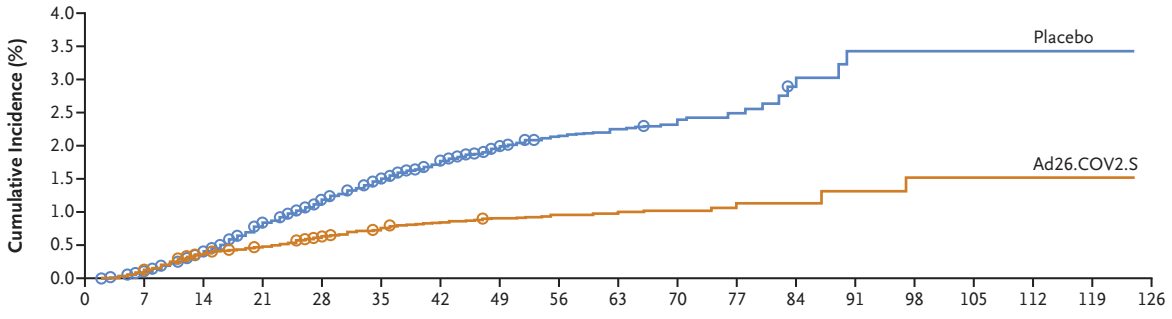
** A supportive analysis with the use of a Cox proportional-hazards regression model of the time to moderate to severe–critical Covid-19 was used to estimate vaccine efficacy.

pants with an onset of moderate illness at least 28 days after administration (Fig. S1).

The estimates of vaccine efficacy against severe–critical disease were consistently high across countries that had sufficient cases for analysis (Table 3). On the basis of interim sequencing data from 512 unique RT-PCR–positive samples obtained from 714 participants (71.7%) with SARS-CoV-2 infection, the reference sequence (Wuhan-Hu-1 including the D614G mutation) was detected predominantly in the United States (190 of 197 sequences [96.4%]) and the 20H/501Y.V2 variant (also called B.1.351) was detected predominantly in South Africa (86 of 91 sequences [94.5%]), whereas in Brazil, the reference sequence was detected in 38 of 124 sequences (30.6%) and the reference sequence with the E484K mutation (P.2 lineage) was detected in 86 of 124 sequences (69.4%). Despite the high prevalence of the 20H/501Y.V2 variant in South Africa and in Covid-19 cases in the trial, vaccine efficacy was maintained (52.0% against moderate to severe–critical disease and 73.1% against severe–critical disease with onset ≥14 days after administration; 64.0% against moderate to severe–critical disease and 81.7% against severe–critical disease with onset at ≥28 days after administration) (Fig. 2C and Table 3). In South Africa, no hospitalizations of participants with an onset of Covid-19 at least 28 days after administration occurred in the vaccine group, as compared with 6 hospitalizations in the placebo group. All five Covid-19–related deaths in the trial occurred in the placebo group in South Africa.

No meaningful differences in vaccine efficacy were observed among subgroups defined according to sex, race, or ethnic group (Fig. S7 and Table S11). A lower point estimate of vaccine efficacy was observed among participants 60 years of age or older with coexisting conditions in the analysis of cases with onset at least 28 days after administration (15 cases of moderate to severe–critical Covid-19 among vaccine recipients vs. 26 cases among placebo recipients) but not in the analysis of cases with onset at least 14 days after administration (22 vs. 63 cases) (Fig. S7). Estimates of efficacy over time that were based on Kaplan–Meier analysis were similar among participants 60 years of age or older with coexisting conditions and those without coexisting conditions (Figs. S4C and S8). Two participants 60 years of age or older with coexisting conditions in the

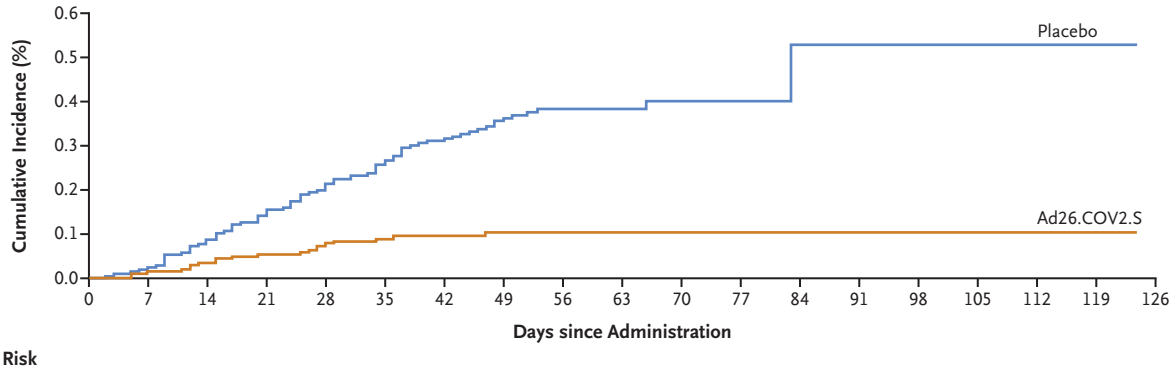
A Moderate to Severe–Critical Cases of Covid-19



No. at Risk																			
Placebo	19,822	19,804	19,745	19,652	19,579	19,488	18,411	14,814	10,823	7740	3876	1439	708	485	482	480	133	27	0
Ad26.COV2.S	19,744	19,725	19,669	19,642	19,612	19,578	18,541	14,909	10,930	7831	3998	1468	713	484	483	482	142	31	0

No. of Cases																			
Placebo	0	22	81	168	237	299	351	387	407	416	423	425	430	432	432	432	432	432	432
Ad26.COV2.S	0	27	76	96	126	151	168	178	184	188	189	191	191	192	193	193	193	193	193

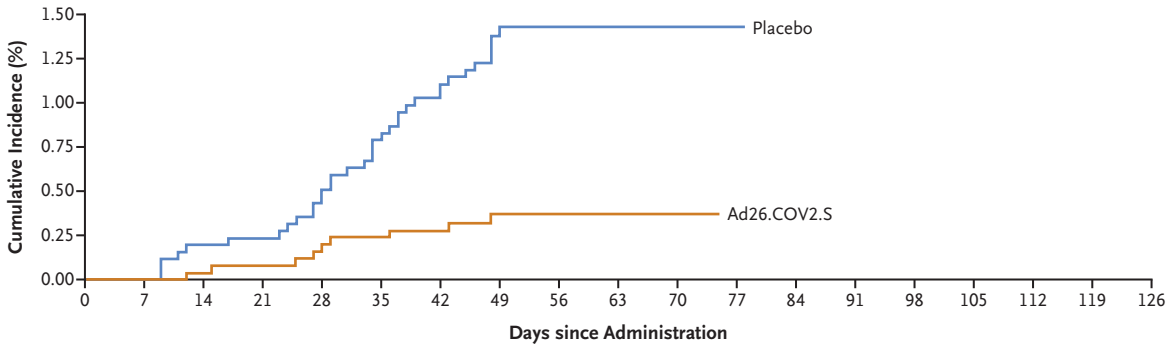
B Severe–Critical Cases of Covid-19



No. at Risk																			
Placebo	19,822	19,817	19,799	19,779	19,760	19,725	18,682	15,088	11,069	7939	3995	1485	732	500	497	495	137	29	0
Ad26.COV2.S	19,744	19,741	19,734	19,725	19,718	19,705	18,685	15,043	11,046	7919	4039	1481	720	490	490	489	146	31	0

No. of Cases																			
Placebo	0	5	18	32	44	55	65	73	76	76	77	77	78	78	78	78	78	78	78
Ad26.COV2.S	0	3	7	11	16	18	20	21	21	21	21	21	21	21	21	21	21	21	21

C Severe–Critical Cases of Covid-19 in South Africa



No. at Risk																			
Placebo	2536	2536	2531	2528	2521	2510	2502	1963	1283	712	143	2	0	0	0	0	0	0	0
Ad26.COV2.S	2504	2504	2503	2501	2497	2495	2494	1941	1284	694	157	0	0	0	0	0	0	0	0

No. of Cases																			
Placebo	0	0	5	6	13	21	28	35	35	35	35	35	35	35	35	35	35	35	35
Ad26.COV2.S	0	0	1	2	5	6	7	9	9	9	9	9	9	9	9	9	9	9	9

Figure 2 (facing page). Cumulative Incidence of Covid-19 with Onset at Least 1 Day after Vaccination and Vaccine Efficacy over Time.

Panel A shows the cumulative incidence of moderate to severe–critical cases of coronavirus disease 2019 (Covid-19); circles indicate severe–critical cases. Panel B shows the cumulative incidence of severe–critical cases. Cases included in the analyses in Panels A and B were centrally confirmed cases in the full analysis set among participants who were seronegative at baseline. Panel C shows the cumulative incidence of severe–critical cases in South Africa among participants who were seronegative at baseline; these cases were those that were positive on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) testing from all sources, whether centrally confirmed or not.

vaccine group were hospitalized, as compared with 11 such participants in the placebo group (vaccine efficacy, 81.6%; 95% CI, 15.8 to 98.0).

DISCUSSION

This international, phase 3 ENSEMBLE trial showed the efficacy of a single dose of the Ad26.COV2.S vaccine in preventing Covid-19. Efficacy against moderate to severe–critical Covid-19 was 67% against disease with onset at least 14 days after administration and 66% against disease with onset 28 days after administration. Because the number of primary end-point cases was similar to the number of cases according to the FDA harmonized definition, this estimate essentially captures most of the cases of symptomatic Covid-19. Higher efficacy against severe–critical Covid-19 was observed, with vaccine efficacy of 77% against disease with onset at least 14 days after administration and 85% against disease with onset at least 28 days after administration.

The onset of efficacy was evident as of 14 days after administration for moderate to severe–critical disease and as of 7 days after administration for severe–critical disease. Efficacy continued to increase through approximately 8 weeks after administration, especially for severe–critical Covid-19. 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, a finding that is consistent with the persistence of humoral immunity that was observed in a phase 1–2a trial.[9]

Efficacy against severe–critical Covid-19 was consistently high overall and in individual countries that had sufficient cases for analysis, which is particularly important because severe disease has the greatest effect on individual persons and health care systems.[19] Efficacy against Covid-19 involving hospitalization was 93% with regard to onset at least 14 days after administration (2 cases in the vaccine group and 29 in the placebo group) and 100% with regard to onset at least 28 days after administration (no hospitalizations in the vaccine group and 16 in the placebo group). Although hospitalization can be influenced by local practice and resource availability, all the hospitalizations that were reported were justified by clear clinical findings and were consistent across countries. Moreover, identical management practices would have applied to the Ad26.COV2.S group and the placebo group in each country. Five deaths that were related to Covid-19 occurred in the placebo group, but there were no such deaths in the vaccine group. The reduction in the incidence of death and the high efficacy against hospitalization are expected to substantially reduce the effect of this disease on individual persons and dramatically decrease the burden on health care systems.

Vaccine recipients with breakthrough Covid-19 reported fewer and less severe symptoms than did placebo recipients with Covid-19, which suggests that illness is milder after vaccination. The data are consistent with studies reporting higher efficacy of the influenza vaccine against more severe influenza[20-22] and the attenuation of influenza among vaccinees.[23-25] A preliminary analysis indicated that Ad26.COV2.S provided at least 66% protection against serologically confirmed asymptomatic infection with SARS-CoV-2. The effect on the incidence of symptomatic and asymptomatic SARS-CoV-2 infection by the vaccine suggests that it might be useful in reducing community-wide transmission.

New SARS-CoV-2 virus lineages have emerged, with mutations in the N-terminal and receptor-binding domains of the spike protein that are known targets for neutralizing antibodies; in particular, the E484K mutation is associated with reduced neutralization sensitivity.[26-31] Of main concern are variants that were first identified in Brazil, South Africa, and the United Kingdom.[2-4] In our trial, 95% of the Covid-19 cases in South Africa in which SARS-CoV-2 was sequenced were caused by the 20H/501Y.V2 variant, whereas a

Table 3. Vaccine Efficacy against Covid-19 with Onset at Least 14 Days and at Least 28 Days after Administration of Vaccine or Placebo, According to Country (Per-Protocol at-Risk Population).*

Variable	≥14 Days after Administration†					≥28 Days after Administration‡				
	Ad26.COV2.S		Placebo		Vaccine Efficacy (95% CI)	Ad26.COV2.S		Placebo		Vaccine Efficacy (95% CI)
	no.	*person-yr*	*no.*	*person-yr*	%	*no.*	*person-yr*	*no.*	*person-yr*	%
Worldwide										
No. of participants	19,514		19,544			19,306		19,178		
Moderate to severe–critical Covid-19	173	3113.9	509	3089.1	66.3 (59.9 to 71.8)	113	3100.3	324	3065.9	65.5 (57.2 to 72.4)
Severe–critical Covid-19	19	3124.7	80	3121.0	76.3 (57.9 to 87.5)	8	3106.0	48	3082.0	83.5 (54.2 to 96.9)
United States										
No. of participants	9,119		9,086			8,958		8,835		
Moderate to severe–critical Covid-19	51	1414.0	196	1391.3	74.4 (65.0 to 81.6)	32	1403.4	112	1375.6	72.0 (58.2 to 81.7)
Severe–critical Covid-19	4	1417.2	18	1404.8	78.0 (33.1 to 94.6)	1	1405.2	7	1382.2	85.9 (−9.4 to 99.7)
Brazil										
No. of participants	3,370		3,355			3,354		3,312		
Moderate to severe–critical Covid-19	39	555.7	114	548.8	66.2 (51.0 to 77.1)	24	554.8	74	546.1	68.1 (48.8 to 80.7)
Severe–critical Covid-19	2	558.9	11	556.8	81.9 (17.0 to 98.1)	1	556.2	8	549.8	87.6 (7.8 to 99.7)
South Africa										
No. of participants	2,473		2,496			2,449		2,463		
Moderate to severe–critical Covid-19	43	377.6	90	379.2	52.0 (30.3 to 67.4)	23	376.1	64	376.9	64.0 (41.2 to 78.7)
Severe–critical Covid-19	8	380.2	30	382.9	73.1 (40.0 to 89.4)	4	377.0	22	379.0	81.7 (46.2 to 95.4)

* All cases of Covid-19 occurred in participants who had been seronegative at baseline and RT-PCR–negative before 14 or 28 days after the administration of vaccine or placebo, for the respective end points, and were therefore at risk for Covid-19; these participants were positive on RT-PCR testing from all sources. Adjusted 95% confidence intervals are shown for Covid-19 cases worldwide; unadjusted 95% confidence intervals are shown for country-specific end points. The adjusted confidence interval implements type I error control for multiple testing.
† The at-risk population for this analysis excluded participants who were RT-PCR–positive between days 1 and 14 after the administration of vaccine or placebo.
‡ The at-risk population for this analysis excluded participants who were RT-PCR–positive between days 1 and 28 after the administration of vaccine or placebo.

variant from the P.2 lineage carrying the E484K mutation was identified in 69% of the cases in Brazil with a sequenced sample. However, despite the high prevalence of SARS-CoV-2 variants of concern, vaccine efficacy remained high. This finding shows that a Covid-19 vaccine that was based on the original Wuhan-Hu-1 strain can elicit cross-protective efficacy against new variants in South Africa and Brazil. Nonneutralizing antibodies against SARS-CoV-2 variants are probably preserved because they are not limited to the N-terminal or receptor-binding domains, where most mutations occur. Antibodies with Fc-mediated functions are induced by Ad26.COV2.S against SARS-CoV-2 in humans,[32] and these Fc functional antibodies show no decrease in potency against new variants (personal communication: G. Alter and D. Barouch). In addition, CD8+ T-cell responses to the SARS-CoV-2 spike protein were seen in a phase 1–2a trial.[9] T-cell epitopes were shown to be conserved between SARS-CoV-2 variants according to immunoinformatics analyses.[33-35] These factors might contribute to the high efficacy against severe–critical disease, hospitalization, and death in South Africa, where the relatively neutralization-resistant 20H/501Y.V2 variant predominates.[26,36]

Efficacy against symptomatic infection was similar among younger and older participants and among participants with coexisting conditions and those without coexisting conditions. A subgroup analysis involving participants 60 years of age or older showed that vaccine efficacy against symptomatic disease with onset at least 14 days after administration was similar in subgroups defined according to the presence or absence of coexisting conditions. With regard to onset at least 28 days after administration, vaccine efficacy appeared lower among participants with coexisting conditions than among those without coexisting conditions. This finding can be attributed to imprecision owing to fewer cases and shorter follow-up in this subgroup. Furthermore, Kaplan–Meier curves indicated that the cumulative incidence of cases among vaccine recipients 60 years of age or older with coexisting conditions was similar to that in the overall trial population, which suggests a similar vaccine efficacy. Vaccine efficacy against hospitalization among vaccine recipients 60 years of age or older with coexisting conditions was 82%, a finding consistent with this result.

This trial confirmed the findings from a phase 1–2a trial[9] showing that Ad26.COV2.S had an acceptable safety and reactogenicity profile. Reactogenicity to Ad26.COV2.S was transient, was lower in older participants than in younger participants, and resolved quickly. Severe reactogenicity (grade ≥3) was uncommon, and serious adverse events were rare. Data from the current trial are supported by long-term and robust safety data on the Ad26 platform.[10-12]

A key strength of this trial is that it showed vaccine efficacy in an ethnically and geographically diverse population, including participants in regions with emerging SARS-CoV-2 variants, as well as in participants with coexisting conditions that have been associated with an increased risk of severe Covid-19. A limitation of the trial is the relatively short follow-up, which was necessitated, as in other Covid-19 vaccine trials, by the urgent need for vaccine. The data do not suggest a waning of protection. Long-term unblinded follow-up is planned to compare results in initial Ad26.COV2.S recipients with those in placebo recipients who are expected to receive Ad26.COV2.S after a protocol amendment has been approved.

This trial was conducted during a time of an extraordinarily high incidence of SARS-CoV-2 infection. Lower vaccine efficacy has been associated with a higher incidence of disease.[37-39] This situation, combined with the emergence of viral variants, precludes the comparison of vaccine trials. In this trial, we robustly field-tested a simple regimen under high attack-rate conditions on three continents and consistently found early and increasing protection from severe disease.

In this trial, we found that a single dose of Ad26.COV2.S protected against symptomatic Covid-19 and was particularly efficacious against severe–critical disease (including hospitalization and death), including in countries where variants that are considered to be relatively resistant to antibody neutralization predominate. Safety appeared to be similar to that seen in previous phase 3 trials of Covid-19 vaccines. The single-dose schedule and favorable storage conditions of this vaccine provide major advantages in its deployment and effect worldwide.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

The authors' full names and academic degrees are as follows: Jerald Sadoff, M.D., Glenda Gray, M.B., B.Ch., An Vandebosch, Ph.D., Vicky Cárdenas, Ph.D., Georgi Shukarev, M.D., Beatriz Grinsztejn, M.D., Paul A. Goepfert, M.D., Carla Truyers, Ph.D., Hein Fennema, Ph.D., Bart Spiessens, Ph.D., Kim Offergeld, M.Sc., Gert Scheper, Ph.D., Kimberly L. Taylor, Ph.D., Merlin L. Robb, M.D., John Treanor, M.D., Dan H. Barouch, M.D., Jeffrey Stoddard, M.D., Martin F. Ryser, M.D., Mary A. Marovich, M.D., Kathleen M. Neuzil, M.D., Lawrence Corey, M.D., Nancy Cauwenberghs, Ph.D., Tamzin Tanner, Ph.D., Karin Hardt, Ph.D., Javier Ruiz-Guiñazú, M.D., Mathieu Le Gars, Ph.D., Hanneke Schuitemaker, Ph.D., Johan Van Hoof, M.D., Frank Struyf, M.D., and Macaya Douoguih, M.D.

The authors' affiliations are as follows: Janssen Vaccines and Prevention, Leiden, the Netherlands (J. Sadoff, G. Shukarev, G. Scheper, M.L.G., H.S., J.V.H., M.D.); South African Research Council, Cape Town, South Africa (G.G.); Janssen Research and Development, Beerse, Belgium (A.V., C.T., H.F., B.S., K.O., M.F.R., N.C., T.T., K.H., J.R.G., F.S.); Janssen Research and Development, Spring House, PA (V.C.); Evandro Chagas National Institute of Infectious Diseases–Fiocruz, Rio de Janeiro (B.G.); the University of Alabama at Birmingham, Birmingham (P.A.G.); the National Institute of Allergy and Infectious Diseases, Rockville (K.L.T., M.A.M.), Walter Reed Army Institute of Research, Silver Spring (M.L.R.), and the Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore (K.M.N.) — all in Maryland; Biomedical Advanced Research and Development Authority, Washington, DC (J.T.); the Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center, Boston (D.H.B.); Janssen Research and Development, Raritan, NJ (J. Stoddard); and Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle (L.C.).

REFERENCES

1. Johns Hopkins University Coronavirus Resource Center. COVID-19 dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University. 2021 (https://coronavirus.jhu.edu/map.html).
2. Tegally H, Wilkinson E, Giovanetti M, et al. Emergence and rapid spread of a new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa. December 22, 2020 (https://www.medrxiv.org/content/10.1101/2020.12.21.20248640v1). preprint.
3. Voloch CM, da Silva Francisco R Jr, de Almeida LGP, et al. Genomic characterization of a novel SARS-CoV-2 lineage from Rio de Janeiro, Brazil. J Virol 2021 March 1 (Epub ahead of print).
4. Public Health England. Investigation of novel SARS-CoV-2 variant: variant of concern 202012/01: technical briefing 3. 2021 (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/950823/Variant_of_Concern_VOC_202012_01_Technical_Briefing_3_-_England.pdf).
5. Krammer F. SARS-CoV-2 vaccines in development. Nature 2020;586:516-27.
6. World Health Organization. Draft landscape and tracker of COVID-19 candidate vaccines. April 9, 2021 (https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines).
7. Abbink P, Lemckert AAC, Ewald BA, et al. Comparative seroprevalence and immunogenicity of six rare serotype recombinant adenovirus vaccine vectors from subgroups B and D. J Virol 2007;81:4654-63.
8. Bos R, Rutten L, van der Lubbe JEM, et al. Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 spike immunogen induces potent humoral and cellular immune responses. NPJ Vaccines 2020;5:91.
9. Sadoff J, Le Gars M, Shukarev G, et al. Interim results of a phase 1–2a trial of Ad26.COV2.S Covid-19 vaccine. N Engl J Med. 10.1056/NEJMoa2034201.
10. Barouch DH, Tomaka FL, Wegmann F, et al. Evaluation of a mosaic HIV-1 vaccine in a multicentre, randomised, double-blind, placebo-controlled, phase 1/2a clinical trial (APPROACH) and in rhesus monkeys (NHP 13-19). Lancet 2018;392:232-43.
11. Custers J, Kim D, Leyssen M, et al. Vaccines based on replication incompetent Ad26 viral vectors: standardized template with key considerations for a risk/benefit assessment. Vaccine 2020 October 3 (Epub ahead of print).
12. Williams K, Bastian AR, Feldman RA, et al. Phase 1 safety and immunogenicity study of a respiratory syncytial virus vaccine with an adenovirus 26 vector encoding prefusion F (Ad26.RSV.preF) in adults aged ≥60 years. J Infect Dis 2020;222:979-88.
13. Salisch NC, Stephenson KE, Williams K, et al. A double-blind, randomized, placebo-controlled phase 1 study of Ad26.ZIKV.001, an Ad26-vectored anti-Zika virus vaccine. Ann Intern Med 2021 February 16 (Epub ahead of print).
14. Mercado NB, Zahn R, Wegmann F, et al. Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques. Nature 2020;586:583-8.
15. Dragalin V, Fedorov V, Cheuvart B. Statistical approaches to establishing vaccine safety. Stat Med 2002;21:877-93.
16. Dragalin V, Fedorov V. Multistage designs for vaccine safety studies. J Biopharm Stat 2006;16:539-53.
17. Nauta J. Statistics in clinical vaccine

trials. New York: Springer-Verlag, 2011: 95-7.
18. Mehrotra DV, Janes HE, Fleming TR, et al. Clinical endpoints for evaluating efficacy in COVID-19 vaccine trials. Ann Intern Med 2021;174:221-8.
19. Hodgson SH, Mansatta K, Mallett G, Harris V, Emary KRW, Pollard AJ. What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2. Lancet Infect Dis 2021;21(2):e26-e35.
20. Jain VK, Rivera L, Zaman K, et al. Vaccine for prevention of mild and moderate-to-severe influenza in children. N Engl J Med 2013;369:2481-91.
21. Claeys C, Zaman K, Dbaibo G, et al. Prevention of vaccine-matched and mismatched influenza in children aged 6-35 months: a multinational randomised trial across five influenza seasons. Lancet Child Adolesc Health 2018;2:338-49.
22. Beran J, Reynales H, Poder A, et al. Prevention of influenza during mismatched seasons in older adults with an MF59-adjuvanted quadrivalent influenza vaccine: a randomised, controlled, multicentre, phase 3 efficacy study. Lancet Infect Dis 2021 February 9 (Epub ahead of print).
23. Arriola C, Garg S, Anderson EJ, et al. Influenza vaccination modifies disease severity among community-dwelling adults hospitalized with influenza. Clin Infect Dis 2017;65:1289-97.
24. Castilla J, Godoy P, Domínguez A, et al. Influenza vaccine effectiveness in preventing outpatient, inpatient, and severe cases of laboratory-confirmed influenza. Clin Infect Dis 2013;57:167-75.
25. Deiss RG, Arnold JC, Chen W-J, et al. Vaccine-associated reduction in symptom severity among patients with influenza A/H3N2 disease. Vaccine 2015;33:7160-7.
26. Wibmer CK, Ayres F, Hermanus T, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. Nat Med 2021 March 2 (Epub ahead of print).
27. Weisblum Y, Schmidt F, Zhang F, et al. Escape from neutralizing antibodies by SARS-CoV-2 spike protein variants. Elife 2020;9:e61312.
28. Zhou D, Dejnirattisai W, Supasa P, et al. Evidence of escape of SARS-CoV-2 variant B.1.351 from natural and vaccine-induced sera. Cell 2021 February 23 (Epub ahead of print).
29. Rees-Spear C, Muir L, Griffith SA, et al. The effect of spike mutations on SARS-CoV-2 neutralization. Cell Rep 2021;34:108890.
30. Wu K, Werner AP, Moliva JI, et al. mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. January 25, 2021 (https://www.biorxiv.org/content/10.1101/2021.01.25.427948v1). preprint.
31. Xie X, Liu Y, Liu J, et al. Neutralization of SARS-CoV-2 spike 69/70 deletion, E484K and N501Y variants by BNT162b2 vaccine-elicited sera. Nat Med 2021 February 8 (Epub ahead of print).
32. Stephenson KE, Le Gars M, Sadoff J, et al. Immunogenicity of the Ad26.COV2.S vaccine for COVID-19. JAMA 2021 March 11 (Epub ahead of print).
33. Prakash S, Srivastava R, Coulon P-G, et al. Genome-wide asymptomatic B-cell, $CD4^+$ and $CD8^+$ T-cell epitopes, that are highly conserved between human and animal coronaviruses, identified from SARS-CoV-2 as immune targets for pre-emptive pan-coronavirus vaccines. September 28, 2020 (https://www.biorxiv.org/content/10.1101/2020.09.27.316018v1.full). preprint.
34. Lee E, Sandgren K, Duette G, et al. Identification of SARS-CoV-2 nucleocapsid and spike T-cell epitopes for assessing T-cell immunity. J Virol 2021;95(6):e02002-20.
35. Lee CH, Pinho MP, Buckley PR, et al. Potential CD8+ T cell cross-reactivity against SARS-CoV-2 conferred by other coronavirus strains. Front Immunol 2020;11:579480.
36. GISAID. Map of tracked variant occurrence. 2021 (https://www.gisaid.org/hcov19-variants).
37. Langwig KE, Gomes MGM, Clark MD, et al. Limited available evidence supports theoretical predictions of reduced vaccine efficacy at higher exposure dose. Sci Rep 2019;9:3203.
38. Gomes MGM, Gordon SB, Lalloo DG. Clinical trials: the mathematics of falling vaccine efficacy with rising disease incidence. Vaccine 2016;34:3007-9.
39. Margheri A, Rebelo C, Gomes MGM. Heterogeneity in disease risk induces falling vaccine protection with rising disease incidence. Dyn Syst 2017;32:148-63.

RESEARCH LETTER

Public Trust and Willingness to Vaccinate Against COVID-19 in the US From October 14, 2020, to March 29, 2021

The development of vaccines showing high efficacy against SARS-CoV-2 has offered a way to protect against the health effects of the virus. Yet national surveys suggest that willingness to vaccinate declined throughout 2020 and may be insufficient to provide population immunity.[1-3] Public trust in the development of vaccines and the government approval process represents a potential crucial reason for this hesitancy. This study tested changes in trust in vaccination and vaccine hesitancy.

Supplemental content

Methods | Participants were from 7 waves of the probability-based Understanding America Study (UAS) of US adults,[2,4] conducted between October 14, 2020, and March 29, 2021. The UAS is an internet panel in which panel members are invited to complete questionnaires every 14 to 28 days; internet-connected tablets are provided to households if necessary. The response rate from panel members in this study was 75% to 79% (Supplement).

Participants were asked how likely they were to get vaccinated against the coronavirus and were classed as hesitant (unsure or somewhat/very unlikely to vaccinate) or willing to vaccinate (somewhat likely/very likely to vaccinate or already vaccinated). Participants were also asked to rate how much they trust "the governmental approval process to ensure the COVID-19 vaccine is safe for the public" and "the process in general (not just for COVID-19) to develop safe vaccines for the public" (1 [fully trust] to 4 [do not trust]). Responses to both questions were highly correlated (r = 0.84). Responses were reverse scored and combined to form a single indicator of public trust in vaccination (ranging from 0-6).

Logistic regression analysis with cluster robust SEs followed by the Stata 17 margins postestimation command was used to estimate percentage-point differences in the level of vaccine hesitancy between October 2020 and March 2021, with statistical significance defined as 2-sided $P < .05$. All analyses incorporated sampling weights to ensure each survey wave

Table. Changes in COVID-19 Vaccine Hesitancy and Public Trust in Vaccination Between October 14, 2020, and March 29, 2021, in the Understanding America Study

	COVID-19 vaccine hesitancy, % (95% CI)[a,b]			Public trust in vaccination, mean (95% CI)[c,d]		
	Survey wave			Survey wave		
Demographic characteristic	October 2020 (n = 6016)	March 2021 (n = 6035)	Change in hesitancy by March 2021	October 2020 (n = 6016)	March 2021 (n = 6035)	Change in trust by March 2021
Overall sample	46.0 (44.2 to 47.7)	35.2 (33.4 to 36.9)	−10.8 (−12.7 to −8.9)	2.6 (2.5 to 2.6)	3.0 (2.9 to 3.0)	0.4 (0.3 to 0.5)
Age, y						
18-39	50.7 (47.5 to 53.8)	44.1 (40.8 to 47.3)	−6.6 (−10.1 to −3.2)	2.4 (2.3 to 2.5)	2.7 (2.6 to 2.9)	0.3 (0.2 to 0.5)
40-59	49.7 (46.8 to 52.6)	38.6 (35.6 to 41.6)	−11.1 (−14.2 to −8.0)	2.4 (2.3 to 2.5)	2.8 (2.6 to 2.9)	0.3 (0.2 to 0.4)
≥60	36.2 (33.5 to 39.0)	21.0 (18.6 to 23.4)	−15.2 (−18.1 to −12.4)	3.0 (2.9 to 3.1)	3.5 (3.4 to 3.6)	0.5 (0.4 to 0.6)
Sex						
Men	39.9 (37.3 to 42.4)	30.7 (28.2 to 33.2)	−9.3 (−11.9 to −6.4)	2.8 (2.7 to 2.9)	3.2 (3.1 to 3.3)	0.4 (0.3 to 0.5)
Women	51.8 (49.4 to 54.1)	39.4 (37.0 to 41.8)	−12.4 (−15.0 to −9.7)	2.3 (2.3 to 2.4)	2.7 (2.6 to 2.8)	0.4 (0.3 to 0.5)
Race/ethnicity						
White	42.4 (40.4 to 44.3)	34.8 (32.8 to 36.8)	−7.6 (−9.6 to −5.5)	2.8 (2.7 to 2.8)	3.1 (3.0 to 3.1)	0.3 (0.2 to 0.4)
Hispanic	52.3 (47.0 to 57.5)	36.4 (31.2 to 41.7)	−15.8 (−21.8 to −9.8)	2.4 (2.2 to 2.6)	3.0 (2.7 to 3.2)	0.6 (0.4 to 0.8)
Black	63.9 (58.7 to 69.2)	43.0 (37.3 to 48.7)	−20.9 (−27.2 to −14.6)	1.7 (1.5 to 1.8)	2.3 (2.1 to 2.5)	0.6 (0.4 to 0.8)
Other[e]	33.7 (26.7 to 40.8)	20.4 (14.3 to 26.6)	−13.3 (−20.9 to −5.8)	3.0 (2.8 to 3.2)	3.5 (3.2 to 3.8)	0.5 (0.2 to 0.7)
College degree						
No	54.6 (52.3 to 56.8)	42.9 (40.6 to 45.2)	−11.7 (−14.2 to −9.1)	2.3 (2.2 to 2.4)	2.5 (2.5 to 2.6)	0.2 (0.2 to 0.3)
Yes	30.5 (27.9 to 33.0)	20.9 (18.6 to 23.2)	−9.6 (−12.1 to −7.1)	3.1 (3.0 to 3.2)	3.8 (3.7 to 3.9)	0.7 (0.6 to 0.8)
Income, $						
<50 000	54.0 (51.3 to 56.6)	43.7 (40.9 to 46.4)	−10.3 (−13.3 to −7.3)	2.2 (2.1 to 2.3)	2.5 (2.4 to 2.6)	0.3 (0.2 to 0.4)
≥50 000	39.7 (37.5 to 41.9)	28.2 (26.1 to 30.4)	−11.5 (−13.8 to −9.1)	2.9 (2.8 to 3.0)	3.4 (3.3 to 3.5)	0.5 (0.4 to 0.6)

[a] Vaccine hesitancy is defined as being unsure or somewhat or very unlikely to be vaccinated against COVID-19.

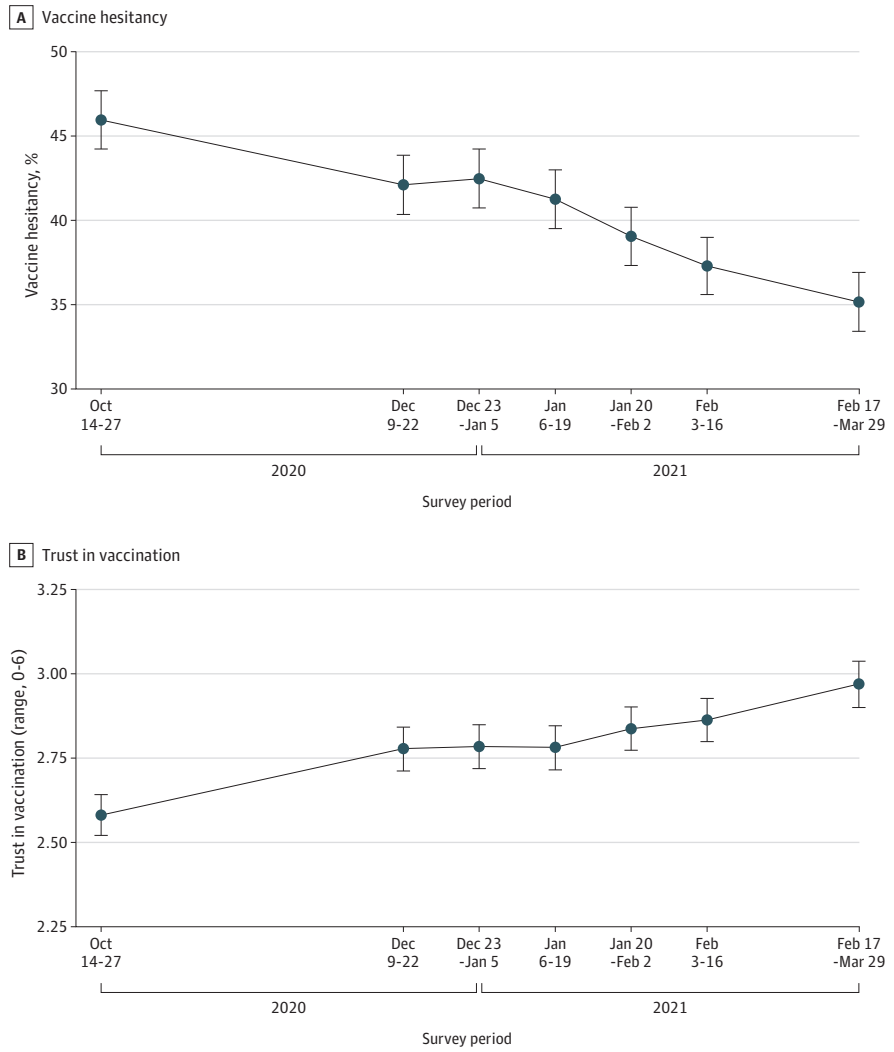
[b] Estimates are derived from predicted probabilities calculated after logistic regression with cluster robust SEs.

[c] Public trust in vaccination ranged from 0 (do not trust development/approval processes) to 6 (fully trust development/approval processes).

[d] Estimates are from linear regression with cluster robust SEs.

[e] Race/ethnicity was self-reported by panel members. The other race/ethnicity group includes Asian, American Indian/Alaska Native, and Native Hawaiian orother Pacific Islander, which were combined owing to small group sizes.

Figure. Changes in COVID-19 Vaccine Hesitancy and Public Trust in Vaccination Across 7 Waves of the Understanding America Study Conducted Between October 14, 2020, and March 29, 2021



Based on an analysis of 42 154 observations on 7420 participants; error bars indicate 95% CIs. Vaccine hesitancy is defined as being unsure or somewhat or very unlikely to be vaccinated against COVID-19. Public trust in vaccination ranges from 0 (do not trust development/approval processes) to 6 (fully trust processes). Details of survey date ranges are provided in the Supplement.

remained nationally representative despite missing data owing to nonresponse (Supplement). Participants provided informed consent via the UAS website and data collection was approved by the University of Southern California institutional review board.

Results | In total, 7420 participants provided 42 154 survey responses (mean, 5.7 of 7 waves completed). Estimates of vaccine hesitancy declined significantly by 10.8 percentage points (95% CI, 8.9-12.7), from 46% in October 2020 to 35.2% in March 2021 (**Table**, **Figure**). Significant declines in estimates of hesitancy were observed across demographic groups and were largest among Hispanic (15.8 percentage point decrease, from 52.3% to 36.5%) and Black participants (20.9 percentage point decrease, from 63.9% to 43%). In March 2021 hesitancy was high among adults aged 18-39 years (44.1%), those without a degree (42.9%), and households earning $50 000 or less (43.7%).

Estimates of public trust in vaccination were low across all demographic groups in October 2020 (1.7 to 3.1 on a 0-6 scale) and increased significantly across all groups by March 2021 (Table). The largest increases were reported by Black and Hispanic participants (0.6-point increase) and those with a college degree (0.7-point increase).

Discussion | After increased reluctance to vaccinate in 2020,[1-3] this nationally representative study showed a longitudinal decline in reported vaccine hesitancy in late 2020 and early 2021. Reduced hesitancy occurred in tandem with the regulatory approval of COVID-19 vaccines and rollout of mass vaccination programs. A significant decline in vaccine hesitancy was reported across all demographic groups, especially Black and Hispanic participants. This decrease is important because COVID-19 vaccine acceptance has been particularly low among these groups, who have experienced a disproportionate burden of severe illness and death because of

COVID-19.[3,5,6] Declines in hesitancy were reported alongside an increase in public trust in vaccine development and the governmental approval process.

Despite these gains, in March 2021 estimates of vaccine hesitancy remained high, especially among young adults and Black and low socioeconomic status participants. Further steps are needed to build public trust, extend outreach and educational programs, and increase vaccination opportunities to ensure high levels of vaccination uptake.

The study is limited by the low UAS panel recruitment rate, participation by community-dwelling adults comfortable completing internet-based surveys in English or Spanish, and reliance on self-reported measures.

Michael Daly, PhD
Andrew Jones, PhD
Eric Robinson, PhD

Author Affiliations: Department of Psychology, Maynooth University, Kildare, Ireland (Daly); Department of Psychology, University of Liverpool, Liverpool, United Kingdom (Jones); Institute of Population Health Sciences, University of Liverpool, Liverpool, United Kingdom (Robinson).

Corresponding Author: Michael Daly, PhD, Department of Psychology, Maynooth University, 1.1.7 Education House, Maynooth, Ireland (michael.a.daly@mu.ie).

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1. Daly M, Robinson E. Willingness to vaccinate against COVID-19 in the US: representative longitudinal evidence from April to October 2020. *Am J Prev Med*. 2021;60(6):766-773. doi:10.1016/j.amepre.2021.01.008

2. Szilagyi PG, Thomas K, Shah MD, et al. National trends in the US public's likelihood of getting a COVID-19 vaccine—April 1 to December 8, 2020. *JAMA*. 2020;325(4):396-398. doi:10.1001/jama.2020.26419

3. Robinson E, Jones A, Lesser I, Daly M. International estimates of intended uptake and refusal of COVID-19 vaccines: a rapid systematic review and meta-analysis of large nationally representative samples. *Vaccine*. 2021;39(15):2024-2034. doi:10.1016/j.vaccine.2021.02.005

4. Kapteyn A, Angrisani M, Bennett D, et al Tracking the effect of the COVID-19 pandemic on the lives of American households. *Surv Res Methods*. 2020;14(2):179-186. doi:10.18148/srm/2020.v14i2.7737

5. Lopez L III, Hart LH III, Katz MH. Racial and ethnic health disparities related to COVID-19. *JAMA*. 2021;325(8):719-720. doi:10.1001/jama.2020.26443

6. Gold JAW, Rossen LM, Ahmad FB, et al. Race, ethnicity, and age trends in persons who died from COVID-19—United States, May–August 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(42):1517-1521. doi:10.15585/mmwr.mm6942e1

Association of California's Prescription Drug Coupon Ban With Generic Drug Use

Drug manufacturers sometimes offer co-payment coupons to offset patient out-of-pocket costs. Although coupons can help patients afford necessary medications, they increase overall drug spending by encouraging use of expensive brand-name drugs over less expensive generics.[1,2] Coupons are prohibited by Medicare and Medicaid, but they are available for commercially insured patients. Several states are considering restricting coupon use to promote generic substitution and control drug spending. In October 2017, California passed a law that banned use of co-payment coupons for brand-name drugs once interchangeable generic versions of those products have become available.[3] We investigated how generic substitution changed in California after its law took effect in January 2018.

Supplemental content

Methods | We identified brand-name drugs facing first-time generic competition from 2014 through October 2016, excluding clinician-administered drugs. Archived manufacturer websites and an online drug coupon database were searched to identify whether the manufacturer for each drug offered a co-payment coupon after generic competition began and through December 2018.

From a large national health insurance claims database (IBM MarketScan), we identified commercially insured patients younger than 65 years in California and other Western states (Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming) who filled prescriptions for these drugs in 2017-2018. We measured the monthly percentage of generic claims in California compared with surrounding states for drugs with coupons (primary cohort) and those without coupons (control cohort). We fit segmented linear regression time-series models assuming first-order autocorrelation (eAppendix in the Supplement) and identified significant changes using a 2-sided $P<.05$. We obtained approval from the Mass General Brigham institutional review board and analyzed data using the Aetion Evidence Platform (Aetion Inc) and SAS software, version 9.4 (SAS Institute Inc).

Results | We identified 15 drugs with coupons and 26 drugs without coupons, accounting for a combined 1.26 million claims in California and surrounding states (**Figure 1**).

Among drugs with coupons, generic use increased from January 2017 to December 2018 from 91.3% to 96.3% in California and from 92.1% to 96.9% in surrounding states

Medical News & Perspectives | QUICK UPTAKES

Despite Big Buildup, Few Benefit From Medicare's Advance Care Planning Coverage

Mary Chris Jaklevic, MSJ

In 2016 Medicare launched a much-anticipated advance care planning (ACP) benefit that pays physicians to counsel patients about living wills, advance directives, and end-of-life care options. During the ACP process clinicians can help patients determine the type of care they would want in a medical crisis or at the end of life and reassure them that their preferences will be observed. Numerous medical and patient advocacy organizations backed the Medicare initiative, asserting that compensation for physicians would encourage proactive end-of-life care discussions. These conversations are associated with patients receiving care that respects their wishes as well as fewer in-hospital deaths and more hospice use.

However, the benefit isn't being widely used. An analysis of outpatient claims published in *Health Affairs* found that although ACP billing increased steadily during the first 4 years, only 2.9% of beneficiaries overall had an ACP claim in 2017, including 4.7% who were older than 85 years and 7.2% of beneficiaries who ultimately died that year. Compared with previous studies, the researchers' data showed smaller differences in the odds between White patients and Black and Hispanic patients having ACP discussions, but the differences were still significant.

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A Fraught History

The push for ACP Medicare reimbursement had a rocky start. Provisions to authorize the payments and promote end-of-life planning were dropped from the Affordable Care Act after health reform opponents charged that the legislation would create heartless "death panels" to arbitrate who lives or dies. PolitiFact deemed the death panel claim 2009's "lie of the year."

The Obama administration revived the idea in 2015 with a proposal to adopt ACP billing codes. That year an Institute of Medicine report, Dying in America, mentioned financial support for ACP along with the development of quality standards for such discussions among its key findings and recommendations. In a letter of support to US Department of Health and Human Services Secretary Sylvia Mathews Burwell, 66 organizations—including the AARP, the American Medical Association, and the American Academy of Palliative and Hospice Medicine—noted that ACP was already part of physician quality reporting. The codes took effect on January 1, 2016.

What's Covered

Medicare pays $86 for 16 to 30 minutes of ACP as a stand-alone service at any outpatient visit, subject to a 20% co-payment, with an additional $75 for up to a half hour of additional counseling. To encourage ACP prior to a serious illness, the co-payment is waived if the service occurs during an annual wellness visit. No limit has been set on the number of ACP claims a beneficiary can have. But to avoid a co-pay, the discussions have to take place during an annual wellness visit, which Medicare covers only once a year.

Physicians, nurse practitioners, and physician assistants of any specialty may bill for the service, and they should offer a patient or surrogate an opportunity to decline the discussion. Medicare does not require that counseling lead to the completion of an advance directive, a legal document often called a "living will."

A Trickle of Claims

Previous studies found low utilization, even for patients considered to have great need:

- Less than 1% of Medicare beneficiaries in New England were represented among 26 522 ACP claims filed in the region during 2016, the inaugural year.
- Among beneficiaries aged 65 years or older who were seriously ill or frail, 5.2% had a billed ACP discussion in 2017, compared with 2.3% of those who didn't have extensive medical needs. Among patients younger than 65 years with dual eligibility for Medicare and Medicaid, 2.7% with end-stage kidney disease and 1.3% of those with a disability had a billed ACP discussion.
- In a large practice that educated physicians in ACP billing and gave them a small financial incentive for ACP documentation, 5.4% of 113 612 hospitalized patients aged 65 years or older had a billed ACP conversation. The figure rose to 8.3% among patients whose physician answered "no" to the question: "Would you be surprised if the patient died in the next year?" Data covered the first 3 months of 2017.

- ACP claims among beneficiaries who died within a given year rose from 3.3% in 2016 to 5.8% in the first 3 quarters of 2017, according to national claims data. Internists billed for 48% of claims and family physicians billed for 28% in 2016.

Scrutinizing Outpatient Claims

For the *Health Affairs* study, researchers examined outpatient claims for beneficiaries who were continuously enrolled in fee-for-service Medicare from 2016 to 2019, including enrollees younger than 65 years who qualified for Medicare due to a disability. That amounted to 133 million beneficiary-years. They captured whether patients had been diagnosed in the previous 12 months with a medical condition that conferred a greater risk of dying, such as cancer, a heart attack, or Alzheimer disease.

Among the findings:

- The number of ACP claims rose from 17 000 in January 2016 to 120 000 per month in 2019. In 2018, the last year with complete data, 3.7% of beneficiaries had a claim. About half occurred during a wellness visit.
- Except for hypertension, all the newly diagnosed conditions analyzed were associated with greater rates of claims. Patients with a hip fracture had the highest rate, 7.4%. Next were those with lung cancer.
- Dual-eligible beneficiaries, most of whom have low incomes, had higher rates of ACP claims than more affluent beneficiaries.
- Overall, the likelihood of having an ACP claim was similar for Black beneficiaries and their White counterparts. Among patients with an ACP claim, Black and Hispanic patients were less likely to have had the counseling at an annual wellness visit, which does not incur a co-pay.

Some Caveats

This study didn't capture ACP discussions that occurred in institutional settings such as hospitals, skilled nursing facilities, or with hospice personnel or in the home. In addition, it didn't capture conversations that were too short to be billable or conversations that weren't billed. Some clinicians may not be aware of ACP billing codes or have them integrated into their billing systems, the researchers noted. In addition, some patients may have completed advance care directives on their own or with an attorney. The analysis didn't include Medicare beneficiaries who were enrolled in Medicare Advantage plans.

Getting to Greater Adoption

Ultimately, it's hard to say what the optimal rate of ACP billing should be, lead author Makayla Palmer, PhD, an assistant professor in economics at the University of Nevada in Las Vegas, said via email. However, she added, "Most experts would agree that ACP should be revisited as health status changes or individuals receive new diagnoses." Given that 5% of the Medicare population dies each year, she said, "it would not be unrealistic to expect annual ACP rates to be considerably higher" than what the study found.

Given public interest in ACP—which COVID-19 has boosted in some regions—the researchers said health care organizations should address barriers to ACP in the outpatient setting, where it can occur before health issues arise. In some cases, institutional changes may be needed to incorporate ACP into the physician workflow; machine learning mortality predictions accompanied by behavioral nudges to clinicians and nurse navigators have been found to increase ACP.

In addition, Medicare might have to increase reimbursement rates to encourage ACP discussions, the researchers wrote, noting that current payments might be insufficient to motivate physicians to engage in training that could enhance their skills. ■

Note: Source references are available through embedded hyperlinks in the article text online.