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ORIGINAL ARTICLE

Randomized trial of BCG in healthcare workers to reduce absenteeism during the COVID-19 pandemic in sub-Saharan Africa

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Background: We tested whether providing BCG vaccine to healthcare workers (HCWs) could reduce non-planned absenteeism and thereby reduce the potential impact of the COVID-19 pandemic on healthcare systems in Africa.

Methods: We conducted a multicenter, single-blinded, placebo-controlled randomized trial in Guinea-Bissau and Mozambique between December 2020 and June 2022. Participants were randomized 1:1 to BCG vaccine or placebo (saline) and followed by biweekly telephone calls for 6 mo. The incidence of unplanned absenteeism due to illness was analyzed using Bayesian negative binomial regression yielding relative RRs. Secondary outcomes included infectious disease episodes, COVID-19 infection and all-cause hospitalizations.

Results: We enrolled 668 HCWs (Guinea-Bissau, n=503; Mozambique, n=165). The RR for absenteeism of BCG vs placebo was 1.29 (0.81 to 1.94) with comparable effects by country. No protection against infectious disease episodes (HR=1.18 [0.97 to 1.45]) or COVID-19 infection (HR=1.19 [0.80 to 1.75]) was observed. Two trial deaths (1 BCG, 1 control) were registered and nine admissions (3 BCG, 6 control), the all-cause admission HR being 0.51 (0.13 to 2.03).

Conclusions: With 64% of the planned sample size and unplanned absenteeism rates lower than expected, BCG did not reduce self-reported absenteeism due to illness. Rather, BCG tended to increase the risk of self-reported absenteeism, infectious disease episodes and COVID-19 infections.

Short summary: This was a randomized control trial assessing non-specific effects of BCG vaccination in healthcare workers. There was no beneficial effect on self-reported absenteeism due to illness within 6 mo of follow-up during the COVID-19 pandemic, but a trend towards fewer all-cause hospital admissions.

Keywords: bacillus Calmette-Guérin (BCG), COVID-19 pandemic, healthcare workers, non-specific effects of vaccines, sub-Saharan Africa

Introduction

Coronavirus disease-2019 (COVID-19) became a global pandemic at the beginning of 2020. While new vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were still being developed, it was hypothesized[1,2] that the beneficial non-specific effects of existing live vaccines could help mitigate the impact of COVID-19, primarily among healthcare workers (HCWs) and older people.

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The BCG is a vaccine against TB that has been used for more than 100 years. Currently, more than 120 million doses are administered each year, primarily to newborns.[3] Several randomized controlled trials (RCTs) have shown that at-birth BCG to healthy infants induces protection against infections other than TB.[4–7] For example, BCG vaccination has been associated with lower infant mortality, primarily because of a reduced risk of neonatal sepsis.[8–10] On the other hand, BCG provided to frail newborns admitted for intensive care treatment did not reduce in-hospital mortality risk.[11,12] The non-specific effects of BCG have also been investigated in adults.[13,14] An Indonesian trial thus indicated that providing consecutive BCG vaccination for 3 mo to older individuals could reduce the incidence of acute upper tract respiratory infections by 80% (95% CI: 22 to 95%).[14] In a South African RCT among adolescents, the risk of upper respiratory tract infections was 2.1% and 7.9% in the BCG and placebo group ($p<0.001$), respectively.[15] The probable immunological pathways are *trained innate immunity y*[16] and *emergency granulopoiesis*.[17]

We conducted a multicenter, single-blinded, placebo-controlled randomized trial in two Lusophone African countries: Guinea-Bissau and Mozambique. The primary outcome was to test whether providing BCG to HCWs would induce a 20% reduction in the incidence of non-planned absenteeism due to illness, including COVID-19, thereby decreasing the burden of the COVID-19 pandemic. Secondary outcomes included the incidence of COVID-19 and the risk of hospitalization due to COVID-19.

Materials and Methods

Trial design

This was a single-blinded, placebo-controlled multicenter trial of BCG vaccination (https://clinicaltrials.gov/study/NCT04641858).

Trial sites

The trial was conducted at two sub-Saharan research centers: Bandim Health Project (http://www.bandim.org) in Bissau, the capital of Guinea-Bissau, and the Manhiça Health Research Center (www.cismmanhica.org) located in Manhiça, Mozambique.

In Guinea-Bissau, recruitment took place from December 2020 to December 2021 at Simão Mendes National Hospital, Raoul Follereau Tuberculosis Hospital and health centers in the capital Bissau (Antula, Bandim, Belém, Cuntum, Djoló, Quelele and Luanda).

In Mozambique, recruitment took place from April to December 2021 at Manhiça District Hospital, Xinavane Rural Hospital and nearby health posts in Manhiça district (Taninga, Malavele, Palmeiras, Xinavane, Maluana, 3 de Fevereiro, Munguine, Ilha Josina and Chekwa), and at Mavalane General Hospital in Maputo city.

Despite official numbers of COVID-19 infections being very low in Guinea-Bissau and Mozambique by the end of 2020 (<0.2%), the real extent of the COVID-19 pandemic was de facto unknown, since test capacity was very limited. A serosurvey conducted among workers (partly HCWs) at the Bandim Health Project in Guinea-Bissau in November 2020 suggested that 18% had already been infected and in particular HCWs had an increased risk of infection.[18]

Study participants

The study aimed to include 1050 HCWs and follow them for health outcomes during a 6 mo period, with 350 participants recruited in each of the three Lusophone African countries: Mozambique, Cape Verde and Guinea-Bissau. However, ethical approval could not be obtained in Cape Verde, due to the lack of a legal framework to conduct RCTs.[19]

Eligibility criteria

An HCW was defined as an individual working in health facilities assisting with the provision of healthcare to patients, either directly as a doctor or nurse, or indirectly as auxiliaries, aides, administrative staff, laboratory technicians or medical waste handlers. HCWs were eligible for enrollment if they were 18 y old. Exclusion criteria included previous, active or latent infection with *Mycobacterium tuberculosis* or other mycobacterial species; severely immunocompromised subjects; self-reported HIV infection (in Guinea-Bissau participants were HIV-tested before enrollment; this was not deemed necessary by the ethics committee in Mozambique, as HCWs are regularly tested for HIV); self-reported pregnancy; other contraindications against BCG vaccine. Furthermore, from December 2020 to April 2021, participants with a positive COVID-19 antibody test were excluded from participation (recruitment had only begun in Guinea-Bissau during this period). After April 2021, in both Guinea-Bissau and Mozambique, COVID-19 vaccines had been introduced, and the seronegativity requirement was removed meaning that also COVID-19-vaccinated HCWs could be recruited into the trial.

To avoid any potential negative vaccine interactions, it was decided, based on the evidence available at the time, that participants should not be recruited between doses of COVID-19 vaccines, and participants were therefore only included 2 w after the last dose of COVID-19 vaccines (for Johnson & Johnson after one dose, for the other vaccine types after two doses). Participants were also asked to await 2 w before receiving COVID-19 vaccines after enrollment in the RCT.

Study intervention and randomization

The intervention consisted of a standard dose of 0.1 ml of attenuated *Mycobacterium bovis* BCG (almost exclusively the Danish strain 1331 [AJ Vaccines, Copenhagen, Denmark], but for a short period in February and again from October 2021 in Guinea-Bissau, the BCG-Japan strain [Tokyo strain 172, Japan BCG Laboratory] was used). BCG was administered by intradermal injection in the upper-right deltoid area by a trained nurse/doctor.

Participants were randomized 1:1 to BCG or placebo (0.1 ml saline solution, NaCl 0.9%). Data collection and randomization was done in REDCap version 13.7.18, 2024 Vanderbilt University[20] and stratified by country (Guinea-Bissau, Mozambique), sex (male, female) and profession (doctor, nurse, other). The randomization table was prepared with varying

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Table 1. Baseline characteristics of HCWs from Mozambique and Guinea-Bissau

	Mozambique		Guinea-Bissau	
Background variable, % (n/N)	BCG (n=82)	Placebo (n=83)	BCG (n=251)	Placebo (n=252)
Demographic factors				
Male sex	29 (24/82)	29 (24/83)	49 (123/251)	50 (126/252)
Age in years (mean (IQR))	35 (26–41)	33 (24–38)	35 (28–40)	34 (27–39)
Profession				
Doctor	1 (1/82)	2 (2/83)	7 (18/251)	7 (17/252)
Nurse	17 (14/82)	16 (13/83)	29 (74/251)	31 (77/252)
Other	82 (67/82)	82 (68/83)	63 (159/251)	63 (158/252)
Place of recruitment				
Hospital	54 (44/82)	43 (36/83)	77 (194/251)	83 (209/252)
Health center	46 (38/82)	57 (47/83)	23 (57/251)	17 (43/252)
Hospital department				
Emergency	11 (9/82)	7 (6/83)	4 (10/251)	4 (11/252)
Medicine	4 (3/82)	2 (2/83)	13 (32/251)	10 (24/252)
Surgery	2 (2/82)	2 (2/83)	2 (4/251)	2 (5/252)
Consultation	7 (6/82)	8 (7/83)	4 (9/251)	3 (8/252)
Maternity	17 (14/82)	11 (9/83)	12 (30/251)	11 (27/252)
Pediatric	16 (13/82)	20 (17/83)	21 (52/251)	26 (65/252)
Other	43 (35/82)	48 (40/83)	45 (114/251)	44 (112/252)
Risk factors				
Adults living in house (mean (IQR))	3 (2–4)	3 (2–4)	**4 (2–5)**	**5 (2–6)**
Positive COVID-19 test in house ever, % Yes (n/N)	10 (8/82)	14 (12/83)	4 (9/251)	1 (2/252)
Any symptoms during the last 2 w	1 (1/82)	2 (2/83)	5 (13/251)	7 (18/252)
Days absent from work during the last 2 w (mean (IQR)) [n]	2 (1–2) [2]	N/A [0]	**1 (1–1) [6]**	**4 (2–7) [15]**
Any non-communicable disease	15 (12/82)	18 (15/83)	8 (19/251)	9 (23/252)
Regular medication use	15 (12/82)	23 (19/83)	4 (10/251)	4 (11/252)
Vaccination history				
Has BCG scar(s)	87 (71/82)	84 (70/83)	76 (192/251)	75 (188/252)
Has smallpox scar(s)	0 (0/82)	0 (0/83)	4 (11/251)	2 (6/252)
Other vaccines in the last 2 y	30 (25/82)	36 (30/83)	14 (34/250)	13 (32/251)
Positive COVID-19 POC test at recruitment[1]	43 (35/82)	37 (31/83)	**65 (74/114)**	**81 (90/111)**
Had received COVID-19 vaccine	73 (60/82)	69 (57/83)	57 (65/114)	61 (68/111)

[1]Only among participants enrolled from April 2021, since positive POC test was cause for exclusion before April 2021.
Abbreviations: BCG, bacillus Calmette-Guérin; HCW, healthcare worker; IQR, interquartile range (25th percentile to 75th percentile); N/A, not applicable. **Bold numbers** indicate imbalanced characteristics ($p<0.05$).

blocks of sizes 4 and 6, and uploaded by an independent statistician to maintain the blinding of the RCT team. Outcome assessors and participants were likewise blinded to the randomization and only the study vaccinator knew the allocation.

Sample size

The sample size was calculated based on the primary hypothesis that BCG could reduce unplanned absenteeism due to illness by 20%, when compared with placebo. We expected that there would be an average of 5 d of absenteeism in the control group during the 6 month period of follow-up. With 5% loss to follow-up, we would need to include a total of 1050 HCWs (350 per country) to have 80% power to demonstrate a difference of 20% between the two groups, with an α of 0.05. Since Cape Verde was not able to participate in the RCT, the target sample was increased to 525 HCWs in both Guinea-Bissau and Mozambique, maintaining the total of 1050 HCWs.

Enrollment procedures and informed consent

The study was explained to eligible trial participants in the local language (Portuguese Creole in Guinea-Bissau and Portuguese in Mozambique) and accompanied by a written explanation in the official language, Portuguese. They were told that participation was completely voluntary, and consent could be withdrawn at any time. If they provided consent for participation, they were asked to provide written consent. For illiterate participants,

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Table 2. The effect of BCG vaccine on number of days with absenteeism due to unplanned illness during the COVID-19 pandemic

	Rate per 1000 workdays (days absent/total workdays)				RR of BCG vs placebo (95% credibility interval)
	Mozambique		Guinea-Bissau		
	BCG (n=82)	Placebo (n=83)	BCG (n=251)	Placebo (n=252)	
Overall	26 (274/10 467)	24 (250/10 465)	18 (458/26 074)	14 (351/25 933)	1.29 (0.81 to 1.94)
By sex					
Male	27 (82/2999)	19 (59/3127)	15 (215/13 936)	10 (135/13 794)	1.49 (0.63 to 3.08)
Female	26 (192/7468)	26 (191/7338)	20 (243/12 138)	18 (216/12 139)	1.17 (0.64 to 1.96)
BCG scar					
Yes	29 (266/9050)	24 (210/8836)	18 (356/19 954)	13 (249/19 136)	1.55 (0.94 to 2.44)
No	6 (8/1417)	25 (40/1629)	17 (102/6120)	15 (102/6797)	0.95 (0.25 to 2.58)
Profession					
Doctor	114 (15/132)	0 (0/262)	10 (17/1640)	4 (7/1566)	10.3 (0.06 to 36.2)
Nurse	23 (41/1769)	38 (62/1643)	22 (153/7093)	15 (103/6988)	1.61 (0.57 to 3.70)
Other	25 (218/8566)	22 (188/8560)	17 (288/17 341)	14 (241/17 379)	1.16 (0.64 to 1.93)
Age					
<45 y	19 (162/8458)	26 (224/8704)	20 (432/21 997)	13 (299/22 377)	1.32 (0.77 to 2.05)
≥45 y	56 (112/2009)	15 (26/1761)	6 (26/4077)	15 (52/3556)	0.89 (0.16 to 2.91)
Place of enrollment					
Hospital	40 (220/5550)	22 (96/4357)	17 (354/20 828)	15 (327/21 759)	1.29 (0.67 to 2.29)
Health center	11 (54/4917)	25 (154/6108)	20 (104/5246)	6 (24/4174)	1.57 (0.54 to 3.84)
Recruitments before and after introduction of COVID-19 vaccines					
Before[3]	–	–	15 (211/13 886)	12 (173/13 878)	1.15 (0.52 to 2.19)
After	26 (274/10 467)	24 (250/10 465)	20 (247/12 188)	15 (178/12 055)	1.46 (0.80 to 2.51)

[1]Analyzed in Bayesian negative binomial model adjusted for stratification covariates (sex and profession) with exposure as expected workdays.
[2]Adjusted for country.
[3]No data from Mozambique as recruitments were initiated after the introduction of COVID-19 vaccines.
Abbreviations: BCG, bacillus Calmette-Guérin.

someone they trusted was given the consent to read on their behalf and inform the participant. Participants were provided with several phone numbers for the trial staff and informed that trial staff could always be contacted if the participants had any questions or doubts, or wished to withdraw their consent. All participants were informed that any adverse events related to the trial were covered by a health insurance.

Before recruitment, each participant was examined by a doctor and interviewed about their health status. Enrollment data regarding non-communicable diseases and treatment, lifestyle (family structure, socioeconomic factors, smoking), and vaccination history including previous BCG vaccination and the presence of BCG and smallpox scars were collected.

Using a well-performing[21] point-of-care (POC) lateral flow rapid antibody test (CTK OnSite COVID-19 IgG/IgM Rapid Test), participants were tested for antibodies against SARS-CoV2. By April 2021, COVID-19 vaccination had been introduced in both countries, and therefore a negative antibody test was no longer required for enrollment in the trial. However, participants remained tested at the time of enrollment throughout the trial period.

Follow-up

Follow-up was performed every 2 w through telephone interviews to document absenteeism from work, symptoms, hospitalizations and COVID-19 test results (when applicable), for 24 w (12 phone interviews). A final follow-up interview (interview 13) was conducted 6 mo after enrollment, where participants were invited back to the health facility for a SARS-COV-2 antibody test, and a final questionnaire was filled out.

Data from all interviews were entered in electronic forms in the REDCap browser-based data collection platform.[20]

Outcomes

Primary outcome: unplanned absenteeism due to illness (see Table 2)

Unplanned absenteeism was defined as being absent from work for reasons other than holiday, parental leave, other planned leave, family assistance and COVID-19 quarantine measures. The number of workdays and days of absence was continuously reported by the participants at the biweekly follow-up interview.

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Table 3. Incidence of disease by country and combined. Randomized trial of BCG to HCWs from Mozambique and Guinea-Bissau, 2020–2022

	Mozambique		Guinea-Bissau		Ratio of BCG vs placebo (95% CI)[a]
	BCG	Placebo	BCG	Placebo	
Incidence of COVID-19[b]					
% positive (number positive/total participants)					
Overall	35 (6/17)	8 (2/24)	23 (38/167)	22 (34/156)	1.19 (0.80 to 1.75)
All-cause hospitalization[c]					
Rate of hospitalization (hospitalization/total days of follow-up)					
Overall	0.1 (2/14 742)	0.3 (4/14 995)	0.02 (1/45 332)	0.04 (2/45 405)	0.51 (0.13 to 2.03)
Incidence of infectious disease episodes[c]					
Rate of episodes (disease episodes/total days of follow-up)					
Overall	5.1 (75/14 658)	4.2 (63/14 924)	3.0 (134/44 968)	2.5 (114/45 052)	1.18 (0.97 to 1.45)
Incidence of respiratory infectious disease episodes[c]					
Rate of episodes (disease episodes/total days of follow-up)					
Overall	3.2 (47/14 728)	2.95 (44/14 925)	1.1 (49/45 318)	0.7 (33/45 293)	1.24 (0.92 to 1.67)

[a]Different baseline hazards functions (in Cox proportional hazards models) for each country or otherwise included as covariate in the combined analysis.
[b]Analyzed in binomial regression model adjusted for stratification covariates (sex and profession). This analysis only included participants before they received COVID-19 vaccines and who tested negative for COVID-19 antibodies at the time of enrollment.
[c]Analyzed in Cox proportional hazards model adjusted for stratification covariates (sex and profession).
Abbreviations: BCG, bacillus Calmette-Guérin; HCW, healthcare worker.

Secondary outcome measures (see Table 3)

The main secondary outcomes were unplanned absenteeism due to documented COVID-19 infection and cumulative incidence of all-cause hospital admissions (minus accidents) and incidence of death.

Additional secondary outcomes were:
days of unplanned absenteeism due to:

- infection, respiratory infection and absenteeism for reasons other than COVID-19

cumulative incidence of hospitalization for:

- infections, respiratory infections, COVID-19, infectious intensive care admission and intensive care admission due to documented COVID-19 infection.

Furthermore, the incidence of COVID-19 infection and the cumulative incidence of infectious and respiratory infectious disease episodes were secondary outcomes.

COVID-19 infection data were collected in two ways: as self-reported COVID-19 infection, or as having a negative COVID-19 antibody test at the time of enrollment but a positive test at the end of follow-up, and not received COVID-19 vaccine during follow-up. A more detailed description of the outcomes is available in the supplementary material.

Statistical analysis

We report the primary outcome, unplanned absenteeism due to illness, as the mean number of sick days with standard deviation out of the total self-reported number of work days. The incidence rates of absenteeism were calculated per 1000 workdays.

We analyzed the total number of days using a negative Bayesian binomial regression with a fixed effect for BCG, hospital, sex, profession and country. The brm function in the R package 'brms' was used to fit the negative binomial model. Effect estimates are reported as RRs with 95% credibility intervals (CrI).

Other outcomes were analyzed using Stata V.17 (Stata Corp., College Station, TX, USA). Time-to-event outcomes were analyzed in Cox proportional hazards models and reported with HRs and 95% CIs. Disease episodes and hospitalizations were analyzed as repeated-event outcomes using the Andersen-Gill Cox model, and we used a 14 d grace period between each episode, since we did not collect information on the precise date of illness within the 2 w follow-up period reported at each telephone interview.

For all non-absenteeism outcomes, the denominator was total number of days of follow-up. Depending on the analysis in question, either total days of follow-up or total workdays were used as the denominator.

The incidence of COVID-19 was analyzed in binomial regression models providing RRs with 95% CIs, since the exact timing of the infection was unknown for most participants.

Numerical scale variables were reported as mean and standard deviation or median and interquartile range, as appropriate. In nominal or ordinal scale variables, count and percentage were used.

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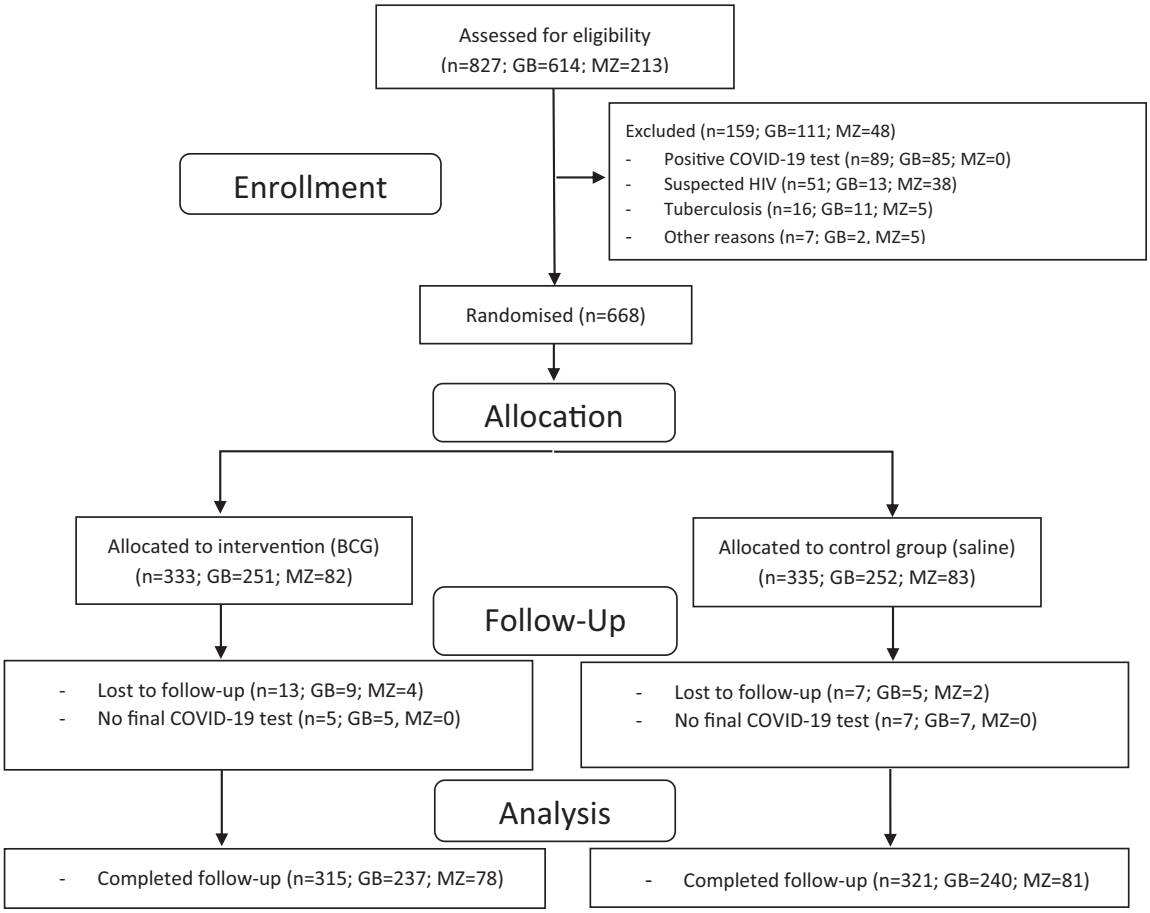

Figure 1. CONSORT trial flow chart.
Abbreviations: BCG, bacillus Calmette-Guérin; GB, Guinea-Bissau; MZ, Mozambique.

We examined the following potential effect modifiers for the main outcome and for secondary outcomes where sufficient power permitted meaningful analysis: country, sex and profession (stratification variables), as well as the presence or absence of BCG scar(s) at enrollment, place of enrollment, and being enrolled before or after COVID-19 vaccines became available. However, there was very limited power to conduct country-specific analyses, and therefore only the main result is presented by country.

Results

Recruitment and follow-up adherence

The RCT was initiated in Guinea-Bissau, on 3 December 2020; recruitment took place until 17 December 2021. In Mozambique, participants were included from 28 April to 15 December 2021.

A total of 827 HCWs were screened for eligibility in the two countries. Of these, 111 (18%) from Guinea-Bissau and 48 (23%) from Mozambique were excluded (Figure 1). Before introduction of COVID-19 vaccines in April 2021, the main reason for exclusion in Guinea-Bissau was previous COVID-19 infection identified by a positive SARS-CoV2 antibody test at enrollment (n=85, 77%). In Mozambique, the main reason was self-reported HIV infection (n=38, 79%) (Figure 1). A total of 668 (Guinea-Bissau, n=503; Mozambique, n=165) HCWs were randomized and 95% completed follow-up (636/668), with follow-up rates being comparable in the intervention and control groups (Figure 1).

Baseline characteristics

The baseline characteristics were balanced between the two randomization groups. In Guinea-Bissau, participants in the placebo group had more other adults living in the house (p=0.019), had been more absent in the 2 w prior to recruitment (p=0.010) and had a higher proportion of positive COVID-19 tests at enrollment among participants enrolled after COVID-19 vaccines had been introduced (p=0.006) (Table 1). These imbalances

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had only minor impact on the main analysis (supplementary material).

There were several differences between the HCWs recruited in the two countries. For example, Mozambican participants had more comorbidities, lived in smaller households, comprised fewer males and had a greater number recruited at smaller health centers, compared with participants enrolled in Guinea-Bissau (Table 1).

Unplanned absenteeism due to illness

During the 6 mo of follow-up, the rate of unplanned absenteeism from all causes was higher in Mozambique (BCG group: 26 [274/10 467]; placebo group: 24 [250/10 465]) than in Guinea-Bissau (BCG group: 18 [458/26 074]; placebo group: 14 [351/25 933]) (Table 2). This was mainly due to a much higher rate of reported COVID-19 absenteeism in Mozambique, where participants reported 8 d of absence due to COVID-19 per 1000 workdays (170/20 932), while the same number was 0.1 (5/52 007) in Guinea-Bissau.

The RR of absenteeism (BCG vs placebo) was 1.29 (0.81 to 1.94) in the combined analysis (1.34 [0.75 to 2.20] for Guinea-Bissau, 1.21 [0.52 to 2.46] for Mozambique). The RR for unplanned absenteeism besides COVID-19 was 1.18 (0.71 to 1.84) (Table 2). Remaining secondary absenteeism outcomes had limited power (Supplementary Table S1).

Secondary outcomes

COVID-19 infection

There were 80 cases of confirmed COVID-19 infections among the participants during follow-up. Ten of these were self-reported cases, based on a self-reported positive PCR test. All had been antibody-negative at enrollment. The remaining 70 cases were identified among the 364 participants, who had tested antibody-negative for COVID-19 at enrolment (323 in Guinea-Bissau; 41 in Mozambique) and received no COVID-19 vaccines during follow-up, but who tested antibody-positive at follow-up. Overall, 22% (80/364) of the initially antibody-negative participants were thus infected with COVID-19 during follow-up. Comparing the incidence in the BCG and placebo group yielded a combined COVID-19 infection HR of 1.19 (0.80 to 1.75) (Table 3).

Infectious disease episodes

There was a trend for increased risk of self-reported illness episodes associated with BCG in the combined analysis, the HR being 1.18 (0.97 to 1.45) (Table 3).

All-cause hospitalization

There was a total of nine hospitalizations reported during the study (BCG: 3, placebo: 6). The time-to-event analysis yielded an HR of 0.51 (0.13 to 2.03) in the combined analysis (Table 3).

Effect modifiers

There were no significant interactions between BCG and the potential effect modifiers, sex, BCG scar status at enrollment, occupation, place and time of recruitment, or age (Table 2).

Secondary outcomes with limited power

For disease-specific hospitalization outcomes, including intensive care hospitalizations, the numbers of events were too few to conduct any meaningful analyses. Two deaths occurred during the trial (BCG=1; placebo=1). One death (in the BCG group) occurred 5.5 mo after enrollment; the participant became ill a few weeks after COVID-19 vaccination and died some weeks thereafter with final renal failure. The death was reported as a possible adverse event to the COVID-19 vaccine. The death in the placebo group, 5 mo post-enrollment, was deemed to have been caused by malaria and diabetes. None of the deaths was suspected to be related to the trial intervention or due to COVID-19 infection. Other secondary outcomes with limited power included absenteeism due to infections, respiratory infections and COVID-19 (Supplementary Table S1).

Discussion

Main observations

We could not confirm the hypothesis that BCG vaccination reduces unplanned absenteeism among HCWs by 20%. Instead, the combined analysis yielded an RR of 1.29 (0.81 to 1.94). We also did not find that BCG protected HCWs against COVID-19 infection. There was a tendency that BCG reduced the all-cause hospital admission risk, but there were few admissions and deaths in the trial.

Strengths and weaknesses

The study was a multicenter randomized trial with two different teams enrolling participants at several different health facilities. Several practical obstacles hampered the conduct of the RCT. As a result, we only managed to recruit 64% of the anticipated 1050 participants. These obstacles included the impossibility of Cape Verde participating in the recruitment of participants. This delayed recruitment and extended the recruitment period. In the remaining two countries, ethical approval took longer than anticipated (4 mo in Guinea-Bissau and 8 mo in Mozambique), despite COVID-19 research being prioritized by the ethical committees. Introduction of COVID-19 vaccines also halted recruitments, as the trial team prioritized not including participants between doses of COVID-19 vaccines as a precautionary principle.[22] Additionally, in Guinea-Bissau healthcare workers were on strike during most of 2021.

Our power to study COVID-19 infection was low, as test capacity was low and only few participants reported being diagnosed with PCR-positive COVID-19 infection. Since the POC COVID-19 tests used in the trial could not differentiate between natural COVID-19 infections and COVID-19 vaccination, we could only

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identify additional cases among participants initially enrolled as antibody-negative and who remained unvaccinated during follow-up.

Fortunately, loss to follow-up was less than the expected 5%; less than 3% of participants were completely lost to follow-up. However, 5% did not complete the final COVID-19 antibody test after 6 mo of follow-up.

Despite the limited loss of power due to incomplete follow-up, the trial was underpowered as only 64% of the expected sample size was reached. The main outcome was also quite underpowered with only an average of around 2 d of absenteeism reported per participant during follow-up, which was 50–60% lower than the expected rates.

Consistency with previous findings and interpretation

Although the BCG vaccine was created for specific protection against severe forms of TB, principally in children, studies from before the pandemic had brought attention to the marked beneficial non-specific effects of BCG against other diseases.[6,8–10] During the pandemic, several clinical trials were thus carried out to investigate the effects of BCG against COVID-19 in adults, among HCWs, older people and those with diabetes.[23–31] Only one other RCT of BCG, among HCWs, has been conducted in Africa: this was a trial in South Africa that also reported no beneficial effects of BCG on respiratory tract infections, COVID-19 and hospitalizations. Notably, however, the trial reported four deaths in the placebo group and zero in the BCG group.[27] Recently, the BRACE trial and a Danish trial reported no beneficial effect of BCG among HCWs regarding COVID-19, infections and hospitalizations. Again, BCG did not reduce incidences of absenteeism, COVID-19 infection, hospitalization or reported infectious disease. Instead, those randomized to BCG if anything had a tendency towards more absenteeism and more self-reported infections, but with the possibility of being protected from severe morbidity.[28,32] Marked beneficial effects of BCG against the risk of respiratory infections, including COVID-19, were observed in trials of BCG in populations with weakened immune systems, such as older people, multimorbid patients and patients with type 1 diabetes. This was mainly in studies where participants had received prior BCG vaccinations.[25,29,31] It has previously been suggested that BCG revaccination carries stronger beneficial non-specific effects.[33] However, in the present trial we did not see a trend for a more beneficial effect of BCG on unplanned absenteeism among participants with a BCG scar, and in fact the trend was opposite.

The inconsistent results underline the importance of context-dependent factors when studying the non-specific effects of vaccines.[34]

Importantly, almost all trials reported fewer deaths in the BCG than in the placebo group. In a combined analysis across eight available trials, BCG vs placebo was associated with a mortality reduction of 39% (3–62%) during the 6–12 mo follow-up.[35] Similarly, it has previously been observed in children that BCG was not associated with a reduced risk of hospitalization, but instead with a markedly lower in-hospital mortality risk among hospitalized infants, suggesting that BCG reduces the severity of all-cause disease rather than the incidence of all-cause disease.[10]

Conclusion

In this trial, BCG was not associated with reduced absenteeism, and to the contrary there was a tendency towards a greater risk of self-reported absenteeism and an increased frequency of infectious disease episodes and COVID-19 infections.

Supplementary data

Supplementary data are available at *Transactions* online.

Authors' contributions: The study was planned and initiated by CSB, IF, PF, PA, IA, ML, SN and FSB. Training and supervision of field assistants was done by CSB, SN, FSB, EC, IS, LM and LN. SN conducted the statistical analyses and LN and IS wrote the first draft of the paper. All authors contributed to the final version. SN and CB were responsible for the decision to submit the manuscript and will act as guarantors of the study.

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Data availability: De-identified participant data with a data dictionary can be shared after approval of a data-sharing proposal sent to Professor Christine Stabell Benn (cbenn@health.sdu.dk).

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