ORIGINAL ARTICLE

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

S.A. Madhi, V. Baillie, C.L. Cutland, M. Voysey, A.L. Koen, L. Fairlie, S.D. Padayachee, K. Dheda, S.L. Barnabas, Q.E. Bhorat, C. Briner, G. Kwatra, K. Ahmed, P. Aley, S. Bhikha, J.N. Bhiman, A.'.E. Bhorat, J. du Plessis, A. Esmail, M. Groenewald, E. Horne, S.-H. Hwa, A. Jose, T. Lambe, M. Laubscher, M. Malahleha, M. Masenya, M. Masilela, S. McKenzie, K. Molapo, A. Moultrie, S. Oelofse, F. Patel, S. Pillay, S. Rhead, H. Rodel, L. Rossouw, C. Taoushanis, H. Tegally, A. Thombrayil, S. van Eck, C.K. Wibmer, N.M. Durham, E.J. Kelly, T.L. Villafana, S. Gilbert, A.J. Pollard, T. de Oliveira, P.L. Moore, A. Sigal, and A. Izu, for the NGS-SA Group Wits–VIDA COVID Group*

ABSTRACT

BACKGROUND

Assessment of the safety and efficacy of vaccines against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in different populations is essential, as is investigation of the efficacy of the vaccines against emerging SARS-CoV-2 variants of concern, including the B.1.351 (501Y.V2) variant first identified in South Africa.

METHODS

We conducted a multicenter, double-blind, randomized, controlled trial to assess the safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) in people not infected with the human immunodeficiency virus (HIV) in South Africa. Participants 18 to less than 65 years of age were assigned in a 1:1 ratio to receive two doses of vaccine containing 5×10^{10} viral particles or placebo (0.9% sodium chloride solution) 21 to 35 days apart. Serum samples obtained from 25 participants after the second dose were tested by pseudovirus and live-virus neutralization assays against the original D614G virus and the B.1.351 variant. The primary end points were safety and efficacy of the vaccine against laboratory-confirmed symptomatic coronavirus 2019 illness (Covid-19) more than 14 days after the second dose.

RESULTS

Between June 24 and November 9, 2020, we enrolled 2026 HIV-negative adults (median age, 30 years); 1010 and 1011 participants received at least one dose of placebo or vaccine, respectively. Both the pseudovirus and the live-virus neutralization assays showed greater resistance to the B.1.351 variant in serum samples obtained from vaccine recipients than in samples from placebo recipients. In the primary end-point analysis, mild-to-moderate Covid-19 developed in 23 of 717 placebo recipients (3.2%) and in 19 of 750 vaccine recipients (2.5%), for an efficacy of 21.9% (95% confidence interval [CI], −49.9 to 59.8). Among the 42 participants with Covid-19, 39 cases (92.9%) were caused by the B.1.351 variant; vaccine efficacy against this variant, analyzed as a secondary end point, was 10.4% (95% CI, −76.8 to 54.8). The incidence of serious adverse events was balanced between the vaccine and placebo groups.

CONCLUSIONS

A two-dose regimen of the ChAdOx1 nCoV-19 vaccine did not show protection against mild-to-moderate Covid-19 due to the B.1.351 variant. (Funded by the Bill and Melinda Gates Foundation and others; ClinicalTrials.gov number, NCT04444674; Pan African Clinical Trials Registry number, PACTR202006922165132).

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Madhi at the University of the Witwatersrand, Phillip Tobias Bldg., Princess of Wales St., Parktown, 2193, Gauteng, South Africa, or at shabir.madhi@wits.ac.za.

*The members of the Wits–VIDA COVID Group are listed in the Supplementary Appendix, available at NEJM.org.

Drs. Baillie, Cutland, Gilbert, Pollard, de Oliveira, Moore, Sigal, and Izu and Drs. Koen, Fairlie, Padayachee, Dheda, Barnabas, Bhorat, and Briner contributed equally to this article.

This article was published on March 16, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2102214

Development of vaccines to prevent coronavirus disease 2019 (Covid-19) has occurred with unprecedented speed.[1-4] ChAdOx1 nCoV-19, a replication-deficient chimpanzee adenoviral vector containing the sequence for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) structural surface glycoprotein antigen, is one of six Covid-19 vaccines based on different platforms that have been authorized for emergency use,[5-11] with efficacy results for two additional vaccines having recently been reported.[12,13]

Meanwhile, the SARS-CoV-2 spike gene has accumulated mutations within the receptor-binding domain (RBD) and the N-terminal domain (NTD).[14,15] These domains are major targets of the antibody response elicited by the vaccines. The RBD mutations include the N501Y mutation, which is associated with increased affinity of SARS-CoV-2 to the angiotensin-converting enzyme 2 (ACE2) receptor.[16] In contrast, the E484K and K417N RBD mutations and mutations in the NTD have been associated with neutralizing antibody escape.[17] The B.1.1.7 (N501Y.V1) lineage, first identified in the United Kingdom, includes the N501Y mutation, which has been associated with 53% increased transmissibility.[18] Neutralizing antibody activity elicited by infection or by mRNA vaccines against the B.1.1.7 variant are largely unaffected.[19] The B.1.1.7 variant, however, has now evolved to include the E484K mutation in the United Kingdom.[20]

The B.1.351 (N501Y.V2) lineage first identified in South Africa contains the three RBD mutations and five additional NTD mutations.[14,15] The sensitivity of B.1.351 to neutralizing antibodies from convalescent donors infected with the prototype lineage virus, assessed with a spike-pseudovirus neutralization assay, indicated that 48% of serum samples were unable to neutralize B.1.351, with the rest showing a reduction in neutralization titers by a factor of 3 to 86.[21] This finding was corroborated by a live-virus neutralization assay, with reduction in antibody activity ranging from a factor of 6 to complete knockout for the B.1.351 variant.[14] Another independent lineage of SARS-CoV-2 (P.1) also containing the E484K, K417N, and some B.1.351 NTD mutations has been identified in Brazil.[22,23]

A pooled analysis of the efficacy of the ChAdOx1 nCoV-19 vaccine in the United Kingdom, Brazil, and South Africa, performed before the emergence of the B.1.351 and P.1 variants, reported an overall vaccine efficacy of 66.7% (95.8% confidence interval [CI], 57.4 to 74.0).[24] Recent analysis of the efficacy of the ChAdOx1 nCoV-19 vaccine against the B.1.1.7 variant in the United Kingdom was 74.6% (95% CI, 41.6 to 88.9).[25]

Here, we report findings from a multicenter phase 1b–2 trial in South Africa evaluating the safety, immunogenicity, and efficacy of the ChAdOx1 nCoV-19 vaccine in preventing symptomatic Covid-19. This interim analysis is limited to addressing the primary objective evaluating safety and the primary and key secondary objectives evaluating vaccine efficacy, including efficacy specifically against the B.1.351 variant. Furthermore, we report on immunogenicity of ChAdOx1 nCoV-19 and on post hoc pseudovirus and live-virus neutralization assay investigations of the sensitivity of the original D614G virus and the B.1.351 variant to vaccine-elicited antibodies.

Methods

Trial Objectives, Participants, and Oversight

In this multisite, double-blind, randomized, placebo-controlled trial conducted in South Africa, we assessed the safety and efficacy of two standard doses of the ChAdOx1 nCoV-19 vaccine, administered 21 to 35 days apart, as compared with saline (0.9% sodium chloride) placebo. Adults 18 to less than 65 years of age, with no or well-controlled chronic medical conditions, were eligible for participation. Included among the participants were 70 HIV-negative persons enrolled as group 1, in whom intensive safety and immunogenicity studies were planned. Key exclusion criteria were human immunodeficiency virus (HIV) positivity at screening (for the efficacy cohort), previous or current laboratory-confirmed Covid-19, a history of anaphylaxis in relation to vaccination, and morbid obesity (body-mass index [BMI, the weight in kilograms divided by the square of the height in meters], ≥40). Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. The ChAdOx1 nCoV-19 vaccine was developed at the University of Oxford, which was responsible for the conduct and oversight of the trial (see the Supplementary Appendix).

The authors had full access to the trial data, confirm the accuracy and completeness of the data reported, and vouch for the fidelity of the trial to the protocol (available at NEJM.org). An independent data and safety monitoring committee reviewed efficacy and unblinded safety data. A local trial-safety physician reviewed all serious adverse events as they occurred. The trial was monitored by an external clinical research organization, which ensured adherence to the protocol.

The trial was reviewed and approved by the South African Health Products Regulatory Authority and by the ethics committees of the University of the Witwatersrand, Cape Town, Stellenbosch, and OxTREC before trial initiation. All participants were fully informed about the trial procedures and the possible risks, and all signed written informed consent documents before enrollment in the trial.

TRIAL PROCEDURES

Trial participants were randomly assigned to receive either a 0.33-to-0.5-ml dose (depending on the lot) of the ChAdOx1 nCoV-19 vaccine or placebo by intramuscular injection on the day of randomization and a second injection 21 to 35 days later. Injections were administered into the deltoid muscle of the nondominant arm, and participants were observed for 30 minutes after the injection for acute reactions. Injections were prepared and administered by site staff who were aware of participants' trial-group assignments but were not involved in any other trial procedures. Trial participants and all other trial staff remain unaware of trial-group assignments. Details of the trial procedures are provided in the protocol (pages 68–73). Follow-up is ongoing.

SAFETY

The safety analysis evaluated the occurrence of solicited local and systemic reactogenicity within the first 7 days after an injection, unsolicited adverse events within 28 days after an injection, changes from baseline in safety laboratory measures, and serious adverse events. Further details of methods used to evaluate safety and reactogenicity are provided in the Supplementary Appendix. Adverse event data through January 15, 2021, are included in this report.

SARS-COV-2 TESTING, WHOLE-GENOME SEQUENCING, AND GENOME ASSEMBLY

Use of a nucleic acid amplification test for SARS-CoV-2 infection included sampling at routine scheduled visits (detailed in the protocol) and at nonroutine visits when participants had any symptom suggestive of Covid-19 illness. Participants were advised at the time of randomization as to which clinical symptoms should trigger a visit for investigation of possible SARS-CoV-2 infection (Table S1 in the Supplementary Appendix). In addition, short messages were sent to participants every 2 weeks as a reminder to present for investigation if they had symptoms. Details of nucleic acid amplification testing, whole-genome sequencing, and phylogenetic analysis are described in Supplementary Appendix.

NEUTRALIZATION ASSAYS

SARS-CoV-2 serostatus at randomization was evaluated with the use of an IgG assay of the nucleoprotein (N), as described elsewhere.[8] For antibody-neutralization studies, pseudovirus neutralization assays (see the Methods section in the Supplementary Appendix) were performed at Monogram Biosciences, to prototype virus on serum samples obtained 2 weeks after the second dose of vaccine in 107 randomly selected ChAdOx1 nCoV-19 vaccine recipients who were seronegative for IgG N protein at enrollment.

To assess neutralization activity of vaccine-elicited antibodies against B.1.351, serum samples from group 1 participants who had negative SARS-CoV-2 serostatus at enrollment and varying pseudovirus neutralization assay titers to the original D614G spike virus at 14 days after the second injection were tested with pseudovirus and live-virus neutralization assays for activity against the B.1.351 variant.[14,21] Testing of neutralizing antibody activity against the original virus and the B.1.351 variant was undertaken before unblinding of trial-group assignments. The pseudovirus assays for neutralization activity against the original D614G spike, an RBD triple mutant (containing only K417N, E484K, and N501Y), and the B.1.351 spike were performed at the National Institute for Communicable Diseases (South Africa).[14] Live-virus neutralization assay testing was performed by a microneutralization focus-forming assay in Vero E6 cells at the African Health Research Institute, South

Africa.[14,21] Details of the pseudovirus and live-virus neutralization assays have been published and are described briefly in the Supplementary Appendix.[14,21]

Figure 1 (facing page). Enrollment of Participants, Randomization, Vaccine or Placebo Administration, and Follow-up.

NAAT denotes nucleic acid amplification test.

EFFICACY OBJECTIVES

The primary end point was efficacy against nucleic acid amplification test–confirmed symptomatic Covid-19 with onset more than 14 days after the second injection in participants who were seronegative at randomization. Confirmed symptomatic Covid-19 and the grading of mild, moderate, and severe disease were prespecified and are defined in Tables S1 and S2. Covid-19 cases were evaluated by at least two physicians who were independent of the trial and were unaware of trial-group assignments. Discordant assessments were discussed between the two reviewers. Vaccine efficacy against the B.1.351 variant was a prespecified secondary objective.

Other secondary efficacy objectives included efficacy against Covid-19 in the overall population (including participants who were seropositive at randomization), efficacy specific to the baseline seropositive group, and efficacy against Covid-19 with onset more than 14 or more than 21 days after the first dose. Further details of secondary efficacy analyses are included in the Supplementary Appendix. Furthermore, a post hoc analysis was performed for the overall and seronegative populations, to evaluate vaccine efficacy against illness occurring more than 14 days after the first injection, with end-point cases restricted until October 31, 2020, as a proxy for non–B.1.351 variant Covid-19. The B.1.351 variant only began to be identified in the areas where the trial sites (Johannesburg and Tshwane in Gauteng, and Cape Metro in Western Cape Province) were based from mid-November 2020 onward (Fig. S1).[15]

STATISTICAL ANALYSIS

Participants who received at least one dose of the ChAdOx1 nCoV-19 vaccine or placebo and who returned diary cards completed until day 7 after the first injection were included in the safety reactogenicity analysis. The occurrence of each solicited local and systemic reactogenicity sign and symptom for 7 days after vaccination, adverse events, and serious adverse events through January 15, 2021, are presented according to trial group.

The primary efficacy analysis was end-point–driven for the composite of mild, moderate, or severe Covid-19 and required 42 cases to detect a vaccine efficacy of at least 60% (with a lower bound of 0% for the 95% confidence interval), with 80% power. Vaccine efficacy was calculated as 1 minus the relative risk, and 95% confidence intervals calculated with the Clopper–Pearson exact method are reported. Only participants in the per-protocol population (all participants who received two doses of vaccine or placebo and were grouped according to the injection they received, regardless of their planned group assignment) who were seronegative for SARS-CoV-2 at enrollment were included in the primary efficacy analysis. A sensitivity analysis was conducted that included seronegative participants in the modified intention-to-treat population (all participants who received two doses and were grouped by their planned assignment, irrespective of the injection they received). Confidence intervals reported in this article have not been adjusted for multiple comparisons.

RESULTS

PARTICIPANTS

We screened 3022 persons across seven sites and enrolled 2026 HIV-negative persons in the trial between June 24 and November 9, 2020. All participants except 5 who did not receive vaccine or placebo were included in the safety analysis. The initiation of enrollment coincided with the peak of the first Covid-19 wave in South Africa (Fig. S2). Overall, 1010 participants received the vaccine and 1011 received the placebo (Fig. 1). A total of 1467 seronegative participants (750 assigned to the vaccine and 717 to placebo) were eligible for the primary efficacy analysis; reasons for exclusion are listed in Figure 1.

The median age of the participants was 30 years, 56.5% identified as male, and the racial distribution included 70.5% Black Africans, 12.8% Whites, and 14.9% identifying as mixed race. Nineteen percent of participants were obese (BMI, 30 to 39.9), 42.0% were smokers,

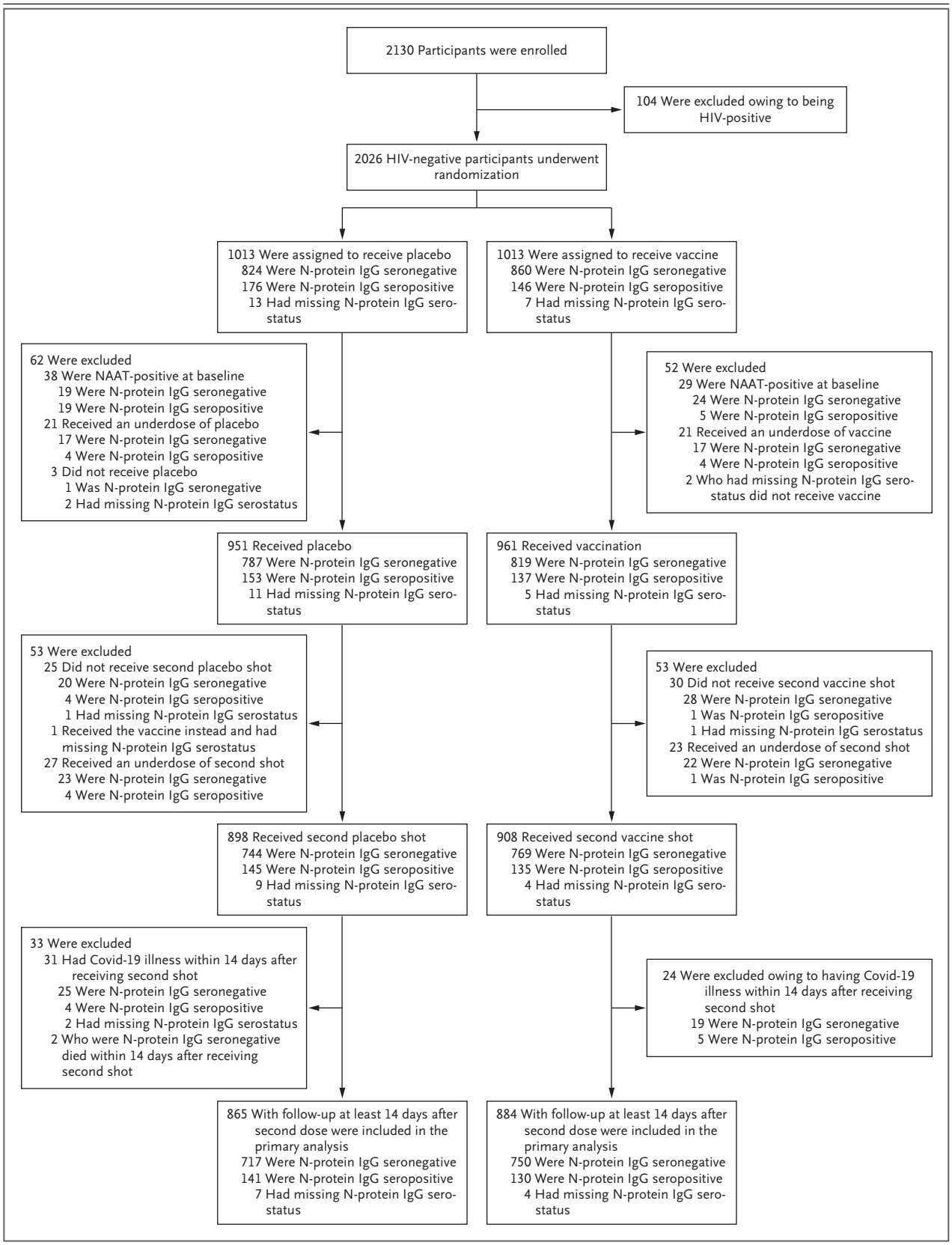

2130 Participants were enrolled
104 Were excluded owing to being HIV-positive
2026 HIV-negative participants underwent randomization
1013 Were assigned to receive placebo
824 Were N-protein IgG seronegative
176 Were N-protein IgG seropositive
13 Had missing N-protein IgG serostatus
1013 Were assigned to receive vaccine
860 Were N-protein IgG seronegative
146 Were N-protein IgG seropositive
7 Had missing N-protein IgG serostatus
62 Were excluded
38 Were NAAT-positive at baseline
19 Were N-protein IgG seronegative
19 Were N-protein IgG seropositive
21 Received an underdose of placebo
17 Were N-protein IgG seronegative
4 Were N-protein IgG seropositive
3 Did not receive placebo
1 Was N-protein IgG seronegative
2 Had missing N-protein IgG serostatus
52 Were excluded
29 Were NAAT-positive at baseline
24 Were N-protein IgG seronegative
5 Were N-protein IgG seropositive
21 Received an underdose of vaccine
17 Were N-protein IgG seronegative
4 Were N-protein IgG seropositive
2 Who had missing N-protein IgG serostatus did not receive vaccine
951 Received placebo
787 Were N-protein IgG seronegative
153 Were N-protein IgG seropositive
11 Had missing N-protein IgG serostatus
961 Received vaccination
819 Were N-protein IgG seronegative
137 Were N-protein IgG seropositive
5 Had missing N-protein IgG serostatus
53 Were excluded
25 Did not receive second placebo shot
20 Were N-protein IgG seronegative
4 Were N-protein IgG seropositive
1 Had missing N-protein IgG serostatus
1 Received the vaccine instead and had missing N-protein IgG serostatus
27 Received an underdose of second shot
23 Were N-protein IgG seronegative
4 Were N-protein IgG seropositive
53 Were excluded
30 Did not receive second vaccine shot
28 Were N-protein IgG seronegative
1 Was N-protein IgG seropositive
1 Had missing N-protein IgG serostatus
23 Received an underdose of second shot
22 Were N-protein IgG seronegative
1 Was N-protein IgG seropositive
898 Received second placebo shot
744 Were N-protein IgG seronegative
145 Were N-protein IgG seropositive
9 Had missing N-protein IgG serostatus
908 Received second vaccine shot
769 Were N-protein IgG seronegative
135 Were N-protein IgG seropositive
4 Had missing N-protein IgG serostatus
33 Were excluded
31 Had Covid-19 illness within 14 days after receiving second shot
25 Were N-protein IgG seronegative
4 Were N-protein IgG seropositive
2 Had missing N-protein IgG serostatus
2 Who were N-protein IgG seronegative died within 14 days after receiving second shot
24 Were excluded owing to having Covid-19 illness within 14 days after receiving second shot
19 Were N-protein IgG seronegative
5 Were N-protein IgG seropositive
865 With follow-up at least 14 days after second dose were included in the primary analysis
717 Were N-protein IgG seronegative
141 Were N-protein IgG seropositive
7 Had missing N-protein IgG serostatus
884 With follow-up at least 14 days after second dose were included in the primary analysis
750 Were N-protein IgG seronegative
130 Were N-protein IgG seropositive
4 Had missing N-protein IgG serostatus

Table 1. Baseline Characteristics of the Overall Population Contributing to the Safety Analysis and of the Population Contributing to the Primary Efficacy End Point Analysis.*

Variable	Overall Safety Population†			Seronegative Efficacy Population‡		
	Total (N=2021)	Placebo (N=1010)	Vaccine (N=1011)	Total (N=1467)	Placebo (N=717)	Vaccine (N=750)
Male sex — no. (%)	1142 (56.5)	568 (56.2)	574 (56.8)	838 (57.1)	397 (55.4)	441 (58.8)
Median age (IQR) — yr	30 (24–40)	30 (24–39)	31 (24–40)	31 (24–41)	31 (24–41)	31 (24–41)
Age category — no. (%)						
18 to <45 yr	1695 (83.9)	852 (84.4)	843 (83.4)	1206 (82.2)	593 (82.7)	613 (81.7)
45 to <60 yr	283 (14.0)	133 (13.2)	150 (14.8)	223 (15.2)	102 (14.2)	121 (16.1)
≥60 yr	43 (2.1)	25 (2.5)	18 (1.8)	38 (2.6)	22 (3.1)	16 (2.1)
Body-mass index — no. (%)§						
0 to <18.5	151 (7.5)	68 (6.7)	83 (8.2)	119 (8.1)	50 (7.0)	69 (9.2)
18.5 to <25	1021 (50.6)	521 (51.6)	500 (49.6)	752 (51.4)	371 (51.7)	381 (51.0)
25 to <30	456 (22.6)	221 (21.9)	235 (23.3)	330 (22.5)	156 (21.8)	174 (23.3)
≥30	390 (19.3)	200 (19.8)	190 (18.8)	263 (18.0)	140 (19.5)	123 (16.5)
Current smoker — no. (%)	849 (42.0)	415 (41.1)	434 (42.9)	644 (43.9)	304 (42.4)	340 (45.3)
Consumes alcohol on a weekly basis — no. (%)	990 (49.0)	501 (49.6)	489 (48.4)	729 (49.7)	365 (50.9)	364 (48.5)
Health worker — no. (%)	167 (8.3)	88 (8.7)	79 (7.8)	144 (9.8)	80 (11.2)	64 (8.5)
Race — no. (%)¶						
Black African	1421 (70.5)	708 (70.3)	713 (70.6)	949 (64.9)	453 (63.4)	496 (66.2)
Mixed	300 (14.9)	149 (14.8)	151 (15.0)	251 (17.2)	128 (17.9)	123 (16.4)
White	259 (12.8)	132 (13.1)	127 (12.6)	231 (15.8)	119 (16.7)	112 (15.0)
Other	37 (1.8)	18 (1.8)	19 (1.9)	32 (2.2)	14 (2.0)	18 (2.4)
Hypertension — no. (%)	56 (2.8)	25 (2.5)	31 (3.1)	42 (2.9)	20 (2.8)	22 (2.9)
Chronic respiratory condition — no. (%)	62 (3.1)	26 (2.6)	35 (3.5)	53 (3.6)	22 (3.1)	31 (4.1)
Diabetes — no. (%)	9 (0.4)	5 (0.5)	4 (0.4)	5 (0.3)	3 (0.4)	2 (0.3)
Median time between doses (IQR) — days	28 (28–32)	28 (28–32)	28 (28–32)	28 (28–32)	28 (28–32)	28 (28–32)
Median follow-up period since randomization (IQR) — days	156 (140–171)	156 (140–171)	156 (140–171)	161 (143–172)	160 (142–172)	161 (143–174)
Median time since second injection (IQR) — days	121 (114–143)	121 (114–142)	121 (114–143)	122 (114–143)	122 (114–142)	128 (114–143)
Person-days of follow-up since randomization	290,394	143,962	146,432	229,129	111,471	117,658
Person-days of follow-up since second injection	228,506	113,063	115,443	184,595	89,714	94,881

* IQR denotes interquartile range.

† The overall safety population included all participants who received at least one dose of vaccine or placebo, irrespective of baseline serologic status suggestive of past SARS-CoV-2 infection or positive results on nucleic acid amplification testing within 96 hours before randomization and on the day of randomization. Five participants who were randomly assigned to a trial group but never received an injection of placebo or vaccine were excluded.

‡ The seronegative efficacy population included all participants in the vaccine efficacy analysis for the primary end point who had a negative nucleic acid amplification test within 96 hours before randomization and on the day of randomization and tested negative for SARS-CoV-2 N-protein IgG.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters. In both the overall safety population and the seronegative efficacy population, data on body-mass index were missing for 3 participants, all of whom were in the vaccine group.

¶ Race was reported by the participants. In both the overall safety population and the seronegative efficacy population, data on race were missing for 4 participants, 3 in the placebo group and 1 in the vaccine group.

2.8% had underlying hypertension, and 3.1% had chronic respiratory conditions. The median time between doses was 28 days, and the median duration of follow-up from enrollment and from 14 days after the second dose of vaccine or placebo was 156 and 121 days, respectively (as of January 15, 2021). Demographic characteristics of the baseline seronegative population were similar to those of the overall population (Table 1).

SAFETY

Local and systemic reactogenicity data are presented in Figures S3 and S4. The incidence of adverse events and serious adverse events was similar among vaccine and placebo recipients (Tables S3 and S4). The only serious adverse event attributed to the ChAdOx1 nCoV-19 vaccine was a body temperature above 40°C after the first dose; the fever subsided within 24 hours, and no reactogenicity was observed after the second dose. All other events were considered unrelated or unlikely to be related to the injection received.

IMMUNOGENICITY

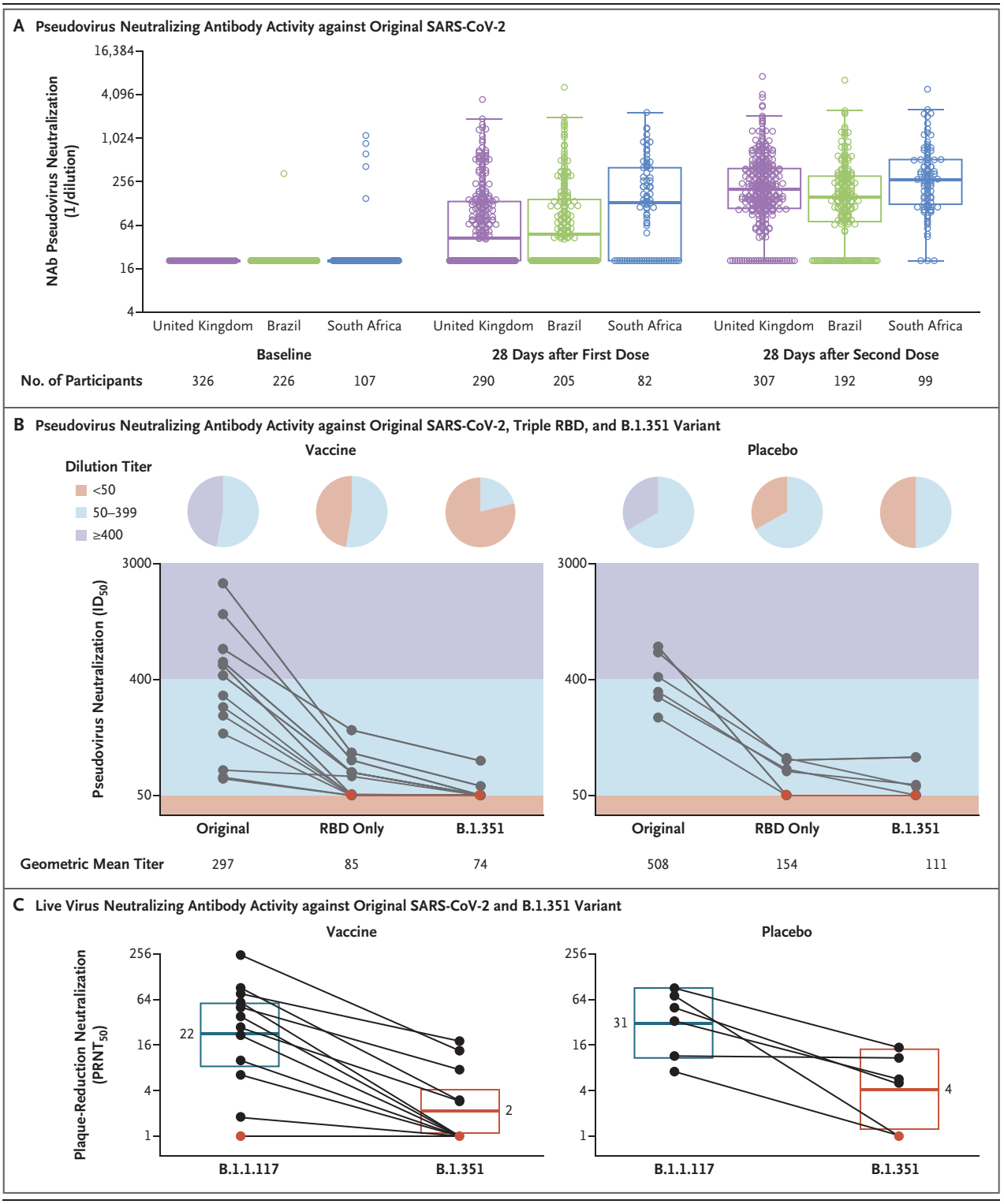
Humoral response to the ChAdOx1 nCoV-19 vaccine induced strong neutralizing antibodies at 28 days after the first dose (geometric mean titer, 132; interquartile range, 20 to 404), which rose further after a second dose (geometric mean titer, 277; interquartile range, 124 to 526) (Fig. 2A and Table S5).

There were 25 participants in group 1 (the group of 70 participants who also had laboratory measures evaluated as part of their safety analysis) who were SARS-CoV-2 seronegative at enrollment and had neutralizing antibody activity against the original D614G virus on the pseudovirus neutralization assay at 14 days after the second dose. The serum samples from these participants, obtained 14 days after the second dose, were further tested with pseudovirus and live-virus assays for neutralizing activity against the B.1.351 variant. After unblinding of the data, 6 of the 25 serum samples were identified as having been obtained from placebo recipients likely to have been infected with the original SARS-CoV-2 (which predated the emergence of the B.1.351 variant in South Africa) during the follow-up period. Furthermore, nucleic acid amplification testing showed that 6 of the vaccine recipients were also infected with SARS-CoV-2 by 14 days after the second dose. Six of 13 vaccine recipients (46%) without evidence of previous SARS-CoV-2 infection showed no neutralization activity against an RBD triple-mutant pseudovirus (containing K417N, E484K, and N501Y variants), and 11 of the 13 (85%) had no neutralization activity against B.1.351 pseudovirus (Fig. 2B).

Geometric mean titers dropped from 297 against the original virus to 85 against the RBD-only mutant and 74 against the B.1.351 variant. Vaccine recipients with nucleic acid amplification test–confirmed illness (before the emergence of B.1.351) showed results similar to those among participants with no confirmed illness (Fig. S6). Samples from the SARS-CoV-2–infected placebo recipients showed similarly low neutralizing activity, with residual titers of less than 100 (or undetectable) against the RBD triple-mutant pseudovirus and the B.1.351 variant (Fig. 2B).

Live-virus assay showed lower neutralization overall, relative to pseudovirus assay (Fig. 2C). Of the 13 vaccine recipients without evidence of previous SARS-CoV-2 infection before or during follow-up, one had undetectable neutralization activity against B.1.1 and B.1.351. Seven of the 12 participants (58%) with neutralization activity against B.1.1 had undetectable neutralization activity against the B.1.351 variant, and the remaining 5 showed neutralization that was lower by a factor of 4.1 to 31.5 (Fig. 2C). As with the pseudovirus neutralization assay, six vaccine recipients with nucleic acid amplification test–confirmed illness showed results similar to those among participants with no confirmed illness (Fig. S6B, light gray points). Among the six placebo recipients recently infected with SARS-CoV-2, all had detectable neutralization of the B.1.1 variant, whereas neutralization activity against the B.1.351 variant was undetectable in two cases, lower neutralization by a factor of 6.0 to 9.5 was noted in three cases, and no change was seen in one case (Fig. 2C).

Given the potential importance of T cells in protection from severe disease,[26] we include data on 17 recipients of the ChAdOx1 nCoV-19 vaccine from the United Kingdom, who were evaluated with T-cell–receptor variable beta-chain sequencing for expansion of spike-specific T cells (see the Supplementary Appendix). The ChAdOx1 nCoV-19 vaccine caused expansion of CD4+ and CD8+ T lymphocytes to specific epitopes of the



spike protein. Of 87 spike-specific antigens identified by the sequencing, 75 remained unaffected by the B.1.351 mutations. Of note, the D215G mutation found in the B.1.351 variant is within a region that had prevalent T-cell antigen responses (Fig. S7).

Figure 2 (facing page). Pseudovirus and Live-Virus Neutralization Assay Findings.

Panel A depicts the results of pseudovirus assay to assess neutralization of the original SARS-CoV-2 virus in ChAdOx1 nCoV-19 vaccine recipients from the United Kingdom, Brazil, and South Africa. Vaccine serum samples from 107 participants in South Africa who were 18 to 64 years old and seronegative at baseline and were assigned to receive two standard doses were evaluated in a validated pseudovirus neutralization assay at a centralized facility at baseline, at 28 days after the first dose, and at 28 days after the second dose. Results for 226 vaccine recipients enrolled in ChAdOx1 nCoV-19 studies in Brazil and 326 in the United Kingdom have not been published previously but are included for comparative purposes. Boxes show medians and interquartile ranges. In trial participants in the United Kingdom, Brazil, and South Africa, median titers at 28 days after the first dose were 41.35, 46.69, and 131.57, respectively, and 200.44, 154.40, and 276.61 at 28 days after the second dose. The ChAdOx1 nCoV-19 vaccine recipients included in the analysis were randomly selected participants from the efficacy trial who contributed to the pooled vaccine efficacy and safety results reported from those studies.[8] **Panel B** shows the results of the pseudovirus assay to assess neutralization of the original virus, the RBD triple mutant, and the B.1.351 variant. Serum samples obtained from 13 ChAdOx1 nCoV-19 vaccine recipients without SARS-CoV-2 infection through 41 days after vaccination (left) and 6 placebo recipients who had natural infection-induced antibody (right) were assessed with the pseudovirus assay to assess neutralization activity against the original D614G lineage, an RBD-only chimeric virus containing the K417N, E484K, and N501Y substitutions, and the B.1.351 variant. Background colors indicate dilutional titers, and pie charts summarize the proportions according to dilutional titer. Geometric mean titers against each virus are shown below the graphs. **Panel C** shows the results of live-virus neutralization assay against the original virus and the B.1.351 variant in 13 vaccine recipients (left) and 6 placebo recipients who had natural infection–induced antibody (right) of B.1.1.117 (the sublineage [GISAID accession EPI_ISL_602622] of B.1.1 used in the assay) and B.1.351 variants. Participants were as for the pseudovirus neutralization assay. Neutralization is represented by the 50% plaque reduction neutralization titer ($PRNT_{50}$), the reciprocal of the 50% inhibitory dilution per participant. Participants with no detectable neutralization (defined as $PRNT_{50}<1$) are shaded in red. Bars and associated numbers represent geometric means (using the limit of detection of $PRNT_{50} = 1$ for undetectable participants), and boxes 95% confidence intervals.

VACCINE EFFICACY

All 42 cases of Covid-19 were graded as mild (15 vaccine recipients and 17 placebo recipients) or moderate (4 vaccine recipients and 6 placebo recipients); there were no cases of severe disease or hospitalization in either group. The incidence of confirmed mild-to-moderate Covid-19 more than 14 days after the second dose among previously seronegative participants was 93.6 per 1000 person-years in the placebo group and 73.1 per 1000 person-years in the vaccine group; vaccine efficacy was 21.9% (95% CI, −49.9 to 59.8) (Table 2 and Fig. 3). Similarly, among seropositive participants who had had a nonreactive nucleic acid amplification test before or at randomization, the incidence of mild-to-moderate Covid-19 more than 14 days after the second injection did not differ between placebo (81.9 per 1000 person-years) and vaccine (73.2 per 1000 person-years) recipients; vaccine efficacy was 10.6% (95% CI, −66.4 to 52.2) (Table S6).

Forty-one of the 42 nasal swab samples (97.6%) were successfully sequenced and classified; 39 (95.1%) cases were caused by the B.1.351 variant and 2 (4.9%; both in the placebo group) by the B.1.1.1 and B.1.144 lineages (Fig. S8). Further details of phylogenetic characterization are provided in the Supplementary Appendix. In a secondary-outcome analysis, efficacy against B.1.351 was not evident (vaccine efficacy, 10.4%; 95% CI, −76.8 to 54.8) (Table 2).

Results of analyses of other secondary and exploratory efficacy end points are detailed in Table S6. Overall vaccine efficacy for Covid-19 of any degree of severity more than 14 days after the first dose was 33.5% (95% CI, −13.4 to 61.7). Also presented in Table S6 are efficacy estimates for any symptomatic illness or asymptomatic SARS-CoV-2 infection after the first and second injections; differences in efficacy estimates were nonsignificant and were similar to those for mild-to-moderate Covid-19 estimates.

In a post hoc analysis of vaccine efficacy at more than 14 days after a single injection through October 31, 2020, as a proxy for infection by a non–B.1.351 variant (Fig. S1),[15,27] the overall attack rate of mild-to-moderate Covid-19 at least 14 days after the first injection was 1.3% in placebo recipients and 0.3% in vaccine recipients; vaccine efficacy was 75.4% (95% CI, 8.7 to 95.5) (Table S8). Similar efficacy estimates were observed in other post hoc analyses for end points occurring through October 31, 2020.

Table 2. Vaccine Efficacy against Mild-to-Moderate Symptomatic Covid-19 Confirmed by Nucleic Acid Amplification Test.*

End Point	Baseline Serologic Status†	Total No. of Cases	Placebo	Incidence Risk	Vaccine	Incidence Risk	Vaccine Efficacy‡
			no./total no. (%)	*per 1000 person-yr (person-days)*	*no./total no. (%)*	*per 1000 person-yr (person-days)*	*% (95% CI)*
Mild-to-moderate illness with onset >14 days after second injection	Seronegative	42	23/717 (3.2)	93.6 (89,714)	19/750 (2.5)	73.1 (94,881)	21.9 (−49.9 to 59.8)
Mild-to-moderate illness associated with B.1.351 variant with onset >14 days after second injection	Seronegative	39	20/714 (2.8)	81.6 (89,448)	19/750 (2.5)	73.1 (94,881)	10.4 (−76.8 to 54.8)
Mild-to-moderate illness with onset >14 days after second injection, regardless of baseline serostatus	Any	46	24/865 (2.8)	81.9 (106,898)	22/884 (2.5)	73.2 (109,659)	10.6 (−66.4 to 52.2)
Mild-to-moderate illness with onset >14 days after one dose until October 31, 2020, a proxy for non-B.1.351 variant infection	Overall	15	12/938 (1.3)	31.1 (140,774)	3/944 (0.3)	7.6 (143,140)	75.4 (8.9 to 95.5)

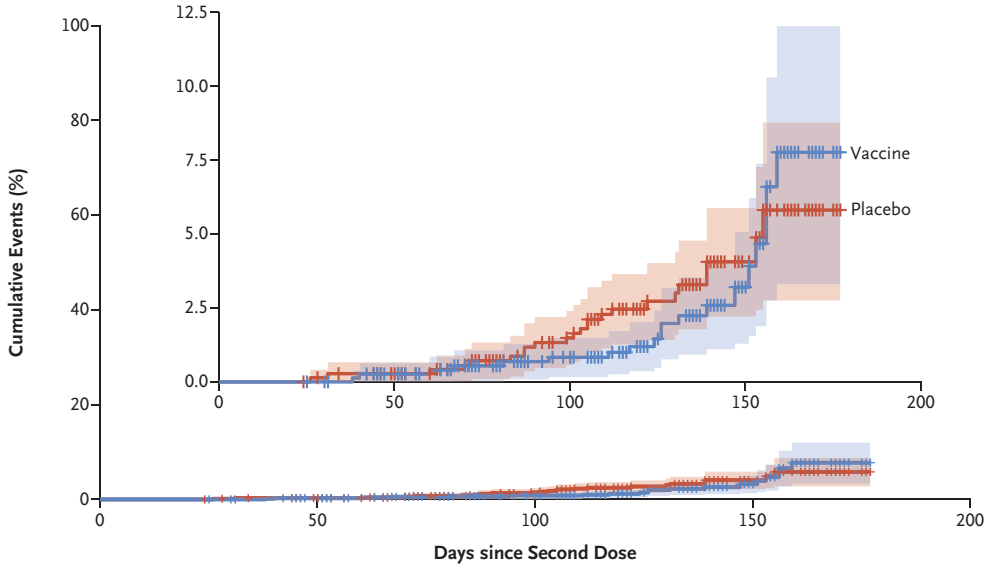
* The prespecified primary end point was Covid-19 illness of any severity, which includes mild, moderate, and severe illness confirmed by nucleic acid amplification test. Because no participants in the trial had severe Covid-19, the term "mild to moderate" is used. Participants were asked to present for investigation of symptoms considered suggestive of Covid-19, including respiratory symptoms (new-onset cough; new-onset rapid breathing; new-onset shortness of breath, or breathlessness, or difficulty breathing; sore throat; loss of smell or smell disturbance; nasal congestion; or runny nose) and nonrespiratory symptoms (fever or feverishness, myalgia, chills, loss of taste, headache, diarrhea, fatigue or weakness, nausea or vomiting, or loss of appetite) (see Table S1). Details of the grading of Covid-19 severity with nucleic acid amplification testing are provided in Table S2. The case-severity distribution was as follows: mild, 32 (17 in placebo recipients and 15 in vaccine recipients), and moderate, 10 (6 in placebo recipients and 4 in vaccine recipients).
† Serologic status was evaluated with the use of an assay to detect IgG to SARS-CoV-2 nucleoprotein in serum obtained on the day of the first injection.
‡ Vaccine efficacy against end points included in the secondary objectives are reported. Confidence intervals have not been adjusted for multiple comparisons.

DISCUSSION

In this trial, we found that two doses of the ChAdOx1 nCoV-19 vaccine had no efficacy against the B.1.351 variant in preventing mild-to-moderate Covid-19. There were no cases of hospitalization for severe Covid-19 observed in the study. The lack of efficacy against the B.1.351 variant should be considered in the context of the 75% efficacy (95% CI, 8.7 to 95.5) in preventing mild-to-moderate Covid-19 with onset at least 14 days after even a single dose of ChAdOx1 nCov-19 vaccine that was observed before the B.1.351 variant emerged in South Africa. Of note, the vaccine efficacy in preventing Covid-19 due to the B.1.351 variant was estimated in a secondary analysis; the trial was powered for the primary objective of a vaccine efficacy of at least 60% in preventing Covid-19 of any severity, irrespective of variants. In addition, the demographic and clinical profile of the enrolled participants contributed to the absence of severe Covid-19 cases; hence, the trial findings are inconclusive with respect to whether the ChAdOx1 nCov-19 vaccine may protect against severe Covid-19 caused by infection with the B.1.351 variant.

The pseudovirus and live-virus neutralization assay experiments, however, provide evidence of reduced or abrogated vaccine-induced antibody neutralization against the B.1.351 variant. Although the degree of attenuation that compromises an effective neutralizing antibody response in vivo is unknown, the highest degree of neutralization achieved against B.1.351 in a vaccinated participant as determined with the live-virus neutralization assay was a 1:20 dilution, and the highest remaining titer against B.1.351 was less than 1:200 with the pseudovirus neutralization assay. Comparison of the RBD triple mutant and the B.1.351 variant in the pseudovirus neutralization assay suggests that much, though not all, of the vaccine-elicited neutralization is directed to the RBD. A similar loss of neutralizing activity against the B.1.351 variant in antibodies induced by natural infection after the first wave of the Covid-19 outbreak has been reported.[14]

The responses to the original SARS-CoV-2 virus as determined by pseudovirus neutralization assays in recipients of the ChAdOx1 nCoV-19 vaccine in our trial were similar to the responses in



No. at Risk					
Vaccine	750	738	674	137	0
Placebo	717	707	632	124	0
Cumulative No. of Events					
Vaccine	0	2	6	14	19
Placebo	0	2	10	21	23

Figure 3. Kaplan–Meyer Plot of ChAdOx1 nCoV-19 Vaccine Efficacy against Symptomatic Covid-19 Illness of Mild or Moderate Severity after Two Doses, as Compared with Placebo.

The shading represents 95% confidence intervals. The tick marks indicate data censored at the time of one of the following events: a Covid-19 infection that did not meet the trial criteria for symptomatic Covid-19 illness, withdrawal from the trial, or death. The inset shows the same data on an expanded y axis.

vaccinated participants in the studies conducted in the United Kingdom and Brazil (Fig. 2A and Table S5). The extent to which the effectiveness of other Covid-19 vaccines may be affected by variants with mutations similar to those of B.1.351 (and P.1) could depend on the magnitude of neutralizing antibody induced by vaccination. Whether an enhanced antibody response resulting from a longer interval between the first and second doses of the ChAdOx1 nCov-19 vaccine, as described elsewhere,[17,24] might confer better residual neutralizing activity against the B.1.351 variant than that observed in our trial is not known.

Although the mRNA Covid-19 vaccines have modest neutralizing antibody activity after the first dose, they produce a greater increase in neutralizing activity after the second dose than that produced by the ChAdOx1 nCoV-19 and heterologous Sputnik V (adenovirus-26 followed by adenovirus-5 vector) Covid-19 vaccines.[5,6,9] Neutralizing activity of the two mRNA vaccines against the B.1.351 variant has also been observed to be lower, by a factor of 8.6 (mRNA-1273 vaccine [Moderna]) or 6.5 (BNT-162b2 vaccine [Pfizer]) on pseudovirus neutralization assay, than activity against the D614G virus, whereas no difference was evident against the N510Y.V1 (B.1.1.7)–like mutant.[19,28,29]

Results of a recent interim analysis of the NVX-CoV2373 nanoparticle spike protein Covid-19 vaccine (Novavax), described in a press release, have not yet been published. However, reports suggest that the vaccine may have lower efficacy against the B.1.351 variant than against the original virus or the B.1.1.7 variant.[12] In the absence of established correlates of protection against Covid-19 caused by the original virus or by B.1.351 or other variants, clinical evidence of the effectiveness of other Covid-19 vaccines

against mild-to-moderate Covid-19 illness is needed.

Another recent multinational study that included South Africa evaluated the efficacy of a single dose of the Ad26.COV2.S nonreplicating adenovirus type 26 vaccine (Janssen). Interim results from South Africa reported a vaccine efficacy of 57% against moderate-to-severe Covid-19 and 89% against severe Covid-19 mainly due to the B.1.351 variant.[13] The Ad26.COV2.S vaccine study, however, submitted for end-point adjudication only cases confirmed by nucleic acid amplification test in patients who had at least three symptoms[30]; consequently, the vaccine-efficacy analyses were likely to have excluded the majority of cases of mild Covid-19 in the study. Of note, the immunogenicity of the Ad26.COV2.S vaccine is similar to that of the ChAdOx1 nCoV-19 vaccine after the first and second doses have been administered.[13,31] The neutralizing antibody response induced by the Ad26.COV2.S vaccine against the B.1.351 variant has not yet been reported.

Although the correlation between antibody response and vaccine efficacy is high, which suggests that the neutralizing antibody response is important, T-cell responses may contribute to protection from Covid-19 even in the presence of lower neutralizing antibody titers.[32] In a post hoc analysis reported here, we found that in spike-specific T cells that expanded after vaccination with ChAdOx1 nCoV-19, the majority of antigens and epitopes remained intact in recognition of the B.1.351 variant.

Although efforts to develop second-generation Covid-19 vaccines targeted against B.1.351 and P1-like variants are under way, the only Covid-19 vaccines likely to be available for most of 2021 have been formulated against the original virus. ChAdOx1 nCoV-19 is likely to be one of the most accessible of all the currently authorized Covid-19 vaccines,[33,34] with expected manufacture of approximately 3 billion doses during 2021, and the least costly.[35] Relative resistance to human neutralizing antibody responses is expected to be a feature of the pandemic coronavirus in the years ahead, as a result of pressure on the virus to select for variants that can transmit despite immunity after natural infection or vaccination. Deliberations on the utility of the ChAdOx1 nCoV-19 vaccine also need to be made in the context of ongoing global spread and community transmission of the B.1.351 variant[36] and the evolution of other SARS-CoV-2 lineages that include similar mutations.

The views expressed in this article are those of the authors and not necessarily those of the South African Medical Research Council, the Bill and Melinda Gates Foundation, the National Institute for Health Research, or the Department of Health and Social Care.

Supported by the Bill and Melinda Gates Foundation (INV-017710), the South African Medical Research Council (96167), U.K. Research and Innovation (MC_PC_19055), and the U.K. National Institute for Health Research. The ChAdOx1 nCoV-19 vaccine was manufactured by Advent (Pomezia, Italy) and COBRA Biologics (Keele, United Kingdom) and was put into vials by Symbiosis (Sterling, United Kingdom). Vaccine production was funded by AstraZeneca. The University of Oxford has legal responsibility as sponsor of the trial. Personnel from the Keertan Dheda laboratory were supported by the South African Medical Research Council–University of Cape Town Centre for the Study of Antimicrobial Resistance (RFA-EMU-02-2017) and the European and Developing Countries Clinical Trials Partnership (EDCTP) (TMA-2015SF-1043 and TMA-1051-TESAII). Dr. Esmail is supported by the EDCTP (TMA-2015CDF-1052). Additional funding was received from the South African Medical Research Council Strategic Health Innovation Partnerships (SHIP) program. Dr. Moore is supported by a grant (98341) from the South African Research Chairs Initiative of the Department of Science and Technology and the National Research Foundation. Dr. Wibmer is supported by the Fogarty International Center, National Institutes of Health (R21TW011454), and by the FLAIR fellowship program (FLR\R1\201782).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org..

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

We thank all the volunteers who participated in this trial; the local safety physician, Guy Richards, for reviewing all serious adverse events; the members of the data safety and monitoring committee (Robert Heyderman and Manish Sadarangani, cochairs, Paul Kaye, Steve Black, George Bouliotis, Gregory Hussey, Bernhards Ogutu, Walter Orenstein, Sonia Ramos, Cornelia L. Dekker, and Elizabeth Bukusi); the independent case-evaluation committee (Jeremy Carr, Steve Chambers, Kim Davis, Simon Drysdale, Charles Feldman, Malick Gibani, Elizabeth Hammershaimb, Michael Harrington, Celina Jin, Seilesh Kadambari, Rama Kandasamy, Carla Leisegang, Toby Maher, Jamilah Meghji, Marc Mendelson, Colin Menezes, Claire Munro, Jeremy Nel, David Pace, Rekha Rapaka, Robindra Basu Roy, Daniel Silman, Gemma Sinclair, Merika Tsitsi, and Jing Wang); key trial team staff members (Wits-VIDA: Joyce Sibuya, Rose Khoza, Nomsa Mlaba, Phindile Khumalo, Sibongile Jauza, Aletta Matywabe, Christinah Klaas, and Farisai Kuonza; Wits RHI: Gabriella Bernade, Mrinmayee Dhar, Alden Geldenhuys, Nakile Mabaso, Nomusa Msweli, Sanele Nkosi, Charmain Norman, Jean Le Roux, Tiffany Seef, Othusitse Segalo, and Sarah Jane Whitaker; and NICD: Bronwen Lambson, Mashudu Madzivhandila, Donald Mhlanga, Zanele Molaudzi, and Frances Ayres); and the teams at Advent (Pomezia, Italy) and COBRA Biologicals (Keele, U.K.) for supply of vaccines. Chris Brooks provided editorial support in the drafting of an earlier version of the manuscript.

APPENDIX

The authors' full names and academic degrees are as follows: Prof. Shabir A. Madhi, Ph.D., Vicky Baillie, Ph.D., Clare L. Cutland, Ph.D., Merryn Voysey, D.Phil., Anthonet L. Koen, M.B., B.Ch., Lee Fairlie, F.C.Paeds., Sherman D. Padayachee, M.B., Ch.B., Keertan Dheda, Ph.D., Shaun L. Barnabas, Ph.D., Qasim E. Bhorat, M.Sc., Carmen Briner, M.B., B.Ch., Gaurav Kwatra, Ph.D., Khatija Ahmed, F.C.Path. (Micro), Parvinder Aley, D.Phil., Sutika Bhikha, M.B., B.Ch., Jinal N. Bhiman, Ph.D., As'ad E. Bhorat, F.R.A.C.G.P., Jeanine du Plessis, B.Sc., Aliasgar Esmail, M.D., Marisa Groenewald, M.B., B.Ch., Elizea Horne, M.B., B.Ch., Shi-Hsia Hwa, M.Sc., Aylin Jose, M.B., B.Ch., Teresa Lambe, Ph.D., Matt Laubscher, M.Sc., Mookho Malahleha, M.B., Ch.B., Masebole Masenya, M.B., Ch.B., Mduduzi Masilela, M.B., Ch.B., Shakeel McKenzie, B.Sc., Kgaogelo Molapo, Nat.Dip.O.H.S., Andrew Moultrie, B.Sc., Suzette Oelofse, M.B., Ch.B., Faeezah Patel, M.B., B.Ch., Sureshnee Pillay, B.Sc., Sarah Rhead, M.B., Ch.B., Hylton Rodel, B.Sc., Lindie Rossouw, M.B., B.Ch., Carol Taoushanis, B.Pharm., Houriiyah Tegally, M.Sc., Asha Thombrayil, M.B., B.Ch., Samuel van Eck, R.N., Constantinos K. Wibmer, Ph.D., Nicholas M. Durham, Ph.D., Elizabeth J. Kelly, Ph.D., Tonya L. Villafana, Ph.D., Sarah Gilbert, Ph.D., Andrew J. Pollard, F.Med.Sci., Tulio de Oliveira, Ph.D., Penny L. Moore, Ph.D., Alex Sigal, Ph.D., and Alane Izu, Ph.D.

The authors' affiliations are as follows: the South African Medical Research Council Vaccines and Infectious Diseases Analytics Research Unit (S.A.M., V.B., A.L.K., G.K., S.B., J.P., A.J., M.L., S.M., A.M., C.T., A.T., A.I.), African Leadership in Vaccinology Expertise (C.L.C.), Wits Reproductive Health and HIV Institute (L.F., E.H., M. Masenya, F.P., S.E.), the Antibody Immunity Research Unit, School of Pathology (J.N.B., C.K.W., P.L.M.), and the Perinatal HIV Research Unit (C.B.), Faculty of Health Sciences, and the Department of Science and Innovation/National Research Foundation South African Research Chair Initiative in Vaccine Preventable Diseases Unit (S.A.M., V.B., A.L.K., G.K., S.B., A.I.), University of the Witwatersrand, and the National Institute for Communicable Diseases (NICD) of the National Health Laboratory Service (NHLS) (J.N.B., C.K.W., P.L.M.), Johannesburg, Setshaba Research Centre, Tshwane (S.D.P., K.A., M. Malahleha, M. Masilela, K.M.), the Division of Pulmonology, Groote Schuur Hospital and the University of Cape Town (K.D., A.E., S.O.), and the Family Centre for Research with Ubuntu, Department of Paediatrics, University of Stellenbosch (S.L.B., M.G., L.R.), Cape Town, Soweto Clinical Trials Centre, Soweto (Q.E.B., A.E.B.), and the Africa Health Research Institute (S.-H.H., H.R., A.S.) and the KwaZulu-Natal Research and Innovation Sequencing Platform (KRISP), University of KwaZulu-Natal (S.P., H.T., T.O., A.S.), Durban — all in South Africa; the Oxford Vaccine Group, Department of Paediatrics (M.V., P.A., S.R., A.J.P.), and Jenner Institute, Nuffield Department of Medicine (T.L., S.G.), University of Oxford, Oxford, the Faculty of Infectious and Tropical Diseases, Department of Immunology and Infection, London School of Hygiene and Tropical Medicine, London (K.D., A.E.), Division of Infection and Immunity, University College London, London (K.D.), and AstraZeneca Biopharmaceuticals, Cambridge (N.M.D., E.J.K., T.L.V.) — all in the United Kingdom; and Max Planck Institute for Infection Biology, Berlin (S.-H.H., H.R.).

REFERENCES

1. Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 vaccines at pandemic speed. N Engl J Med 2020;382:1969-73.
2. Mullard A. COVID-19 vaccine development pipeline gears up. Lancet 2020; 395:1751-2.
3. Collins FS, Stoffels P. Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV): an unprecedented partnership for unprecedented times. JAMA 2020;323:2455-7.
4. Lurie N, Sharfstein JM, Goodman JL. The development of COVID-19 vaccines: safeguards needed. JAMA 2020 July 6 (Epub ahead of print).
5. Pfizer. Pfizer and BioNTech announce vaccine candidate against COVID-19 achieved success in first interim analysis from phase 3 study. November 9, 2020 (https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-vaccine-candidate-against).
6. Moderna. Moderna's COVID-19 vaccine candidate meets its primary efficacy endpoint in the first interim analysis of the phase 3 COVE study. November 16, 2020 (https://investors.modernatx.com/news-releases/news-release-details/modernas-covid-19-vaccine-candidate-meets-its-primary-efficacy).
7. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383:2603-15.
8. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021; 397:99-111.
9. Logunov DY, Dolzhikova IV, Shcheblyakov DV, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet 2021;397:671-81.
10. Xia S, Duan K, Zhang Y, et al. Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes: interim analysis of 2 randomized clinical trials. JAMA 2020;324:951-60.
11. World Health Organization. The COVID-19 candidate vaccine landscape and tracker (https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines).
12. Novavax. Novavax COVID-19 vaccine demonstrates 89.3% efficacy in UK phase 3 trial. January 28, 2021 (https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3).
13. Johnson & Johnson. Johnson & Johnson COVID-19 vaccine authorized by U.S. FDA for emergency use — first single-shot vaccine in fight against global pandemic. February 27, 2021 (https://www.jnj.com/johnson-johnson-announces-single-shot-janssen-covid-19-vaccine-candidate-met-primary-endpoints-in-interim-analysis-of-its-phase-3-ensemble-trial).
14. Cele S, Gazy I, Jackson L, et al. Escape of SARS-CoV-2 501Y.V2 variants from neutralization by convalescent plasma. January 26, 2021 (https://www.medrxiv.org/content/10.1101/2021.01.26.21250224v1). preprint.
15. 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.
16. Barnes CO, Jette CA, Abernathy ME, et al. SARS-CoV-2 neutralizing antibody structures inform therapeutic strategies. Nature 2020;588:682-7.
17. Greaney AJ, Loes AN, Crawford KHD, et al. Comprehensive mapping of mutations in the SARS-CoV-2 receptor-binding domain that affect recognition by polyclonal human plasma antibodies. Cell Host Microbe 2021 February 8 (Epub ahead of print).
18. Volz E, Mishra S, Chand M, et al. Transmission of SARS-CoV-2 Lineage

B.1.1.7 in England: insights from linking epidemiological and genetic data. January 4, 2021 (https://www.medrxiv.org/content/10.1101/2020.12.30.20249034v2). preprint.
19. Wang P, Liu L, Iketani S, et al. Increased resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7 to antibody neutralization. January 26, 2021 (https://www.biorxiv.org/content/10.1101/2021.01.25.428137v1). preprint.
20. Public Health England. Investigation of novel SARS-CoV-2 variant: variant of concern 202012/01. Technical briefing 5. 2021 (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/957504/Variant_of_Concern_VOC_202012_01_Technical_Briefing_5_England.pdf).
21. 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).
22. Voloch CM, da Silva FR Jr, de Almeida LGP, et al. Genomic characterization of a novel SARS-CoV-2 lineage from Rio de Janeiro, Brazil. December 26, 2020 (https://www.medrxiv.org/content/10.1101/2020.12.23.20248598v1). preprint.
23. Gröhs Ferrareze PA, Bonetti Franceschi V, de Menezes Mayer A, Dickin Caldana G, Zimerman RA, Thompson CE. E484K as an innovative phylogenetic event for viral evolution: genomic analysis of the E484K spike mutation in SARS-CoV-2 lineages from Brazil. January 27, 2021 (https://www.biorxiv.org/content/10.1101/2021.01.27.426895v1). preprint.
24. Voysey M, Costa Clemens SA, Madhi SA, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet 2021 February 19 (Epub ahead of print).
25. Emary KRW, Golubchik T, Aley PK, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 VOC 202012/01 (B.1.1.7). February 4, 2021. preprint.
26. Sattler A, Angermair S, Stockmann H, et al. SARS-CoV-2-specific T cell responses and correlations with COVID-19 patient predisposition. J Clin Invest 2020;130:6477-89.
27. National Institute for Communicable Diseases. Dominance of the SARS-CoV-2 501Y.V2 lineage in Gauteng. January 28, 2021 (https://www.nicd.ac.za/wp-content/uploads/2021/01/Dominance-of-the-SARS-CoV-2-501Y.V2-lineage-in-Gauteng-South-Africa-1.pdf.)) preprint.
28. Muik A, Wallisch A-K, Sänger B, et al. Neutralization of SARS-CoV-2 lineage B.1.1.7 pseudovirus by BNT162b2 vaccine-elicited human sera. Science 2021 January 29 (Epub ahead of print).
29. Liu Y, Liu J, Xia H, et al. Neutralizing activity of BNT162b2-elicited serum. N Engl J Med. DOI: 10.1056/NEJMc2102017.
30. Janssen Vaccines & Prevention B.V. 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. Clinical protocol. 2020 (https://www.jnj.com/coronavirus/covid-19-phase-3-study-clinical-protocol).
31. Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet 2020;396:467-78.
32. McMahan K, Yu J, Mercado NB, et al. Correlates of protection against SARS-CoV-2 in rhesus macaques. Nature 2021; 590:630-4.
33. Gavi, the Vaccine Alliance. New collaboration makes further 100 million doses of COVID-19 vaccine available to low- and middle-income countries. 2020 (https://www.gavi.org/news/media-room/new-collaboration-makes-further-100-million-doses-covid-19-vaccine-available-low).
34. Amnesty International. COVID-19: Oxford/AstraZeneca vaccine a boost for global access, but huge inequality remains. November 23, 2020 (https://www.amnesty.org/en/latest/news/2020/11/oxford-astrazeneca-vaccine-a-boost-for-global-access-but-huge-inequality-remains).
35. McCarthy N. The cost per jab of Covid-19 vaccine candidates. Statista. December 1, 2020. (https://www.statista.com/chart/23658/reported-cost-per-dose-of-covid-19-vaccines).
36. PANGO Lineages. Global report investigating novel coronavirus haplotypes. 2021 (https://cov-lineages.org/global_report.html).