ORIGINAL ARTICLE

Randomized Trial of BCG Vaccine to Protect against Covid-19 in Health Care Workers

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ABSTRACT

BACKGROUND

The bacille Calmette–Guérin (BCG) vaccine has immunomodulatory "off-target" effects that have been hypothesized to protect against coronavirus disease 2019 (Covid-19).

METHODS

In this international, double-blind, placebo-controlled trial, we randomly assigned health care workers to receive the BCG-Denmark vaccine or saline placebo and followed them for 12 months. Symptomatic Covid-19 and severe Covid-19, the primary outcomes, were assessed at 6 months; the primary analyses involved the modified intention-to-treat population, which was restricted to participants with a negative test for severe acute respiratory syndrome coronavirus 2 at baseline.

RESULTS

A total of 3988 participants underwent randomization; recruitment ceased before the planned sample size was reached owing to the availability of Covid-19 vaccines. The modified intention-to-treat population included 84.9% of the participants who underwent randomization: 1703 in the BCG group and 1683 in the placebo group. The estimated risk of symptomatic Covid-19 by 6 months was 14.7% in the BCG group and 12.3% in the placebo group (risk difference, 2.4 percentage points; 95% confidence interval [CI], −0.7 to 5.5; P=0.13). The risk of severe Covid-19 by 6 months was 7.6% in the BCG group and 6.5% in the placebo group (risk difference, 1.1 percentage points; 95% CI, −1.2 to 3.5; P=0.34); the majority of participants who met the trial definition of severe Covid-19 were not hospitalized but were unable to work for at least 3 consecutive days. In supplementary and sensitivity analyses that used less conservative censoring rules, the risk differences were similar but the confidence intervals were narrower. There were five hospitalizations due to Covid-19 in each group (including one death in the placebo group). The hazard ratio for any Covid-19 episode in the BCG group as compared with the placebo group was 1.23 (95% CI, 0.96 to 1.59). No safety concerns were identified.

CONCLUSIONS

Vaccination with BCG-Denmark did not result in a lower risk of Covid-19 among health care workers than placebo. (Funded by the Bill and Melinda Gates Foundation and others; BRACE ClinicalTrials.gov number, NCT04327206.)

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*Members of the BRACE Trial Consortium Group are listed in the Supplementary Appendix, available at NEJM.org.

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In addition to protecting against its target disease, tuberculosis, the bacille Calmette–Guérin (BCG) vaccine has immunomodulatory "off-target" effects that may protect against unrelated infections.[1-3] The BCG vaccine has been associated with reduced risk of death from any cause among infants[4] and a reduced risk of respiratory infections among adolescents and adults.[5-7]

Early in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, it was proposed that the BCG vaccine could be repurposed to protect against coronavirus disease 2019 (Covid-19).[8] It was hypothesized that the immunomodulatory properties of this vaccine might enhance protection against SARS-CoV-2, thus bridging the gap until pathogen-specific vaccines were available.[8,9] In this randomized, controlled trial, BCG Vaccination to Reduce the Impact of COVID-19 in Healthcare Workers (BRACE), we aimed to determine whether the incidence and severity of Covid-19 among adult health care workers would be lower among those who received the BCG-Denmark vaccine than among those who received placebo.[10]

Methods

Trial Design and Setting

This phase 3, multicenter, randomized, controlled trial involving health care workers was conducted in two stages. Stage 1 (recruitment from March 2020 through May 2020) took place in Australia only. Stage 2 (recruitment from May 2020 through April 2021) took place in Australia, the Netherlands, Spain, the United Kingdom, and Brazil. In the double-blind stage 2 part of the trial, participants were randomly assigned in a 1:1 ratio to receive intradermal BCG-Denmark vaccine or saline placebo and were followed for 12 months, with the primary outcomes assessed at 6 months.[10] As prespecified in our statistical analysis plan,[11] this report focuses only on stage 2 of the trial because there was negligible SARS-CoV-2 community transmission during stage 1. The protocol, which has been published previously,[10] and the statistical analysis plan are available with the full text of this article at NEJM.org.

Oversight

The trial was approved by the ethics committee at each site and overseen by a steering committee and an independent data and safety monitoring board. The investigators designed the trial. A subgroup of authors collected and analyzed the data. The first four authors and last two authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The funders had no role in the collection, analysis, or interpretation of data or in the preparation, review, or approval of the manuscript.

A Quick Take is available at NEJM.org

Participants and Eligibility Criteria

The eligibility of potential participants was ascertained during a baseline visit. Exclusion criteria included a previous positive SARS-CoV-2 test; contraindication to the BCG vaccine; receipt of BCG vaccine within the past year, any other live-attenuated vaccine within the past month, or any Covid-19–specific vaccine; and involvement in another Covid-19 prevention trial. At baseline, blood samples were obtained from all the participants for SARS-CoV-2 serologic testing; in Brazil, respiratory swab samples were also obtained for SARS-CoV-2 polymerase-chain-reaction (PCR) assay. All the participants provided written informed consent.

Randomization

The computer-generated randomization list was prepared by an independent statistician, and we used Web-based randomization, accessed by trial staff after consent had been obtained and baseline assessments had been performed. Randomization was stratified according to geographic region (Brazil, Europe, or Australia), age group (<40 years, 40 to 59 years, or ≥60 years), and the presence or absence of a coexisting condition. Participants, investigators, outcome assessors, data managers, trial statisticians, and trial staff were unaware of the trial-group assignments throughout the trial.

Interventions

A single dose of 0.1 ml of BCG-Denmark vaccine (AJ Vaccines; corresponding to 2 to 8×10^5 colony-forming units [CFUs] of *Mycobacterium bovis*, Danish strain 1331) or saline placebo was administered as an intradermal injection in the region of the deltoid muscle. A photograph was taken of the injection-site "bleb" (a small blister on the skin) to confirm correct administration.

Outcome Measures

The trial had two primary outcomes: the incidence of symptomatic Covid-19 and the incidence

of severe Covid-19 by 6 months after randomization. Complete definitions of the primary and secondary outcomes are provided in the Supplementary Appendix, available at NEJM.org. In brief, symptomatic Covid-19 was defined, in accordance with the case definition used internationally at the start of the trial, as an episode of illness with fever or at least one symptom of respiratory disease (including sore throat, cough, and shortness of breath) and evidence of SARS-CoV-2 infection on PCR assay, rapid antigen test, or serologic test. Severe Covid-19 was defined as an episode of illness with evidence of SARS-CoV-2 infection (on PCR assay, rapid antigen test, or serologic test) plus at least one of the following as a consequence of Covid-19: death, hospitalization, or severe disease without hospitalization (defined, for the purpose of this trial, as being confined to bed or unable to work for ≥3 consecutive days, not resulting from quarantine or other restrictions).

Secondary outcomes included the time to onset of Covid-19; the number of Covid-19 episodes; the number of days with symptoms, absent from work, or confined to bed; complications (including pneumonia, receipt of oxygen, hospitalization, admission to a critical care unit, use of mechanical ventilation, or death); and asymptomatic infection. All these outcomes were assessed until 6 months after randomization. Vaccine-related adverse reactions were also monitored.

DATA AND SAMPLE COLLECTION

The REDCap platform was used for data collection.[12] Participants were asked weekly if they had been unwell with the use of a custom-built smartphone application (Trial Symptom Tracker, WeGuide), direct contact (telephone call or text message), or both. During each episode of illness, symptoms were recorded daily, and participants were asked to undergo SARS-CoV-2 testing. More detailed questionnaires were completed at baseline and every 3 months during follow-up. Additional information on hospitalizations was obtained from medical records. Blood samples were obtained at baseline and 3, 6, 9, and 12 months after randomization for measurement of anti–SARS-CoV-2 nucleocapsid antibodies (Roche Cobas Elecsys anti–SARS-CoV-2 assay).[13] A biobank of other samples was also established.

STATISTICAL ANALYSIS

The statistical analysis plan[14] was finalized and made publicly available before unblinding; full details, including the sample-size calculation (planned sample, 7244 participants), are available in the Supplementary Appendix. For the primary outcomes, survival analysis (with adjustment for stratification factors) was used to estimate the proportion of participants with a Covid-19 episode by 6 months in each group and the risk difference. Follow-up data were censored at 6 months, or at the time of receipt of the first Covid-19–specific vaccine, or when it could not be ascertained whether a Covid-19 episode had occurred (missing data for ≥3 consecutive days or an illness episode without a Covid-19 test result). Most analyses were performed in the modified intention-to-treat population, which was restricted to participants with a negative baseline SARS-CoV-2 test.

Prespecified supplementary analyses were performed to provide additional insights; separate analyses included follow-up time after receipt of a Covid-19–specific vaccine, excluded episodes that started within 14 days after randomization, censored data from participants at any subsequent vaccination (e.g., influenza vaccine), and involved the intention-to-treat population. Sensitivity analyses were also performed; separate analyses were restricted to episodes occurring on or after the date of receipt of BCG vaccine or placebo, used results from PCR assays and rapid antigen tests only (without serologic results) to define Covid-19 episodes (in the intention-to-treat population), and used less conservative censoring rules for missing data. Table S1 in the Supplementary Appendix details the primary, sensitivity, and supplementary estimands. Prespecified subgroup analyses were performed on the basis of age group (<40 years, 40 to 59 years, or ≥60 years), the presence of a coexisting condition (yes or no, and according to condition), geographic region (Brazil, Europe, or Australia), sex (male or female), and previous BCG vaccination (yes or no) for the primary analysis.

RESULTS

TRIAL POPULATION

From May 14, 2020, through April 1, 2021, a total of 3988 participants were randomly as-

signed to receive BCG vaccine (1999 participants) or placebo (1989 participants) (Fig. 1). Recruitment was stopped prematurely before the planned sample size was reached because of the global rollout of Covid-19–specific vaccines. The baseline characteristics were similar in the two groups (Table 1 and Tables S2 and S3), apart from a slightly higher percentage of female participants in the placebo group than in the BCG group (75.1% vs. 72.3%). Participants were predominantly women (73.7%), with a mean (±SD) age of 42.0±12.1 years. A large proportion of the participants were enrolled in Brazil (64.4%). Information on the representativeness of the trial participants is provided in Table S20. The baseline SARS-CoV-2 serologic status was positive in 14.1% of all the participants, and the baseline SARS-CoV-2 swab was positive in 2.7% of Brazilian participants (and inconclusive or missing in 0.5%). The modified intention-to-treat population consequently included 84.9% of the participants who underwent randomization (Fig. 1): 1703 in the BCG group and 1683 in the placebo group (Table 1). Overall, 98.0% of the participants were followed for 6 months or more, with a similar percentage in the two groups (Table S5).

PRIMARY OUTCOMES

In the first 6 months after randomization (modified intention-to-treat population), symptomatic Covid-19 occurred in 132 participants in the BCG group (adjusted estimated risk, 14.7%) and in 106 participants in the placebo group (12.3%) (difference, 2.4 percentage points; 95% confidence interval [CI], −0.7 to 5.5; P=0.13); severe Covid-19, as defined in this trial, occurred in 75 participants in the BCG group (7.6%) and in 61 participants in the placebo group (6.5%) (difference, 1.1 percentage points; 95% CI, −1.2 to 3.5; P=0.34) (Table 2, Fig. 2, and Tables S7 and S8). The majority of participants who met the trial definition of severe Covid-19 were not hospitalized but were unable to work for at least 3 consecutive days. In supplementary and sensitivity analyses that used less conservative censoring rules, the risk differences were similar but the confidence intervals were narrower (Fig. 2). This included the sensitivity analyses using results from PCR assays and rapid antigen tests only (without serologic results) and the analyses that did not account for Covid-19–specific vaccination.

SECONDARY OUTCOMES

Results for the secondary outcomes are presented in Table 2 and Table S9 through S17. The probability of any Covid-19 episode within 6 months was greater in the BCG group than in the placebo group, although the confidence interval was wide and included no difference between the two groups (adjusted hazard ratio, 1.23; 95% CI, 0.96 to 1.59) (Table 2). In sensitivity analyses that were based on the results of PCR assays and rapid antigen tests only (adjusted hazard ratio, 1.38; 95% CI, 1.05 to 1.81) and the analyses that did not account for Covid-19–specific vaccination (adjusted hazard ratio, 1.24; 95% CI, 1.01 to 1.53), extended follow-up time resulted in more precise estimates and confidence intervals that excluded no difference between the two groups (Fig. S3). Five hospitalizations due to Covid-19 occurred in each group (including one death in the placebo group).

When the number of days with symptoms was compared between the BCG group and the placebo group, there was strong evidence of an interaction between the trial group and two randomization strata (age group and the presence or absence of a coexisting condition), which rendered an overall comparison between randomization groups noninterpretable. Post hoc subgroup analyses showed that among participants 60 years of age or older, the BCG group had fewer days with symptoms than the placebo group (incidence rate ratio, 0.32; 95% CI, 0.19 to 0.53) (Table 2 and Fig. S4), whereas no substantial difference between trial groups was seen among participants younger than 40 years of age and those 40 to 59 years of age. In the subgroup without coexisting conditions, the BCG group had fewer days with symptoms than the placebo group (incidence rate ratio, 0.73; 95% CI, 0.58 to 0.91), but the opposite was true in those with coexisting conditions (incidence rate ratio, 1.49; 95% CI, 0.88 to 2.52).

SUBGROUP ANALYSES

In prespecified subgroup analyses, there was little evidence that the treatment effect differed across most of the subgroups (Fig. 3). With respect to the influence of previous BCG vaccination, the results are consistent with the possibility of a greater risk of severe Covid-19 in the BCG group than in the placebo group among partici-

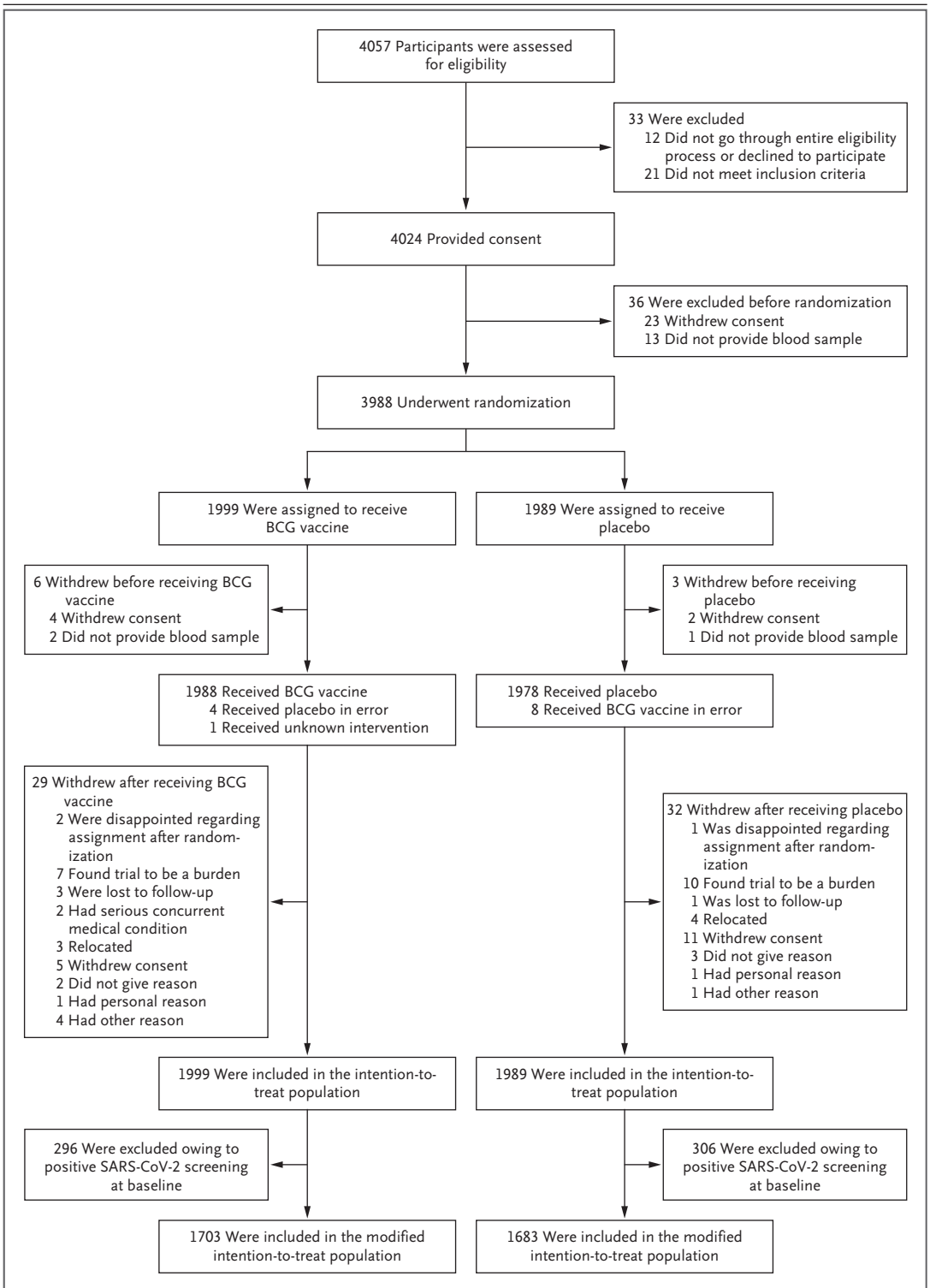


Figure 1. Screening and Randomization.

BCG denotes bacille Calmette–Guérin, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Intention-to-Treat Population		Modified Intention-to-Treat Population	
	BCG Vaccine (N=1999)	Placebo (N=1989)	BCG Vaccine (N=1703)	Placebo (N=1683)
Female sex — no. (%)	1446 (72.3)	1494 (75.1)	1245 (73.1)	1281 (76.1)
Age — yr	42.0±12.1	42.0±12.1	42.8±12.0	42.8±12.0
Any coexisting condition — no. (%)	400 (20.0)	389 (19.6)	356 (20.9)	333 (19.8)
Chronic respiratory disease	126 (6.3)	108 (5.4)	111 (6.5)	92 (5.5)
Cardiovascular disease or hypertension	261 (13.1)	250 (12.6)	233 (13.7)	214 (12.7)
Diabetes mellitus	62 (3.1)	74 (3.7)	52 (3.1)	67 (4.0)
Obesity: BMI ≥30 — no./total no. (%)†	442/1967 (22.5)	417/1941 (21.5)	362/1672 (21.7)	338/1638 (20.6)
Smoker — no. (%)	196 (9.8)	211 (10.6)	176 (10.3)	184 (10.9)
Previous BCG vaccination — no. (%)	1537 (76.9)	1521 (76.5)	1262 (74.1)	1244 (73.9)
Positive SARS-CoV-2 serologic status at baseline — no. (%)	275 (13.8)	286 (14.4)	0	0
Positive SARS-CoV-2 PCR assay at baseline — no./total no. (%)‡	34/1285 (2.6)	36/1283 (2.8)	0/1006	0/999
Direct contact with patients — no. (%)	1622 (81.1)	1617 (81.3)	1363 (80.0)	1341 (79.7)
Occupation — no. (%)				
Nurse or midwife	398 (19.9)	370 (18.6)	359 (21.1)	326 (19.4)
Medical doctor	208 (10.4)	197 (9.9)	197 (11.6)	187 (11.1)
Allied health	384 (19.2)	392 (19.7)	329 (19.3)	339 (20.1)
Administrative or clerical	307 (15.4)	303 (15.2)	257 (15.1)	252 (15.0)
Patient service assistant or hospital maintenance	326 (16.3)	314 (15.8)	246 (14.4)	232 (13.8)
Other	376 (18.8)	413 (20.8)	315 (18.5)	347 (20.6)
Geographic region — no. (%)				
Australia	216 (10.8)	206 (10.4)	214 (12.6)	206 (12.2)
United Kingdom, the Netherlands, or Spain	498 (24.9)	500 (25.1)	483 (28.4)	478 (28.4)
Brazil	1285 (64.3)	1283 (64.5)	1006 (59.1)	999 (59.4)

* Plus–minus values are means ±SD. The intention-to-treat population included all the participants who underwent randomization. The modified intention-to-treat population was restricted to participants with a negative test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at baseline. Percentages may not total 100 because of rounding. BCG denotes bacille Calmette–Guérin, and PCR polymerase chain reaction.

† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

‡ Baseline swabs were obtained in Brazil only.

pants who had not previously received BCG vaccination but not among those who received BCG revaccination. The probability of symptomatic or severe Covid-19 by 6 months appeared to be slightly higher in the BCG group than in the placebo group among participants with cardiovascular disease, those with hypertension, and those with chronic respiratory disease. In the sex subgroup analysis, although there was minimal evidence of an interaction between sex and the effect of BCG vaccination, the disease-free survival curves separated earlier in the male subgroup than in the female subgroup (Figs. S1 and S2).

SAFETY MONITORING

Details on adverse events are provided in Tables S18 and S19. A total of 29 participants reported 30 serious adverse events: 20 in the BCG group and 9 in the placebo group. Apart from a painful injection-site abscess with lethargy in the BCG group, all serious adverse events were considered by the site investigator to be unrelated to the intervention.

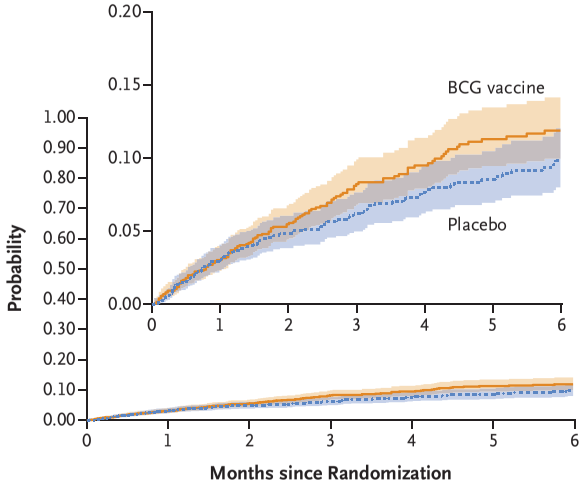
Table 2. Primary and Secondary Outcomes.*

Outcome	BCG Vaccine (N=1703)	Placebo (N=1683)	Difference (95% CI)	P Value
Primary outcomes				
Symptomatic Covid-19 episode by 6 mo	132	106		
Event rate per 100 person-yr (95% CI)	29.4 (24.8 to 34.9)	24.4 (20.1 to 29.5)		
Unadjusted estimated percent (95% CI)	11.9 (9.9 to 13.9)	9.8 (7.9 to 11.8)	2.1 (−0.8 to 4.9)†	
Adjusted estimated percent (95% CI)‡	14.7 (12.0 to 17.3)	12.3 (9.7 to 14.8)	2.4 (−0.7 to 5.5)†	0.13
Severe Covid-19 episode by 6 mo — no.	75	61		
Death — no.	0	1		
Hospitalization — no.	5	4		
Severe disease without hospitalization — no.	70	56		
Too sick to get out of bed for ≥3 consecutive days	12	18		
Too sick to go to work but not in bed for ≥3 consecutive days	58	38		
Event rate per 100 person-yr	16.3 (13.0 to 20.5)	13.8 (10.8 to 17.8)		
Unadjusted estimated percent (95% CI)	6.7 (5.2 to 8.3)	5.5 (4.0 to 7.0)	1.2 (−1.0 to 3.4)†	
Adjusted estimated percent (95% CI)‡	7.6 (5.8 to 9.5)	6.5 (4.7 to 8.2)	1.1 (−1.2 to 3.5)†	0.34
Secondary outcomes by 6 mo				
Symptomatic or severe Covid-19 — no.	135	107	1.23 (0.96 to 1.59)‡§	
Pneumonia due to Covid-19 — no	7	7	0.93 (0.32 to 2.64)‡§	
Hospitalization due to Covid-19 — no.	5	5	0.93 (0.27 to 3.21)‡§	
Oxygen therapy due to Covid-19 — no. (%)	3 (0.2)	3 (0.2)		
Admission to critical care unit due to Covid-19 — no. (%)	2 (0.1)	2 (0.1)		
Mechanical ventilation due to Covid-19 — no. (%)	2 (0.1)	1 (0.1)		
Median no. of days unable to work due to Covid-19 (IQR)¶	3.0 (0.0 to 8.0)	4.0 (0.0 to 11.0)	0.88 (0.61 to 1.26)‡‖	
Median no. of days confined to bed due to Covid-19 (IQR)¶	0.0 (0.0 to 1.0)	0.0 (0.0 to 3.0)	0.76 (0.38 to 1.50)‡‖	
Median no. of episodes of Covid-19 (IQR)¶	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)	0.95 (0.74 to 1.22)‡‖	
Median no. of days of unplanned absenteeism (IQR)	6.0 (3.0 to 11.0)	6.0 (2.0 to 11.0)	1.12 (0.99 to 1.27)‡‖	

Asymptomatic Covid-19 — no./total no.	12/1071	15/978	
Adjusted estimated percent (95% CI)‡	1.1 (0.5 to 1.8)	1.5 (0.8 to 2.3)	−0.4 (−1.4 to 0.6)†
No. of days with symptoms due to Covid-19 (95% CI)¶**			
According to age group			
<40 yr			
No. of participants evaluated	740	734	
Median no. of days (IQR)	15.0 (9.0 to 22.0)	15.0 (11.0 to 25.5)	0.79 (0.61 to 1.01)‡‖
40 to 59 yr			
No. of participants evaluated	811	802	
Median no. of days (IQR)	16.0 (10.0 to 23.0)	14.0 (9.0 to 27.0)	0.92 (0.64 to 1.33)‡‖
≥60 yr			
No. of participants evaluated	152	147	
Median no. of days (IQR)	16.5 (8.0 to 24.0)	38.0 (27.0 to 50.0)	0.32 (0.19 to 0.53)‡‖
According to the presence or absence of a coexisting condition			
Presence of any coexisting condition			
No. of participants evaluated	356	333	
Median no. of days (IQR)	19.5 (15.5 to 31.5)	17.0 (12.0 to 22.0)	1.49 (0.88 to 2.52)‡‖
Absence of any coexisting condition			
No. of participants evaluated	1347	1350	
Median no. of days (IQR)	13.0 (9.0 to 22.0)	15.5 (11.0 to 30.0)	0.73 (0.58 to 0.91)‡‖

* The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing. Covid-19 denotes coronavirus disease 2019, and IQR interquartile range.
† The difference is expressed in percentage points.
‡ Values have been adjusted for stratification factors used at randomization: age (<40 years, 40 to 59 years, or ≥60 years), geographic region, and the presence or absence of coexisting conditions.
§ Shown is the hazard ratio.
¶ Data are for participants with symptomatic or severe Covid-19.
‖ Shown is the incidence rate ratio.
** The number of days with symptoms is presented according to age group and the presence or absence of coexisting conditions, owing to significant interactions between treatment group and age group and between treatment group and the presence or absence of coexisting conditions, which rendered the main between-group comparison noninterpretable.

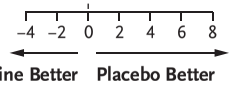
A Symptomatic Covid-19: Unadjusted Primary Analysis



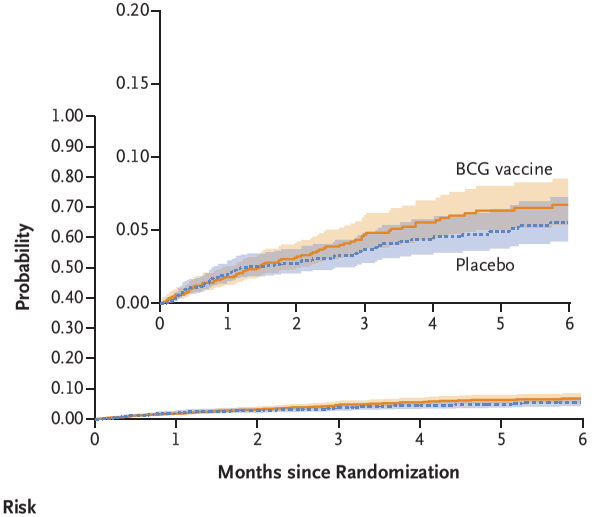
No. at Risk							
BCG vaccine	1695	1451	1049	739	586	480	0
Placebo	1675	1439	1002	704	560	466	0

B Symptomatic Covid-19: Primary, Sensitivity, and Supplementary Analyses

Analysis	Person-Yr	BCG Vaccine	Placebo	Between-Group Difference (95% CI)
		no. with event (estimated percent)		*percentage points*
Primary analysis (modified intention-to-treat population)	876	132 (14.7)	106 (12.3)	2.4 (–0.7 to 5.5)
Including follow-up time after Covid-19 vaccination	1516	196 (12.0)	159 (9.8)	2.2 (0.1 to 4.3)
Excluding episodes ≤14 days after randomization	751	104 (14.0)	81 (11.5)	2.5 (–0.8 to 5.8)
Censoring data from participants at any vaccination	796	122 (14.4)	101 (12.2)	2.1 (–1.1 to 5.3)
Using the intention-to-treat population	990	145 (13.9)	118 (11.4)	2.5 (–0.3 to 5.3)
Including episodes on or after date of receipt of trial intervention	875	132 (14.6)	106 (12.2)	2.4 (–0.9 to 5.7)
Using PCR and RAT results only (intention-to-treat population)	945	125 (12.0)	94 (9.0)	3.0 (0.3 to 5.6)
Using less conservative censoring rules for missing data	886	136 (15.0)	108 (12.4)	2.6 (–0.6 to 5.7)



C Severe Covid-19: Unadjusted Primary Analysis



No. at Risk							
BCG vaccine	1698	1490	1091	776	614	501	0
Placebo	1676	1466	1035	723	576	480	0

D Severe Covid-19: Primary, Sensitivity, and Supplementary Analyses

Analysis	Person-Yr	BCG Vaccine	Placebo	Between-Group Difference (95% CI)
		no. with event (estimated percent)		*percentage points*
Primary analysis (modified intention-to-treat population)	901	75 (7.6)	61 (6.5)	1.1 (–1.2 to 3.5)
Including follow-up time after Covid-19 vaccination	1593	118 (7.0)	94 (5.7)	1.3 (–0.4 to 3.0)
Excluding episodes ≤14 days after randomization	767	59 (7.3)	44 (5.7)	1.5 (–0.9 to 4.0)
Censoring data from participants at any vaccination	818	72 (7.8)	56 (6.3)	1.5 (–0.9 to 4.0)
Using the intention-to-treat population	1028	80 (6.8)	64 (5.6)	1.2 (–0.8 to 3.2)
Including episodes on or after date of receipt of trial intervention	901	75 (7.6)	61 (6.5)	1.1 (–1.2 to 3.4)
Using PCR and RAT results only (intention-to-treat population)	1023	74 (6.1)	58 (4.9)	1.2 (–0.7 to 3.1)
Using less conservative censoring rules for missing data	907	75 (7.6)	61 (6.4)	1.2 (–1.2 to 3.5)

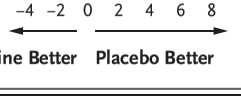


Figure 2 (facing page). Primary Outcomes.

The primary outcomes were symptomatic coronavirus disease 2019 (Covid-19) and severe Covid-19. Panels A and C show Kaplan–Meier curves with 95% confidence intervals in shaded areas (unadjusted primary analyses in the modified intention-to-treat population). Insets show the same data on an expanded y axis. In Panels B and D, forest plots show the between-group difference in the percentage of participants with symptomatic or severe Covid-19, with 95% confidence intervals (adjusted for stratification factors used in randomization; primary, sensitivity, and supplementary analyses). The widths of the confidence intervals for sensitivity and supplementary analyses have not been adjusted for multiplicity and may not be used in place of hypothesis testing. PCR denotes polymerase chain reaction, and RAT rapid antigen test.

DISCUSSION

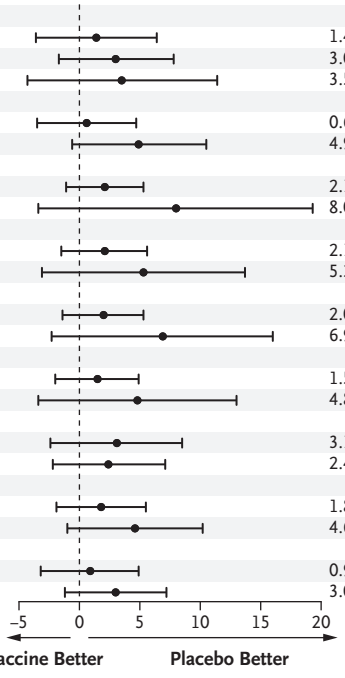
In this multisite, double-blind, randomized, controlled trial involving health care workers in five countries, vaccination with BCG-Denmark did not result in a lower risk of Covid-19 within 6 months than placebo. It is notable that the risk of an episode of Covid-19 was higher in the BCG group than in the placebo group, although the confidence interval around this estimate was wide and crossed zero.

Previous studies that investigated the ability of the BCG vaccine to protect against Covid-19 in adults[15-23] and in animal models[24-27] have shown conflicting results. Retrospective and ecologic studies investigating the association between Covid-19 and history of BCG vaccination or national BCG vaccination policy or coverage are intrinsically limited by many biases, including the long period between BCG vaccination and SARS-CoV-2 exposure.[15] Trials have also shown conflicting results.[16-23] In a nonrandomized trial involving 280 health care workers in the United Arab Emirates, of 71 participants who received BCG revaccination (BCG-Russia), none reported Covid-19, as compared with 18 of 209 participants (8.6%) who declined revaccination.[22] In contrast, randomized, controlled trials of BCG vaccination, with the exception of one, have shown no protective effect against Covid-19. In ACTIVATE-2 (A Randomized Clinical Trial for Enhanced Trained Immune Responses through BCG Vaccination to Prevent Infections by COVID-19), which involved 301 participants 50 years of age or older in Greece, the cumulative incidence of "presumed Covid-19" was lower after the receipt of BCG-Moscow vaccine than after the receipt of placebo, but the primary outcome was defined as possible, probable, or definite Covid-19 (without the requirement for a positive SARS-CoV-2 test).[16] When the incidence of PCR-proven Covid-19 cases was assessed, the difference between the two groups was not significant.[16] The BCG-CORONA trial, which involved 1000 participants in South Africa, showed a higher risk of severe respiratory tract infections after BCG revaccination (BCG-Denmark) than after receipt of placebo but no effect on Covid-19 risk. However, the risk of hospitalization due to Covid-19 was twice as high in the BCG group as in the placebo group, but the confidence interval was wide and included 1 (hazard ratio, 2.0; 95% CI, 0.7 to 5.9; P=0.20).[17] In two trials conducted in the Netherlands, BCG-Denmark vaccination had no effect on the incidence of Covid-19 episodes (as a secondary outcome) among health care workers (1511 participants)[18] or among participants 60 years of age or older (2014 participants).[19] In a trial involving 138 participants in Brazil, BCG revaccination of health care workers with BCG-Moscow did not protect against Covid-19.[20] Similar findings were reported in a trial involving 354 participants in Poland after BCG revaccination with BCG-Moreau.[21] Finally, in an ongoing trial investigating the effect of BCG vaccination on glycemic control in patients with type 1 diabetes in the United States, during a 15-month period, only 1 of 96 participants who had received three doses of BCG-Tokyo (given 2 to 3 years before) had Covid-19, as compared with 6 of 48 participants who received placebo.[23]

The inconsistent results from these and other trials of the off-target effects of the BCG vaccine are probably explained by a number of factors, including differing study designs; varying age (infants, adults, and older adults), sex distribution, and proportion of participants who had previously received BCG vaccine; use of different BCG strains (with varying CFUs or dose)[28,29] and number of doses; and different periods before pathogen exposure. All these factors warrant further investigation. BCG-induced effects might also vary among pathogens. In an animal model, BCG vaccination significantly reduced morbidity and mortality associated with influenza virus but not SARS-CoV-2 infection.[25] In a random-

A Symptomatic Covid-19

Subgroup	Person-Yr	BCG Vaccine	Placebo	Between-Group Difference (95% CI)
		no. with event (estimated percent)		*percentage points*
Age				
<40 yr	360	61 (15.5)	52 (14.1)	1.4 (–3.6 to 6.4)
40–59 yr	427	61 (14.9)	48 (11.8)	3.0 (–1.7 to 7.8)
≥60 yr	89	10 (9.9)	6 (6.3)	3.5 (–4.3 to 11.4)
Coexisting condition				
No	574	84 (14.4)	76 (13.8)	0.6 (–3.5 to 4.7)
Yes	280	46 (15.6)	30 (10.6)	4.9 (–0.6 to 10.5)
Chronic respiratory disease				
No	817	12 (14.6)	10 (12.5)	2.1 (–1.1 to 5.3)
Yes	59	9 (16.4)	4 (8.4)	8.0 (–3.4 to 19.3)
Cardiovascular disease				
No	768	11 (15.2)	99 (13.2)	2.1 (–1.5 to 5.6)
Yes	108	13 (11.0)	7 (5.7)	5.3 (–3.1 to 13.7)
Hypertension				
No	776	11 (15.1)	10 (13.1)	2.0 (–1.4 to 5.3)
Yes	100	13 (12.5)	6 (5.7)	6.9 (–2.3 to 16.0)
Body-mass index				
<30	691	98 (13.7)	82 (12.2)	1.5 (–2.0 to 4.9)
≥30	163	32 (19.5)	24 (14.7)	4.8 (–3.4 to 13.0)
Geographic region				
Brazil	364	92 (20.9)	75 (17.8)	3.1 (–2.4 to 8.5)
Europe	310	40 (11.6)	31 (9.1)	2.4 (–2.2 to 7.1)
Sex				
Female	653	97 (15.1)	88 (13.3)	1.8 (–1.9 to 5.5)
Male	222	35 (13.8)	18 (9.2)	4.6 (–1.0 to 10.2)
Previous BCG vaccination				
No	328	30 (8.8)	26 (7.9)	0.9 (–3.2 to 4.9)
Yes	548	10 (17.0)	80 (14.0)	3.0 (–1.2 to 7.2)



B Severe Covid-19

Subgroup	Person-Yr	BCG Vaccine	Placebo	Between-Group Difference (95% CI)
		no. with event (estimated percent)		*percentage points*
Age				
<40 yr	373	34 (7.7)	30 (7.2)	0.6 (–3.1 to 4.2)
40–59 yr	437	35 (7.8)	26 (5.9)	1.8 (–1.7 to 5.3)
≥60 yr	91	6 (6.1)	5 (5.5)	0.6 (–6.2 to 7.4)
Coexisting condition				
No	592	47 (7.9)	41 (7.2)	0.7 (–2.4 to 3.8)
Yes	287	27 (7.3)	20 (6.0)	1.3 (–2.4 to 5.1)
Chronic respiratory disease				
No	841	69 (7.6)	60 (6.9)	0.7 (–1.6 to 3.1)
Yes	60	6 (8.9)	1 (1.5)	7.4 (1.1 to 13.8)
Cardiovascular disease				
No	791	67 (8.0)	56 (6.9)	1.1 (–1.5 to 3.7)
Yes	110	8 (5.1)	5 (3.6)	1.5 (–3.4 to 6.4)
Hypertension				
No	799	67 (7.9)	57 (7.0)	1.0 (–1.5 to 3.4)
Yes	102	8 (5.6)	4 (3.2)	2.4 (–2.7 to 7.4)
Body-mass index				
<30	711	57 (7.5)	45 (6.2)	1.2 (–1.3 to 3.8)
≥30	168	17 (8.5)	16 (8.8)	–0.3 (–6.1 to 5.5)
Geographic region				
Brazil	382	45 (8.8)	42 (8.6)	0.3 (–3.3 to 3.9)
Europe	317	30 (8.6)	19 (5.5)	3.1 (–0.8 to 6.9)
Sex				
Female	671	58 (8.2)	50 (7.0)	1.3 (–1.5 to 4.0)
Male	229	17 (6.2)	11 (5.0)	1.2 (–2.9 to 5.3)
Previous BCG vaccination				
No	332	24 (7.1)	13 (4.1)	3.0 (–0.2 to 6.2)
Yes	569	51 (7.4)	48 (7.4)	0.1 (–2.7 to 2.9)

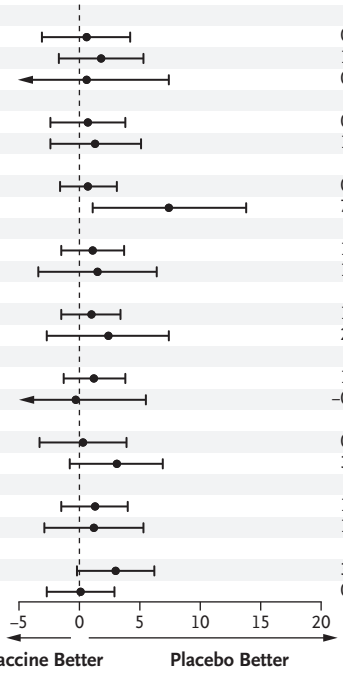


Figure 3 (facing page). Subgroup Analyses.

Subgroup analyses of the primary outcomes — symptomatic Covid-19 (Panel A) and severe Covid-19 (Panel B) — are shown with the use of forest plots of the difference in percentage points and 95% confidence intervals, with adjustment for stratification factors used in randomization. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing. The body-mass index is the weight in kilograms divided by the square of the height in meters. We did not estimate the treatment effect within the geographic region of Australia because there were no episodes of symptomatic Covid-19 or severe Covid-19 there.

ized, controlled trial of neonatal BCG vaccination, in vitro immune responses varied according to pathogen type.[30] Furthermore, in contrast to previously observed BCG-induced enhancement of in vitro cytokine responses to unrelated pathogens,[31,32] responses to SARS-CoV-2 are decreased by BCG vaccination in adults.[33] Factors that could have influenced off-target effects of the BCG vaccine in our trial include the predominance of female participants (in whom off-target effects are proposed to differ as compared with males)[34] and the underrepresentation of participants who had not previously received the BCG vaccine.

Off-target effects of the BCG vaccine are proposed to, at least in part, be underpinned by epigenetic modifications in immune cells that induce a proinflammatory state and stronger cytokine responses to subsequent challenge with unrelated pathogens.[31,32] Stronger immune responses can be beneficial to clear infections but might also increase symptoms. In a human malaria challenge model, participants who received the BCG-Bulgaria vaccine had an earlier onset of symptoms and overall more severe clinical symptoms than unvaccinated controls.[35] In theory, an increased risk of symptomatic Covid-19 could be explained by a BCG-induced stronger immune response. BCG-vaccinated participants in the BRACE trial had more activated and effector T cells in response to in vitro SARS-CoV-2 stimulation than controls.[33] These effects might result in more rapid clearance of SARS-CoV-2, leading to a shorter illness. There was some evidence of this in our trial in post hoc subgroup analyses: the duration of symptoms was lower in the BCG group than in the placebo group, although this finding was limited to participants 60 years of age or older and those without coexisting conditions.

In our trial, more than three quarters of the participants had previously received the BCG vaccine. It has been proposed that the off-target effects of BCG vaccination might be greater in those who have previously received the vaccine than in those who have not.[36] However, it is also possible that revaccination does not induce any incremental off-target benefit over that provided by previous BCG vaccination.[37] It is interesting that in our trial, there was weak evidence of a higher incidence of severe Covid-19 in the BCG group than in the placebo group among participants who had not previously received the BCG vaccine but not among those who received BCG revaccination.

Our trial has several strengths. These include its robust design, large size, recruitment in 36 sites across three continents, blinding of trial-group assignments, stringent Covid-19 case definitions, close active follow-up of participants with daily data collection during illnesses, serologic tests every 3 months, a 98% follow-up rate, and a statistical analysis that accounted for Covid-19–specific vaccination.

The main limitations of our trial were the inability to recruit the planned sample and reduced participant observation time for the primary analysis resulting from the earlier-than-expected availability of Covid-19–specific vaccines. This means that the trial was underpowered and susceptible to type II error, and therefore it is possible that BCG vaccine increases the risk of Covid-19. Another limitation is that the trial definition of severe Covid-19 differed from that more widely used in Covid-19 studies, which commonly includes only hospitalization and death. More than 90% of participants who were categorized as having severe Covid-19 were captured solely by virtue of being "too sick to go to work" (71%) or "unable to get out of bed" (22%) for at least 3 consecutive days. The effect on severe Covid-19 as more commonly defined by hospitalization or death could not be meaningfully analyzed owing to the infrequency of these events. The possibility that BCG vaccine induces a stronger immune response that leads to more

symptomatic disease but more rapid clearance of SARS-CoV-2 and consequent reduced hospitalizations and deaths therefore could not be assessed. Another limitation was that our definition of symptomatic Covid-19 was limited to the original case definition that did not include nonfebrile episodes without respiratory symptoms. Finally, blinding is a challenge in BCG trials, even with a placebo, owing to the injection-site reaction that develops in most persons. This limitation was mitigated by informing participants that BCG vaccination does not always cause a reaction (so that trial-group assignment could not be inferred from the absence of a reaction or scar), using objective primary outcomes, and blinding with respect to data collection and analysis. However, participant presumption of trial group might have influenced adherence to Covid-19 control measures, decisions to receive influenza or Covid-19–specific vaccines, participant reporting of symptoms, or SARS-CoV-2 testing.

In this trial, BCG-Denmark vaccination did not reduce the risk of Covid-19 in health care workers, and the results did not exclude the possibility of an increased risk. Any effect on severe disease as defined by hospitalization or death could not be assessed. It is important that our findings are not extrapolated beyond the effect of BCG-Denmark vaccine on Covid-19 in health care workers. Several studies show beneficial off-target effects of the BCG vaccine in other situations, particularly among infants in high-mortality geographic settings,[4] and ongoing research is examining potential underlying immunologic mechanisms.[38,39]

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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

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