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Using BCG Vaccine to Enhance Nonspecific Protection of Health Care Workers During the COVID-19 Pandemic: A Randomized Controlled Trial

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Background. The BCG (Bacillus Calmette-Guérin) vaccine can induce nonspecific protection against unrelated infections. We aimed to test the effect of BCG on absenteeism and health of Danish health care workers (HCWs) during the coronavirus disease 2019 (COVID-19) pandemic.

Methods. A single-blinded randomized controlled trial included 1221 HCWs from 9 Danish hospitals. Participants were randomized 1:1 to standard dose BCG or placebo. Primary outcome was days of unplanned absenteeism. Main secondary outcomes were incidence of COVID-19, all-cause hospitalization, and infectious disease episodes.

Results. There was no significant effect of BCG on unplanned absenteeism. Mean number of days absent per 1000 workdays was 20 in the BCG group and 17 in the placebo group (risk ratio, 1.23; 95% credibility interval, 0.98–1.53). BCG had no effect on incidence of COVID-19 or all-cause hospitalization overall. In secondary analyses BCG revaccination was associated with higher COVID-19 incidence (hazard ratio [HR], 2.47; 95% confidence interval [CI], 1.07–5.71), but also reduced risk of hospitalization (HR, 0.28; 95% CI, .09–.86). The incidence of infectious disease episodes was similar between randomization groups (HR, 1.09; 95% CI, .96–1.24).

Conclusions. In this relatively healthy cohort of HCWs, there was no overall effect of BCG on any of the study outcomes.

Clinical Trials Registration. NCT0437329 and EU Clinical Trials Register (EudraCT number 2020-001888-90).

Keywords. BCG vaccination; nonspecific effects of vaccines; COVID-19; SARS-CoV-2; epidemic; randomized controlled trial; health care worker.

Health care workers (HCWs) faced an elevated risk of exposure to the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and before the arrival of the coronavirus disease 2019 (COVID-19) vaccines this represented a serious threat to hospital personnel capacity [1, 2]. Strategies to prevent COVID-19 or to mitigate its clinical consequences were urgently needed.

Bacillus Calmette-Guérin (BCG) was developed as a vaccine against tuberculosis but has been shown in some studies to have nonspecific effects (NSEs) on the immune system, providing protection against unrelated infections. BCG has been associated with reduced all-cause child mortality in observational studies and in randomized controlled trials (RCTs), BCG at birth was associated with reductions in neonatal sepsis and respiratory infections [3–8]. The beneficial NSEs of BCG might not be limited to children. A RCT from Greece reported that BCG revaccination reduced the risk of subsequent infection in the elderly by 45%, with the strongest effect on respiratory

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infections, the risk reduction being 79% (95% confidence interval [CI], 28%–94%) [9]. The beneficial NSEs of BCG may be explained by epigenetic and metabolic reprogramming of innate immune cells, leading to increased antimicrobial activity, a process termed trained immunity [10]. Upon stimulation with pathogens after BCG vaccination, the innate immune system reacts more efficiently to various infectious stimuli [11]. This has also been shown in vivo; for example, in a human experimental study, BCG reduced viral load after yellow fever vaccination [12].

We hypothesized that BCG might reduce susceptibility to and/or severity of COVID-19, and as such could serve as a bridge-gap vaccine during this and future pandemics while awaiting pathogen-specific vaccines [13, 14]. The primary objective was to test the efficacy of BCG to reduce unplanned absenteeism among HCWs during the COVID-19 pandemic [15]. We specifically hypothesized that BCG vaccination of HCWs would reduce absenteeism by 20% over a period of 6 months. The secondary objectives were to reduce the risk of COVID-19, all-cause hospitalization, and infectious diseases in general among HCWs during the COVID-19 pandemic.

METHODS

Trial Design and Participants

We conducted a single-blinded, placebo-controlled, randomized trial, aiming to recruit 1500 HCWs at 9 Danish hospitals throughout the country. Enrolment started in May 2020 and ended in January 2021, after COVID-19 vaccines became available. Participation was based on voluntary enrolment after oral and written information was given. HCWs older than 18 years employed at a participating hospital for at least 22 hours per week were eligible. Exclusion criteria were known contraindications to BCG vaccination (Supplementary Material) and previous confirmed SARS-CoV-2 infection (self-reported or documented by positive lateral flow antibody test at enrolment).

The study was approved by the Ethics Committee of the Region of Southern Denmark (approval number S-20200062C) and the Danish Medicines Agency (approval number 2020041936), and conducted according to the principles of the Helsinki Declaration and Good Clinical Practice (GCP) guidelines. The study was monitored by the GCP unit at Odense University Hospital. All participants provided written informed consent.

Trial Procedures

Participants were randomized 1:1 to standard dose BCG vaccination (BCG strain 1331; AJ Vaccines, Denmark) or placebo. BCG (0.1 mL suspended vaccine) was administered intradermally in the right upper arm. Placebo constituted 0.1 mL sterile natrium chloride (saline) injected in the same way. Participants were vaccinated once at enrollment; no further treatment of participants took place.

Before inclusion, subjects were tested for SARS-CoV-2 immunoglobulin M/immunoglobulin G (IgM/IgG) antibodies using a point of care lateral flow test (OnSite Rapid Test; CTK Biotech). If positive, the subject was excluded from participation. Randomization was stratified by hospital, sex, and age group (± 45 years of age) in randomly selected blocks of 4 and 6 using REDCap electronic data capture tools hosted at the Region of Southern Denmark [16, 17]. Only participants were blinded to the treatment provided. Participants were followed for 6 months postrandomization with weekly electronic questionnaires concerning symptoms and absenteeism, sent to participants via secure email with a link to the questionnaire. A summary of the study protocol was published in Trials in 2020 [15].

Outcomes

All outcomes were based on self-reported data.

Primary Outcome, Unplanned Absenteeism

The reason for focusing on absenteeism was lack of testing capacity early in the pandemic. As we expected to conduct this trial during a period with high transmission rates, absenteeism was considered a good indicator of the burden of COVID-19 among HCWs. Number of workdays and days of absence were reported weekly by the participants. Unplanned absenteeism constituted absenteeism caused by illness. We excluded long-term absence because of stress and restitution periods after elective surgery, as well as absence due to pregnancy-related symptoms, caring for a sick child, or quarantine due to COVID-19 exposure.

Secondary Outcomes

The main secondary outcomes were incidence of verified COVID-19, all-cause hospitalization, and infectious disease episodes. Additional secondary outcomes were days of unplanned absenteeism due to infection, respiratory infection, and COVID-19, as well as incidence of self-reported acute respiratory symptoms, intensive care admissions, and death. For some secondary outcomes, the number of events was not sufficient to permit a meaningful analysis: incidence of hospital admission due to infectious diseases (n = 8; 4 BCG, 4 placebo); incidence of hospital admission due to COVID-19 (n = 1; 1 BCG, 0 placebo); incidence of intensive care admissions (n = 0); and death (n = 0).

Verified COVID-19 was defined as having a positive SARS-CoV-2 PCR (polymerase chain reaction) test, rapid antigen test, or antibody test, all based on information retrieved from participant questionnaire responses. All hospital admissions were evaluated by study personnel. Only acute admissions were considered; elective surgery and visits to outpatient clinics were not included in the analysis (n = 7; 3 BCG, 4 placebo). Infectious disease episodes were defined as 1 or more days of self-reported infectious disease and/or

symptoms of infection. An infectious disease episode was considered a new episode if separated from previous symptoms by 7 days or more. Infectious disease episodes were classified as respiratory infections if participants had 1 or more days within an episode with respiratory symptoms (Supplementary Material).

Sample Size

We assumed the average absenteeism among controls would be 5 days during the scheduled 6 months of follow-up and 4 days in the intervention group, corresponding to a 20% reduction, which could be demonstrated with >80% power and an α of .05 in a cohort of 1500 participants with 10% loss to follow-up.

Statistical Analysis

We applied Bayesian negative binomial regression models [18] to assess days of absenteeism, providing risk ratio (RR) estimates with 95% credibility intervals (CrI). For incidence outcomes we used Cox proportional hazards regression models with time since inclusion as underlying time scale providing hazard ratio (HR) estimates with 95% CI. Participants were considered at risk of absenteeism during weeks for which a questionnaire had been filled out, using the average expected workdays per week as exposure. We report the rate of unplanned absenteeism as days absent per 1000 workdays.

The incidence of disease episodes and respiratory symptoms were reported per 1000 follow-up days counting only follow-up days for which a weekly questionnaire had been filled out. The incidence of severe adverse event outcomes was reported per 1000 follow-up days, using total days of follow-up since inclusion, as these more severe outcomes were also captured during extra monthly questionnaires and by end of follow-up.

Possible effect modifiers of NSEs were recently reviewed [7, 19]. NSEs may be sex differential [20] and boosting might increase the effect, indicating that revaccination could be more effective than primary vaccination [21]. Furthermore, the sequence in which vaccines are given is important, as the NSEs of a vaccine can be altered once a new vaccine is given [7, 22]. We included prespecified stratified analyses of potential effect modifiers: sex, presence of BCG scar at inclusion, and receipt of other vaccines during follow-up. When we analyzed the effect of other vaccines during follow-up, participants were divided into groups according to which vaccine(s) they received: influenza vaccine, COVID-19 vaccine, or both. Individuals could thus contribute risk time to more than 1 group. The few individuals, who received any other vaccine, were censored at the time of receipt of that vaccine (n = 8). We also assessed potential interactions with age and by follow-up adherence.

COVID-19 Epidemic in Denmark

In 2020, following a period of lockdown in the spring, infection rates decreased, coinciding with the start of the trial. Infection rates stayed low during the summer months and started increasing in October 2020. COVID-19 testing of HCWs was guided by symptoms and became increasingly available during the study period, always free of charge. Screening of asymptomatic HCWs for COVID-19 was not recommended in this period.

RESULTS

From May 2020 to January 2021, we screened 1293 HCWs for inclusion; 63 fulfilled exclusion criteria and 1230 were included and randomized. Nine participants (3 randomized to BCG and

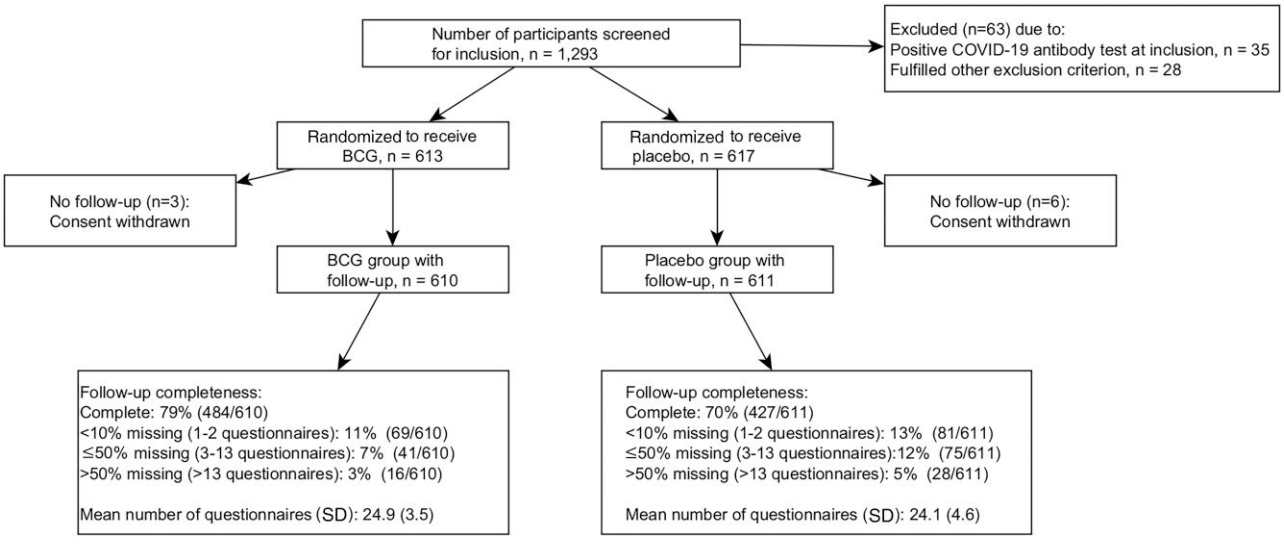

Figure 1. Inclusion, randomization, and follow-up adherence of participants in the Danish health care worker trial. Abbreviations: BCG, Bacillus Calmette-Guérin; COVID-19, coronavirus disease 2019.

Table 1. Baseline Characteristics of Participants in the Danish Health Care Worker Trial According to Randomization Group

Characteristic	BCG (n = 610)	Placebo (n = 611)
Age at inclusion, y, median (IQR)	48 (37–56)	47 (36–57)
Older than 45 y, % (n/N)	56 (344/610)	56 (342/611)
Sex, % female (n/N)	83 (507/610)	83 (505/611)
Smoking, % (n/N)	15 (89/610)	13 (82/611)
Received BCG vaccine previously, % (n/N)	53 (323/610)	54 (328/611)
Had BCG scar from previous BCG vaccination, % (n/N)	47 (285/610)	51 (311/611)
Profession, % (n/N)		
Medical doctor	20 (121/610)	16 (100/611)
Nursing staff or midwife	51 (310/610)	49 (300/611)
Other staff	29 (179/610)	35 (211/611)
Working hours, median (IQR)	37 (33–37)	37 (33–37)
Department, % (n/N)		
Medical department	26 (157/610)	25 (153/611)
Intensive care	13 (77/610)	13 (77/611)
Pediatric department	10 (58/610)	9 (53/611)
Surgical department	5 (29/610)	6 (35/611)
Other department	47 (289/610)	48 (293/611)
COVID-19 patients in care, % (n/N)	46 (278/610)	44 (270/611)
COVID-19 symptoms before inclusion, % (n/N)	25 (154/610)	26 (156/611)
Previously COVID-19 PCR tested, % yes (n/N)	57 (348/610)	55 (338/611)
Has a chronic disease, % (n/N)	36 (220/610)	32 (198/611)
Cardiovascular disease	6 (37/610)	5 (33/611)
Lung disease	4 (26/610)	6 (35/611)
Diabetes	1 (8/610)	1 (5/611)
Other chronic disease	24 (149/610)	20 (125/611)
Regular medicine use, % (n/N)	43 (264/610)	40 (244/611)
Received influenza vaccine 2019/2020, % (n/N)	48 (291/610)	44 (268/611)
Received other vaccine within the last year, % (n/N)	15 (94/610)	15 (89/611)

Abbreviations: BCG, Bacillus Calmette-Guérin; COVID-19, coronavirus disease 2019; IQR, interquartile range; PCR, polymerase chain reaction.

6 randomized to placebo) were excluded due to a complete lack of follow-up. As they never responded after inclusion, we considered their consent withdrawn. This left a study population of 1221 HCWs randomized to BCG (n = 610) or placebo (n = 611) (Figure 1). Overall, baseline characteristics were comparable between the groups (Table 1).

After 6 months' follow-up, 84% (511/610) of participants allocated to BCG vaccination reported having acquired a scar at the vaccination site. Blood samples from inclusion and end of follow-up were tested for SARS-CoV-2 antibodies. During follow-up, only 2.2% of the COVID-19 unvaccinated participants became seropositive; 2.4% in the BCG group and 2.1% in the placebo group (Madsen AMR, Gehrt L, Barington T, et al unpublished). Participants allocated to BCG were more likely to complete all questionnaires (79%) than participants allocated to placebo (70%) ($P < .001$). The mean number of follow-up days were 174 (SD 23) in the BCG group and 171 (SD 29) in the placebo group ($P = .06$) (Figure 1).

The incidence of serious adverse events was similar in the 2 groups, and none were considered related to the trial vaccines (Supplementary Material). There were no deaths in the cohort and no serious adverse reactions to BCG vaccination.

Other Vaccines During Follow-up

The seasonal influenza vaccines recommended for all hospital staff became available on 1 October and COVID-19 vaccines on 27 December 2020. In total, 29% (348/1189) of eligible participants (under follow-up between 1 October and 31 December 2020) received an influenza vaccine and 82% (596/723) of eligible participants (under follow-up after COVID-19 vaccines became available) received a COVID-19 vaccine (66% Pfizer-BioNTech, 3% Moderna, 11% AstraZeneca, 0.6% AstraZeneca in combination with another vaccine, 20% not specified). Finally, 13.1% (95/723) received both influenza and COVID-19 vaccine.

Unplanned Absenteeism

Main Outcome: Unplanned Absenteeism

The mean number of days of unplanned absenteeism was 19 days per 1000 workdays overall; 20 days in the BCG group compared with 17 days in the placebo group, the RR being 1.23 (95% CrI, 0.98–1.53). Assessed over calendar time, the incidence rate in the 2 groups was similar up to December 2021, thereafter the incidence in the BCG group exceeded that of the placebo group (Figure 2). This was reflected in the effect estimates before and after participants received other vaccines. The effect estimate of BCG versus placebo after receipt of other vaccines was 1.45 (95% CrI, 1.00–2.14). There was no effect modification by age, BCG scar status, or follow-up adherence (Table 2).

Secondary Absenteeism Outcomes

Unplanned absenteeism due to infections (RR, 1.12; 95% CrI, 0.93–1.36), or more specifically due to respiratory infections (RR, 1.21; 95% CrI, 0.94–1.53) did not vary between the randomization groups. There were very few days of absenteeism due to verified COVID-19 (BCG 3 days and placebo 2 days per 1000 workdays, RR, 1.38; 95% CrI, 0.52–3.61).

Incidence of COVID-19

There were 76 cases of verified COVID-19: 43 in the BCG group and 33 in the placebo group, corresponding to an incidence rate per 1000 days of 0.41 and 0.32, respectively, and a HR of 1.31 (95% CI, .83–2.06). BCG was associated with higher incidence of COVID-19 in the age group older than 45 years and in participants with a scar from previous BCG vaccination. The higher incidence of COVID-19 in these subgroups seemed to be driven by BCG scar rather than age. Participants older than 45 years who did not have a BCG scar from previous vaccination did not have an elevated risk of COVID-19 (HR, 1.27; 95% CI, .29–5.50), whereas participants older than 45 years with a BCG scar did (HR, 2.65; 95% CI, 1.09–6.45). The effect of BCG was not modified by sex, follow-up adherence, or other vaccines (Table 3 and Supplementary Figure 2).

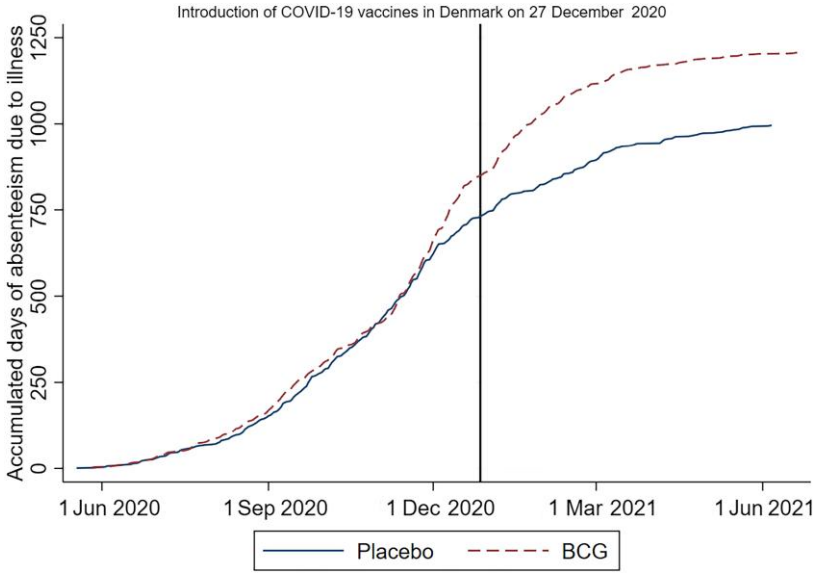

Figure 2. Cumulative incidence of unplanned absenteeism among Danish health care workers during the COVID-19 pandemic by randomization group with calendar time as underlying time scale. Abbreviations: BCG, Bacillus Calmette-Guérin; COVID-19, coronavirus disease 2019.

Table 2. Effect of BCG Vaccine on Unplanned Absenteeism Among Danish Health Care Workers During the COVID-19 Pandemic

	Mean Days Absent per 1000 Workdays (Total Days Absent/Total Workdays)			
	BCG (n = 610) 20 (1207/60 439)	Placebo (n = 611) 17 (996/58 597)	RR (95% CrI) BCG vs Placebo[a] 1.23 (0.98–1.53)	*P* for Interaction
By sex				.87
Men	17 (176/10 418)	15 (151/10 191)	1.33 (0.85–2.01)	
Women	21 (1031/50 021)	17 (845/48 406)	**1.28 (1.07–1.51)**	
By age, y				.50
< 45	21 (550/25 717)	20 (499/25 420)	1.06 (0.88–1.26)	
≥ 45	19 (657/34 722)	15 (497/33 177)	1.17 (0.93–1.46)	
By BCG scar status				.13
BCG scar	14 (410/28 968)	15 (457/29 883)	0.91 (0.62–1.35)	
No scar	25 (797/31 471)	19 (539/28 714)	1.33 (0.98–1.80)	
By follow-up adherence				.74
Complete	20 (985/50 250)	16 (718/44 250)	1.26 (0.96–1.65)	
Incomplete	21 (222/10 189)	19 (278/14 347)	1.14 (0.67–1.93)	
Other vaccine(s) during follow-up				.88
Before	20 (777/39 188)	18 (709/39 143)	1.12 (0.83–1.50)	
After	20 (430/21 251)	15 (287/19 454)	**1.45 (1.00–2.14)**	.29
Influenza vaccine	26 (168/6369)	17 (97/5579)	1.80 (0.95–3.48)	.67
COVID vaccine	16 (211/12 755)	13 (168/12 589)	1.36 (0.76–2.50)	.57
Influenza + COVID vaccine	29 (49/1672)	15 (19/1252)	2.32 (0.16–56.00)	.63

Mean number of days absent per participant per 1000 workdays by randomization group. The BCG group is compared to the placebo group in Bayesian negative binomial regression analysis providing risk ratio with 95% credibility intervals. Statistically significant findings in bold.

Abbreviations: BCG, Bacillus Calmette-Guérin; COVID-19, coronavirus disease 2019; CrI, credibility interval; RR, risk ratio.

[a]Adjusted for the stratification variables and with average workdays per week as exposure time.

Incidence of All-Cause Hospitalization

The incidence of all-cause hospitalization per 1000 days was 0.14 (15 cases) in the BCG group and 0.17 (18 cases) in the placebo group (HR, 0.84; 95% CI, .42–1.66). The association was not the same in participants with and without a scar from previous BCG vaccination. Among participants with a scar, the incidence of hospitalization was significantly lower (HR, 0.28; 95% CI, .09–.86) compared to participants without a scar (HR 2.63; 95% CI, .72–9.61). The effect of BCG was not modified by sex, age group, follow-up adherence, or other vaccines (Table 4 and Supplementary Figure 3).

Table 3. Effect of BCG Vaccine on the Incidence of COVID-19 Among Danish Health Care Workers During the COVID-19 Pandemic

	Incidence Rate per 1000 d (No. of Cases/ Total Days of Follow-up)			
All cases	BCG (n = 610) 0.41 (43/104 597)	Placebo (n = 611) 0.32 (33/103 427)	HR (95% CI) BCG vs Placebo[a] 1.31 (.83–2.06)	*P* for Interaction
By sex				.49
Men	0.28 (5/17 576)	0.39 (7/17 748)	0.84 (.25–2.77)	
Women	0.42 (38/89 839)	0.30 (26/87 959)	1.33 (.81–2.20)	
By age, y				**.045**
< 45	0.47 (21/44 705)	0.52 (23/44 151)	0.91 (.50–1.65)	
≥ 45	0.37 (22/59 892)	0.17 (10/59 276)	**2.23 (1.06–4.73)**	
By BCG scar status				**.043**
BCG scar	0.36 (18/49 726)	0.15 (8/53 634)	**2.47 (1.07–5.71)**	
No scar	0.46 (25/54 871)	0.50 (25/49 793)	0.91 (.52–1.60)	
By follow-up adherence				.47
Complete	0.40 (34/84 644)	0.28 (21/75 498)	1.53 (.89–2.65)	
Incomplete	0.45 (9/19 953)	0.43 (12/27 929)	1.15 (.47–2.83)	
Other vaccine(s) during follow-up				.54
Before	0.44 (30/68 929)	0.27 (19/70 250)	1.66 (.92–3.00)	
After	0.36 (13/35 668)	0.42 (14/33 177)	0.99 (.45–2.15)	.78
Influenza vaccine	0.57 (6/10 589)	0.54 (5/9206)	1.20 (.33–4.36)	.27
COVID vaccine	0.23 (5/21 711)	0.32 (7/21 814)	0.67 (.19–2.31)	.62
Influenza and COVID vaccine	0.78 (2/2578)	0.93 (2/2157)	1.00 (.14–7.24)	.54

The incidence rate of microbiologically or immunologically verified COVID-19 per 1000 follow-up days by randomization group. The BCG group is compared to the placebo group in Cox proportional hazards regression model providing hazard ratio estimates with 95% confidence intervals. Statistically significant findings in bold.

Abbreviations: BCG, Bacillus Calmette-Guérin; CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio.

[a]Adjusted for stratification variables and with average workdays per week as exposure time.

Infectious Disease Episodes

The incidence of infectious disease episodes per 1000 days was 4.54 in the BCG group and 4.16 in the placebo group (HR, 1.09; 95% CI, .96–1.24). Before other vaccines were administered, the incidence rate was similar between the groups while after participants received other vaccines, there were more episodes in the BCG group. The effect was not modified by sex, age, BCG scar status, or follow-up adherence (Table 5 and Supplementary Figure 4). There was no difference between the groups when looking at respiratory infection episodes only (HR, 1.08; 95% CI, .92–1.26).

DISCUSSION

In this cohort of generally healthy HCWs, we could not confirm the hypothesis that BCG vaccination would reduce unplanned absenteeism and protect against COVID-19. We found a tendency of BCG being associated with more absenteeism and more infectious disease episodes from December 2020 and onwards, corresponding to the period when other vaccines were administered. In participants with a scar from previous BCG vaccination, randomization to BCG was associated with a higher risk of COVID-19 but a lower risk of all-cause hospitalization.

We only recruited 82% of the anticipated 1500 participants, as we stopped enrolment when the COVID-19 vaccines became available to HCWs. Fortunately, loss to follow-up was <1%, which was less than expected. Absenteeism turned out not to be a good proxy for the burden of COVID-19 among health care workers as the incidence of COVID-19 was low. Substantial infection prevention and control precautions imposed on society also resulted in lower incidences of infections in general, and the HCWs had fewer days of absenteeism than anticipated.

Incomplete blinding of participants is a general problem when working with BCG, which induces a noticeable skin reaction in most recipients. We found significant differences in reporting with a higher rate of completeness of follow-up in the BCG group.

Denmark stopped using BCG vaccine in the early 1980s [23]. Before this, BCG was recommended for all children at school entry, so most participants over the age of 45 years had been BCG vaccinated, whereas most younger participants had not. This provided an opportunity to compare the effect of receiving a first BCG vaccination versus BCG revaccination.

Several RCTs testing BCG's effect against COVID-19 have been conducted during the pandemic [9, 24–30]. Like most trials, ours did not show any significant effect of BCG. In fact, we found a tendency of more absenteeism and more self-reported infections among participants randomized to BCG. Indication of increased symptomatology after BCG vaccination has also been seen in other studies. In a South African trial, allocation to BCG was associated with a higher risk of severe respiratory tract infection although this did not result in more deaths [25].

Table 4. Effect of BCG Vaccine on the Incidence of All-Cause Hospitalization Among Danish Health Care Workers During the COVID-19 Pandemic

	Incidence Rate per 1000 d (No. of Cases/ Total Days of Follow-up)			
All cases	BCG (n = 610) 0.14 (15/107 415)	Placebo (n = 611) 0.17 (18/105 707)	HR (95% CI) BCG vs Placebo[a] 0.84 (.42–1.66)	*P* for Interaction
By sex				.86
Men	0.11 (2/17 576)	0.17 (3/17 748)	0.72 (.12–4.36)	
Women	0.14 (13/89 839)	0.17 (15/87 959)	0.86 (.41–1.80)	
By age, y				.43
Age < 45	0.13 (6/45 869)	0.11 (5/45 850)	1.23 (.38–4.05)	
Age ≥ 45	0.15 (9/61 546)	0.22 (13/59 857)	0.68 (.29–1.60)	
By BCG scar status				**.011**
BCG scar	0.08 (4/51 007)	0.28 (15/54 253)	**0.28 (.09–.86)**	
No scar	0.20 (11/56 408)	0.06 (3/51 454)	2.63 (.72–9.61)	
By follow-up adherence				.92
Complete	0.14 (12/87 110)	0.14 (11/76 842)	1.00 (.44–2.27)	
Incomplete	0.15 (3/20 305)	0.24 (7/28 865)	0.92 (.22–3.85)	
Other vaccine(s) during follow-up				.95
Before	0.14 (10/70 327)	0.18 (13/71 171)	0.85 (.37–1.98)	
After	0.14 (5/36 917)	0.15 (5/34 371)	0.81 (.23–2.86)	.95
Influenza vaccine	0.19 (2/10 701)	0.21 (2/9495)	0.66 (.09–4.90)	.82
COVID vaccine	0.13 (3/22 635)	0.13 (3/22 565)	1.02 (.20–5.10)	.85
Influenza and COVID vaccine	0.00 (0/2791)	0.00 (0/2269)	…	

Incidence rate of all-cause hospital admissions per 1000 follow-up days by randomization group. BCG group is compared to placebo group in Cox proportional hazards regression models providing hazard ratio estimates with 95% confidence intervals. Statistically significant findings in bold.

Abbreviations: BCG, Bacillus Calmette-Guérin; CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio.

[a]Adjusted for stratification variables with average workdays per week as exposure time.

Table 5. Effect of BCG Vaccine on the Incidence of Self-reported Infection Episodes Among Danish Health Care Workers During the COVID-19 Pandemic

	Incidence Rate per 1000 d (No. of Cases/ Total Days of Follow-Up)			
All episodes	BCG (n = 610) 4.54 (487/107 226)	Placebo (n = 611) 4.16 (439/105 600)	HR (95% CI) BCG vs Placebo[a] 1.09 (.96–1.24)	*P* for Interaction
By sex				.21
Men	3.93 (69/17 560)	4.29 (76/17 727)	0.90 (.65–1.25)	
Women	4.66 (418/89 666)	4.13 (363/87 873)	1.13 (.98–1.30)	
By age, y				.20
< 45	5.38 (246/45 760)	5.33 (244/45 802)	1.01 (.84–1.20)	
≥ 45	3.92 (241/61 466)	3.26 (195/59 798)	1.20 (.99–1.45)	
By BCG scar status				.67
BCG scar	3.65 (186/50 944)	3.27 (177/54 204)	1.12 (.91–1.38)	
No scar	5.35 (301/56 282)	5.10 (262/51 396)	1.05 (.89–1.24)	
By follow-up adherence				.43
Complete	4.49 (390/86 945)	3.95 (303/76 781)	1.14 (.98–1.33)	
Incomplete	4.78 (97/20 281)	4.72 (136/28 819)	1.02 (.78–1.34)	
Other vaccine(s) during follow-up				.13
Before	4.29 (299/69 639)	4.15 (292/70 359)	1.02 (.86–1.19)	
After	5.00 (188/37 587)	4.17 (147/35 241)	**1.26 (1.01–1.57)**	
Influenza vaccine	4.34 (49/11 290)	3.96 (46/11 616)	1.05 (.69–1.60)	.90
COVID vaccine	4.69 (107/22 827)	3.68 (85/23 120)	1.32 (.98–1.76)	.13
Influenza and COVID vaccine	5.03 (58/11 537)	3.39 (39/11 504)	**1.67 (1.08–2.57)**	**.04**

Incidence rate of infectious disease episodes per 1000 follow-up days by randomization group. BCG group is compared to placebo group in Cox proportional hazards regression models providing hazard ratio estimates with 95% confidence intervals. Statistically significant findings in bold.

Abbreviations: BCG, Bacillus Calmette-Guérin; CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio.

[a]Adjusted for stratification variables and with average workdays per week as exposure time.

In the BRACE trial, an international multicenter trial including 3988 HCWs which also found no protection of BCG vaccination against COVID-19, results pointed toward a higher risk of symptomatic COVID-19 among the BCG vaccinated, especially among those who had not previously received BCG [30]. A limitation of that study was that the threshold for meeting the trial definition of severe COVID-19 was too low, and consequently mainly moderate disease episodes were captured. As a result, the trial could not test the hypothesis that BCG-induced modulation of the immune response to SARS-CoV-2, while increasing symptomatic disease, may reduce viral load and subsequently severe disease, as defined by hospitalization or death [30, 31].

In our trial, we had an ideal set up for testing the association with previous BCG vaccination. We found allocation to BCG was associated with a higher incidence of symptomatic COVID-19 in participants with a scar from previous BCG vaccination, but interestingly also with a significantly lower incidence of all-cause hospitalization. BCG might lead to increased symptoms, perhaps as a result of activation of the innate immune system [10, 11], but the general strengthening of the immune system may lead to lower all-cause morbidity and mortality. In a meta-analysis of effects of BCG versus placebo in 5 trials conducted during the COVID-19 pandemic, randomization to BCG was associated with a 39% (95% CI, 1%–62%) reduction in overall mortality risk [19].

The current evidence is compatible with a protective effect of receiving BCG in specific study populations characterized by having potentially weakened immune systems (eg, multimorbid elderly [29] or people with type 1 diabetes [32]), and by having previously received at least 1 dose of BCG. The trials that found a protective effect of BCG (trials from Greece [29], Brazil [26], India [33], and US [32]) were conducted in contexts where almost all participants would have been BCG vaccinated before. In contrast, in 2 larger studies performed in the Netherlands where BCG was never used on a routine basis, no protective effect of BCG vaccination in elderly populations at risk was observed [28, 34]. This may suggest important differences between populations depending on BCG vaccination status, but this hypothesis needs to be tested in future studies.

The nonspecific effects of BCG may be modified by the receipt of other vaccines. In children, BCG has been associated with reduced mortality, but once they receive an inactivated vaccine, priming with BCG may actually lead to higher mortality [7, 8]. We therefore investigated possible interactions between BCG and other vaccines given during follow-up [7, 19]. Indeed, the data indicated a possible interaction for the 2 best-powered outcomes, absenteeism and infectious disease episodes. Few of the other BCG–COVID-19 trials have so far investigated the importance of sequence and combination of vaccines, but hopefully a meta-analysis of the trials can throw further light on this research question.

In conclusion, there was no overall effect of BCG on any of the outcomes. In subgroup analyses we found BCG revaccination might increase the risk of COVID-19 but at the same time protect against all-cause hospitalization. Nonlive vaccines given after BCG may negatively modify the effect of BCG. These findings underline the importance of distinguishing between primary vaccination and revaccination when assessing nonspecific effects of vaccines. The possible interaction between BCG and other vaccines leads to further discussion of the importance of the sequence in which vaccines are given and the need for further exploration in this area.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Author contributions. C. S. B., P. A., F. S. B., and A. M. R. M., with help from T. G. K. and M. G. N., conceived and designed the trial and coauthored the protocol. T. B., M. B. A., L. S. D., S. B. D., I. S. J., P. E. K., E. C. L. L., C. B. M., and C. W. helped organizing recruitment at the hospitals. A. M. R. M. was primary investigator and with help from A. O., C. D., E. S. O., F. S. B., G. F., G. S. K., L. M., M. A., M. K. S., and Z. N. H. recruited participants. S. N. conducted the statistical analyses and A. M. R. M. wrote the first draft of the paper. All authors contributed to and approved the final manuscript.

Data availability. Deidentified participant data with a data dictionary can be shared after approval of a data-sharing proposal sent to C. S. B. (cbenn@health.sdu.dk).

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