Safety and efficacy of BCG re-vaccination in relation to COVID-19 morbidity in healthcare workers: A double-blind, randomised, controlled, phase 3 trial

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Summary

Background BCG vaccination prevents severe childhood tuberculosis (TB) and was introduced in South Africa in the 1950s. It is hypothesised that BCG trains the innate immune system by inducing epigenetic and functional reprogramming, thus providing non-specific protection from respiratory tract infections. We evaluated BCG for reduction of morbidity and mortality due to COVID-19 in healthcare workers in South Africa.

Methods This randomised, double-blind, placebo-controlled trial recruited healthcare workers at three facilities in the Western Cape, South Africa, unless unwell, pregnant, breastfeeding, immunocompromised, hypersensitivity to BCG, or undergoing experimental COVID-19 treatment. Participants received BCG or saline intradermally (1:1) and were contacted once every 4 weeks for 1 year. COVID-19 testing was guided by symptoms. Hospitalisation, COVID-19, and respiratory tract infections were assessed with Cox proportional hazard modelling and time-to-event analyses, and event severity with post hoc Markovian analysis. This study is registered with ClinicalTrials.gov, NCT04379336.

Findings Between May 4 and Oct 23, 2020, we enrolled 1000 healthcare workers with a median age of 39 years (IQR 30–49), 70·4% were female, 16·5% nurses, 14·4% medical doctors, 48·5% had latent TB, and 15·3% had evidence of prior SARS-CoV-2 exposure. Hospitalisation due to COVID-19 occurred in 15 participants (1·5%); ten (66·7%) in the BCG group and five (33·3%) in the placebo group, hazard ratio (HR) 2·0 (95% CI 0·69–5·9, $p = 0·20$), indicating no statistically significant protection. Similarly, BCG had no statistically significant effect on COVID-19 ($p = 0·63$, HR = 1·08, 95% CI 0·82–1·42). Two participants (0·2%) died from COVID-19 and two (0·2%) from other reasons, all in the placebo group.

Interpretation BCG did not protect healthcare workers from SARS-CoV-2 infection or related severe COVID-19 disease and hospitalisation.

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Research in context

Evidence before this study

A growing body of evidence suggests that BCG induces trained immunity thereby enhancing host response to infection by viral and bacterial pathogens and reducing morbidity and mortality. Prior BCG vaccination may have other non-specific benefits such as lowering the incidence of lung carcinoma and modifying the course of diabetes and multiple sclerosis. Epidemiological studies early in the pandemic suggested that a regional history of BCG vaccination may protect populations against COVID-19. A literature search of PubMed on Mar 28, 2022, using the terms "SARS-CoV-2" or "COVID-19" and "BCG" and "efficacy," with the filter of "randomised controlled trial," resulted in zero peer-reviewed publications. This study evaluated BCG in a highly exposed population as a potential stopgap measure until more specific treatments and vaccines for COVID-19 became available.

Added value of this study

To our knowledge, this study is the first published randomised, controlled, double-blind trial evaluating the effect of BCG revaccination on morbidity due to COVID-19. BCG revaccination failed to protect healthcare workers in South Africa from COVID-19 and hospitalisation. In addition, BCG revaccination did not offer protection from the morbidity of respiratory tract infections, in contrast to prior studies.

Implications of all the available evidence

Non-specific immune effects of BCG revaccination may be population-, age-, pathogen- or disease-specific. We recommend that BCG not be used for the prevention or mitigation of COVID-19 outside of a clinical trial, at least until results of other trials underway in different settings are known.

Introduction

COVID-19 has devastated healthcare systems globally and continues to pose a serious threat to healthcare workers. In South Africa, with historically limited infrastructure and substantial shortages of nursing staff and doctors, it is imperative to protect healthcare workers to safeguard continuous patient care. Since the first case was reported in the country on 5 March 2020, more than 12 000 healthcare workers have been hospitalised with COVID-19.[1]

The 100-year old Bacillus Calmette–Guérin (BCG) vaccine is given at birth for prevention of paediatric tuberculosis (TB), particularly extrapulmonary TB and death in young children in several settings.[2,3] In South Africa, where TB is highly prevalent (737 per 100,000 population in 2018), BCG was introduced in the 1950s and has been routinely administered to all neonates since 1973.[4,5] Settings with a history of BCG vaccination reported fewer COVID-19 cases and deaths in the early months of the pandemic, and it was hypothesised that non-specific effects of current and historical widescale BCG vaccination could protect from COVID-19.[6,7]

Trained immunity involves a reprogramming of innate immune cells (particularly myeloid and natural killer cells) to enhance cytokine production and antimicrobial functions.[2] This functional reprogramming is still incompletely understood, but is likely the result of epigenetic, metabolic, and transcriptional changes in innate immune cells.[2] In humans, BCG-induced trained immunity has been found to enhance vaccine responses to yellow fever and influenza vaccination.[2] Small clinical studies have demonstrated reduced neonatal mortality in West African settings, primarily from a reduction in neonatal sepsis and respiratory infections, as well as protection from respiratory syncytial virus infection in African children and respiratory tract infections (RTI) in African adults.[2] In other studies, BCG provided protection against leprosy, with an enhanced effect after revaccination; non-tuberculous mycobacteria lymphadenitis; and Buruli ulcer.[2] It has been shown that BCG administered in childhood lowers mortality from natural causes into adult age, the incidence of lung carcinoma, and modifies the course of diabetes and multiple sclerosis.[2] Most recently, the double-blind, placebo-controlled ACTIVATE trial in 202 elderly European patients demonstrated that BCG vaccination resulted in a 45% delay in the time-to-first all-cause infection, and a 42% reduction in all infections compared to placebo, with major reductions in respiratory infections.[8] Such non-specific beneficial effects have been found not only with BCG, but also other live vaccines such as smallpox, polio and measles.[9–11]

At the time this study was conceived there were less than one million reported COVID-19 cases globally and early COVID-19 vaccine trials had only just begun. A rapidly available stopgap strategy against COVID-19 was desperately needed.[6,12] This study aimed to evaluate BCG for impact on RTIs including COVID-19 in a

cohort of highly exposed healthcare workers in South Africa.

Methods

Trial design and participants

In this randomised, double-blind, placebo-controlled trial, adult healthcare workers, defined as any personnel working in a healthcare facility expected to be highly exposed to COVID-19, were enrolled between May 4 and Oct 23, 2020 at three research sites in the Western Cape, South Africa: TASK Cape Town, TASK Eden, and University of Cape Town Lung Institute (UCTLI). All participants provided voluntary informed consent and underwent a screening visit with brief medical history, symptom questionnaire, vital signs, human immunodeficiency virus (HIV) test, and urinary pregnancy test for women of childbearing potential. Participants were excluded if they had a current respiratory tract or other active infection, were receiving an experimental COVID-19 treatment, or had a contraindication to the BCG vaccine including known hypersensitivity to BCG, pregnancy or were breastfeeding, compromised immune system including HIV and cancer, or receiving immunosuppressive therapy. One protocol amendment was made to allow inclusion of healthcare workers without direct contact with COVID-19 patients, exclude those with previous COVID-19, and to add sample collection for genetic sub-studies. The full protocol is available in Supplementary Materials. The study was approved by the South African Health Products Regulatory Authority (Ref: 20200402), Pharma-Ethics (Ref: 200423268) and UCT Human Research Ethics Committee (Ref: 237/2020).

Randomisation and masking

Participants were randomly assigned 1:1 to receive an intradermal injection of either 0·1 ml of the reconstituted BCG vaccine (BCG-Vaccin Statens Serum Institut, Danish strain 1331) or 0·1 ml of placebo composed of 0·9% saline solution. Randomization was done centrally by a computer-generated table in 2 blocks (TASK and UCT cohorts of 500 participants) with no stratification. All staff were blinded to treatment groups with the exception of designated unblinded pharmacists and research nurses who prepared the doses in access controlled areas and were not involved in vaccine administration and collection of outcome data. An independent data safety and monitoring board reviewed data throughout the trial. No safety or futility cut-offs were defined and as such no interim statistical testing was performed. Participants and site staff were unblinded after a participant's final study visit. Unblinding to aggregated outcome data occurred only after final database lock.

Procedures

Participants were followed-up for 52 weeks via telephone, text message or email to collect adverse event data at least once every 4 weeks, though this could be more frequent for adverse event monitoring and during the height of the COVID-19 waves. During follow-up contact, participants were questioned about COVID-19 exposure, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing, COVID-19 or other vaccinations, flu-like symptoms, injection site reactions and any other health concerns. Additional information was requested when necessary to document adverse events which were categorised using Medical Dictionary for Regulatory Activities (MedDRA) terminology. For this study, we defined long COVID-19 as COVID-19 diagnosis with symptom duration more than 2 weeks from onset. Blood samples were collected from participants for TB infection by QuantiFERON-TB Gold Plus (QIAGEN) at enrolment and week 52. SARS-CoV-2 immunoglobulin G (IgG) serology testing (Abbott Architect), to identify prior or intercurrent infection, was conducted at enrolment, week 10 (optional), 26 and 52.

To reduce contact between study staff and participants in line with physical distancing guidelines participants were not actively managed for illness or tested for SARS-CoV-2 by study teams but were requested to adhere to their respective healthcare facility and government mandated protocols, initiate SARS-CoV-2 polymerase chain reaction (PCR) and antigen testing accordingly and report the results to the study team.

Outcomes

Our primary outcome was the incidence of hospitalisation due to COVID-19, defined as admission to a hospital facility at least overnight associated with a positive SARS-CoV-2 PCR test. Secondary outcomes included the incidence of hospitalisation (all causes), PCR or antigen confirmed COVID-19, RTIs (non-specific), SARS-CoV-2 seropositivity, TB infection and disease, and injection site reactions across groups, as well as comparing the severity of RTIs and COVID-19 through the health status (HS) score.

The HS score was a measure of severity of disease, adapted from the World Health Organization Ordinal Scale for Clinical Improvement, captured on a 0–7 scale, defined as healthy (0), mild symptoms (1), moderate symptoms (2), severe symptoms (3), hospitalisation (4), hospitalisation with supplemental oxygen (5), hospitalisation with mechanical ventilation (6), and death (7).[13] The highest score for an adverse event was captured. For RTI adverse events, the score was tracked weekly with the highest score reported per week. RTIs were also characterised by cough, fever or night sweats, rhinitis, dyspnoea, fatigue, sore throat, headaches and body aches. Injection site reactions were captured and characterised by redness, pain, swelling, lymph node

enlargement, and ulceration at or near the injection site. Adverse events were graded based on the Common Terminology Criteria for Adverse Events version 5·0 (27 Nov 2017) and assessed for relatedness to BCG vaccination.

Sample size

Sample size calculations were performed based on the primary endpoint of hospitalisation due to COVID-19. Based on assumptions from published and observed early local attack and hospitalisation rates, and BCG protection from respiratory infections, we estimated that 220 participants per group for one-sided testing and 279 participants per group for two-sided testing were needed to detect a clinically relevant target difference of 75%, shown in prior BCG studies, for the primary endpoint given an attack rate of 30% and 20% hospitalized ($proportion_{placebo}$ = 6%, $proportion_{BCG}$ = 1·5%, α = 0·05, 80% power, two-sample comparison of proportions power calculation) considering a low rate of baseline immunity and a modest loss to follow-up. Due to the clinical insights into the pandemic situation, a two-sided testing was performed in the final analysis. The target was determined to be at least 500 participants to allow upwards adjustment based on emerging local data and additional funding. The protocol allowed for an adaptive design based on interim analyses however no interim analyses were conducted and thus the adaptive design was not implemented. Recruitment was eventually limited by available funding and the total sample size of the trial was 1000 with equal randomisation to the two groups.

Statistical analysis

Cox proportional hazard modelling was used for comparing groups of the primary endpoint. Event data of COVID-19, RTIs and hospitalization for all causes were analysed by parametric time-to-first event analysis. The effect of BCG compared to placebo was expressed as a hazard ratio (HR) with 95% confidence interval (CI). A post hoc Markov Chain model was developed to determine whether BCG reduced the severity of RTIs over time by quantifying the probability of going from one HS to another during an RTI. Statistical testing was done to determine if any of the two groups reduced the severity of RTIs over time, i.e., transitioning from a high to a low HS. Intention-to-treat (ITT) analysis was censored at withdrawal or death of participants only, whereas the per protocol (PP) analysis censored participants at any event that could interfere with the risk COVID-19, such as SARS-CoV-2 specific or influenza vaccination. Both analyses were essentially in agreement for the results. ITT results are presented here and PP results along with detailed statistical methods can be found in the Supplementary Materials. All statistical tests were performed two-sided with α = 0·05.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

1000 healthcare workers were recruited from private and public healthcare facilities in the Western Cape, South Africa between May 4, 2020 and Oct 23, 2020 (Figure 1). Participant demographics and baseline characteristics are described in Table 1. No missing data required imputation. At enrolment, 15·3% of participants had a positive serology test indicating prior SARS-CoV-2 exposure with no known history of COVID-19. A positive QuantiFERON Gold Plus result, indicating latent TB infection, was found in 485 (48·5%) of enrolled participants at baseline. By week 52, 49 previously QuantiFERON negative participants had become positive, 27 (55·1%) and 22 (44·9%) on BCG and placebo, respectively (p = 0·73, point estimate = 0·014, 95% CI = −0·0470–0·0758); 62 previously positive participants became QuantiFERON negative, 27 (43·6%) and 35 (56·5%) on BCG and placebo, respectively (p = 0·499, point estimate = 0·026, 95% CI = −0·094–0·041). No cases of TB disease were reported. Adverse events relating to RTIs, COVID-19 are summarized in Table 2, others in Table 3 and described below.

The primary endpoint of hospitalisation due to COVID-19 occurred in 15 (1·5%) participants (Figure 2A): 10 (67%) on BCG compared to 5 (33%) on placebo, with an HR of 2·0 (95% CI 0·69–5·9, p = 0·20) (Figure 3). The time-to-first hospitalization for all causes included 47 (4·7%) admissions; 27 (57·4%) on BCG and 20 (42·6%) on placebo (Figure 2B) with an HR of 1·36 (95% CI 0·72–2·49, p = 0·31) (Figure 3). Cumulative risk plots are presented in Figure 4.

There was no difference in time-to-first COVID-19, which occurred in 190 (19·0%) participants; 98 (51·6%) on BCG and 92 (48·4%) on placebo; HR: 1·08 (95% CI 0·82–1·42, p = 0·63) (Figures. 2C, 3). There was also no difference in time-to-first RTI. Of 569 events, 291 (51·1%) and 278 (48·9%) were seen on BCG and placebo, respectively; HR: 1·07 (95% CI 0·91–1·28, p = 0·40) (Figures. 2D, 3). SARS-CoV-2 seroconversion occurred in a total of 278 (33·1%) of participants, 146 (52·5%) on BCG and 132 (47·5%) on placebo, respectively (p = 0·16, point estimate = 0·048, 95% CI = −0·018–0·11). Of these, 75 (51·3%) and 62 (47·0%) on BCG and placebo, respectively, reported a COVID-19 event in the seroconversion period (p = 0·54, point

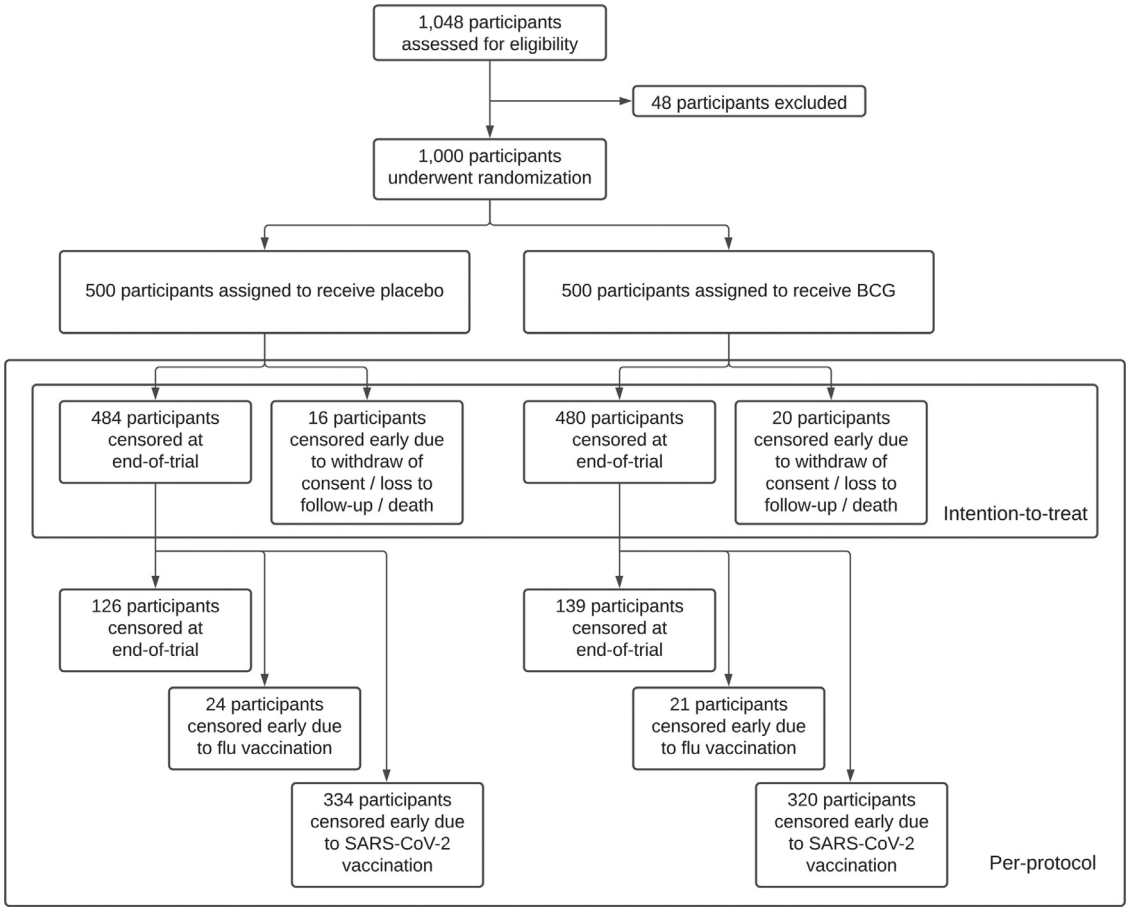

Figure 1. Trial participation, randomisation, and analysis.
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, BCG = Bacillus Calmette–Guérin.

estimate = 0·044, 95% CI = −0·081–0·17). Parametre estimates including 95% CIs are shown in Table S1.

Participants experienced between 0 and 7 RTI adverse events, most commonly categorised as RTI (39·0%), COVID-19 (22·4%), upper RTI (15·4%), or flu-like illness (6·4%), with similar frequency and severity between BCG and placebo (Table 2). A higher proportion of a total of 27 severe COVID-19 events were recorded on BCG (19, 70·4%) compared to placebo (8, 29·6%)($p = 0·051$, point estimate = 0·022, 95% CI = −0·000,045–0·044). Four participants (0·4%) died, two (50·0%) due to COVID-19 and one each (25·0%) due to bowel perforation and a cerebrovascular accident, all on placebo. Long COVID-19 was reported in 35 participants (18·4%), 23 (65·7%) on BCG and 12 (34·3%) on placebo ($p = 0·085$, point estimate = 0·022, 95% CI = −0·0027–0·047). Injection site reactions occurred almost exclusively in the BCG group where 463 (92·6%) participants had mostly mild to moderate reactions with only two participants reporting a severe reaction (Table 3).

Figure 5 visualises the probabilities of staying at the same HS (blue) or transitioning from one HS to another (grey arrows) as quantified by the post hoc Markov Chain model. From symptom onset, recovery from an RTI, i.e., a stable or lower HS, was more likely to occur in both groups than symptom worsening i.e., a higher HS. This is shown in Figure 5 as the thicker arrows going to a lower HS, while the thinner arrows go to a higher HS. However, BCG resulted in a statistically significantly higher probability of transitioning to a higher HS compared to placebo. Transitioning from HS 0 to 3–7 increased 2·2-fold ($p = 0·02$) and from HS 2 to 3–7 increased 2·9-fold ($p = 0·02$) (red arrows in Figure 5). Based on this, BCG may increase the probability of RTI symptom worsening compared to placebo. Graphical diagnostics and parametre estimates including 95% CIs are shown in Table S2.

Characteristic	BCG Group	Placebo Group	Total
N	500	500	1000
Gender (biological)			
female	349 (69·8%)	355 (71·0%)	704 (70·4%)
male	151 (30·2%)	145 (29·0%)	296 (29·6%)
Age (median [IQR], years)	39 (30–49)	39 (30–50)	39 (30–49)
BMI (median [IQR], kg/m^2)	28·8 (23·9–34·3)	28·3 (24·2–34·7)	28·6 (24·1–34·6)
Job category			
Nurse	94 (18·8%)	71 (14·2%)	165 (16·5%)
Doctor	65 (13·0%)	79 (15·8%)	144 (14·4%)
Other Essential worker	341 (68·2%)	350 (70·0%)	691 (69·1%)
Ethnicity			
Mixed Heritage	237 (47·4%)	224 (44·8%)	461 (46·1%)
African	141 (28·2%)	146 (29·2%)	287 (28·7%)
Caucasian	111 (22·2%)	109 (21·8%)	220 (22·0%)
Indian	7 (1·4%)	18 (3·6%)	25 (2·5%)
Other	4 (0·8%)	3 (0·6%)	7 (0·7%)
Comorbidities			
Hypertension	82 (16·4%)	92 (18·4%)	174 (17·4%)
Asthma	39 (7·8%)	29 (5·8%)	68 (6·8%)
Diabetes	32 (6·4%)	31 (6·2%)	63 (6·3%)
Cardiovascular disease	14 (2·8%)	10 (2·0%)	24 (2·4%)
COPD	3 (0·6%)	1 (0·2%)	4 (0·4%)
Smokers	135 (27·0%)	139 (27·8%)	274 (27·4%)
Latent TB infection	240 (48·0%)	245 (49·2%)	485 (48·5%)
SARS-CoV-2 baseline seropositive	85 (17·0%)	68 (13·7%)	153 (15·3%)
BCG scar	237 (47·4%)	259 (51·8%)	496 (49·6%)
COVID-19 Vaccine During Follow-up	329 (65·8%)	350 (70·0%)	679 (67·9%)
Janssen vaccine	315 (95·7%)	329 (94·0%)	644 (94·8%)
Pfizer–BioNTech vaccine (Comirnaty) [a]	12 (3·6%)	20 (5·7%)	32 (4·7%)
Oxford–AstraZeneca vaccine (Covishield)	1 (0·3%)	1 (0·3%)	2 (0·3%)
Unknown	1 (0·3%)	0	1 (0·1%)

***Table 1*: Baseline characteristics of enrolled participants.**
Definitions: IQR = interquartile range, BMI = body mass index, COPD = chronic obstructive pulmonary disease, TB = tuberculosis, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, BCG = Bacillus Calmette–Guérin.
[a] Three participants received combinations of Pfizer-BioNTech, Janssen and Oxford-AstraZeneca vaccinations.

Results of primary and secondary endpoint analyses for per-protocol datasets are presented in the Supplementary Materials.

Discussion

This study showed that BCG vaccination of healthcare workers in South Africa, a TB endemic setting, did not lower the risk of hospitalisation due to COVID-19, SARS-CoV-2 infection, and severe COVID-19. In addition, BCG did not lower the overall incidence or severity of RTIs. A higher probability of developing more severe RTIs was seen with BCG yet this did not result in an increased number of deaths. It is plausible that BCG elicited a more aggressive anti-viral response, resulting in an unexpected trend toward more symptomatic and severe RTIs, while offering protection from death. In the absence of statistically significant findings this should be interpreted with caution. Though underpowered for the primary outcome, the methodology of our study and statistical analysis were robust. Participants were recruited rapidly and early in the pandemic and were generally highly exposed as seen in a surprisingly high baseline seropositivity in asymptomatic individuals and later seroconversions. The recruitment and follow-up periods cover the original SARS-CoV-2 strain, beta and delta variant waves in South Africa.

Limitations to the study are that we set out to study BCG re-vaccination, yet we cannot be sure that all participants received high-quality BCG in childhood. The lower-than-expected attack rate (19.2%) and hospitalisation rate (7.8%) due to COVID-19 decreased the power to detect the expected BCG effect with statistical significance. A post hoc power calculation with these updated

Adverse Event	BCG Group	Placebo Group	Total
N	500	500	1000
COVID-19 Events [a]	99	93	192
Mild	33 (33·3%)	31 (33·3%)	64 (33·3%)
Moderate	47 (47·5%)	54 (58·1%)	101 (52·6%)
Severe [b]	19 (19·2%)	8 (8·6%)	27 (14·1%)
RTI Events (includes COVID-19) [c]	498	460	958
Asymptomatic SARS-CoV-2 infection	4 (0·8%)	4 (0·9%)	8 (0·8%)
Mild	273 (54·8%)	246 (53·5%)	519 (54·2%)
Moderate	197 (39·6%)	201 (43·7%)	398 (41·5%)
Severe [b]	24 (4·8%)	9 (2·0%)	33 (3·4%)
Participants reporting long COVID-19 [a]	23/98 (23·5%)	12/92 (13·0%)	35/190 (18·4%)
Hospitalization [c]	30	26	56
COVID-19	10 (33·3%)	5 (19·2%)	15 (26·8%)
Death	0	4	4
COVID-19	0	2 (50·0%)	2 (50 0%)
Latent TB QuantiFERON Conversion			
Negative baseline to positive	27/235 (11·5%)	22/219 (10·0%)	49/454 (10·8%)
Positive baseline to negative	27/218 (12·4%)	35/233 (15·0%)	62/451 (13·7%)
SARS-CoV-2 Seroconversion	146/410 (35·6%)	132/429 (30·8%)	278/839 (33·1%)

***Table 2*: Respiratory adverse events.**
Definitions: *N* = number of participants in intention-to-treat group, COVID-19 = coronavirus disease 2019, TB = tuberculosis, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, BCG = Bacillus Calmette–Guérin.
Notes:
[a] One participant in each group reported two COVID-19 events in the follow up period, neither developed long COVID-19.
[b] Severe events include events with a health status score of 3–7 (severe symptoms, hospitalization, and death).
[c] Participants may have experienced more than one event.

estimates indicated a power of only 58% to detect a BCG efficacy of 75% in the current study size of 1000 participants with statistical significance, which would drop even further with lower BCG efficacy. Also, the study did not mandate testing for SARS-CoV-2. Our modelling results however showed excellent correlation between participant reported PCR testing and COVID-19 waves in the Western Cape, with the proportion of positive and negative tests fluctuating in line with local COVID-19 incidence (Figure S10). Due to the frequent and expected injection site reactions from BCG most participants were essentially unblinded within a few days of enrollment. We do not believe that this influenced self-reporting and testing across groups as no difference in number of follow-up visits, events, and access to COVID vaccinations are noted (Table 2).

The investigation around the non-specific protective effects of BCG against non-TB infections has amounted

Adverse Event	BCG Group	Placebo Group	Total
N	488/500 (97·6%)	369/500 (73·8%)	857/1000 (85·7%)
Participants with Injection Site Reaction	463/500 (92·6%)	21/500 (4·2%)	484/1000 (48·4%)
Mild	186 (40·2%)	18 (85·7%)	204 (42·1%)
Moderate	275 (59·4%)	3 (14·3%)	278 (57·4%)
Severe	2 (0·4%)	0	2 (0·4%)
Other Events [a]	555	475	1030
Mild	344 (62·0%)	304 (64·1%)	648 (62·9%)
Moderate	178 (32·1%)	140 (29·3%)	318 (31·9%)
Severe [b]	33 (5·9%)	31 (6·5%)	64 (6·2%)

***Table 3*: Non-respiratory adverse events.**
Definitions: *N* = number of participants in intention-to-treat group, BCG = Bacillus Calmette–Guérin.
Notes:
[a] Other events describes all adverse events excluding injection site reactions and RTIs.
[b] Severe events include events with a health status score of 3–7 (severe symptoms, hospitalization, and death).

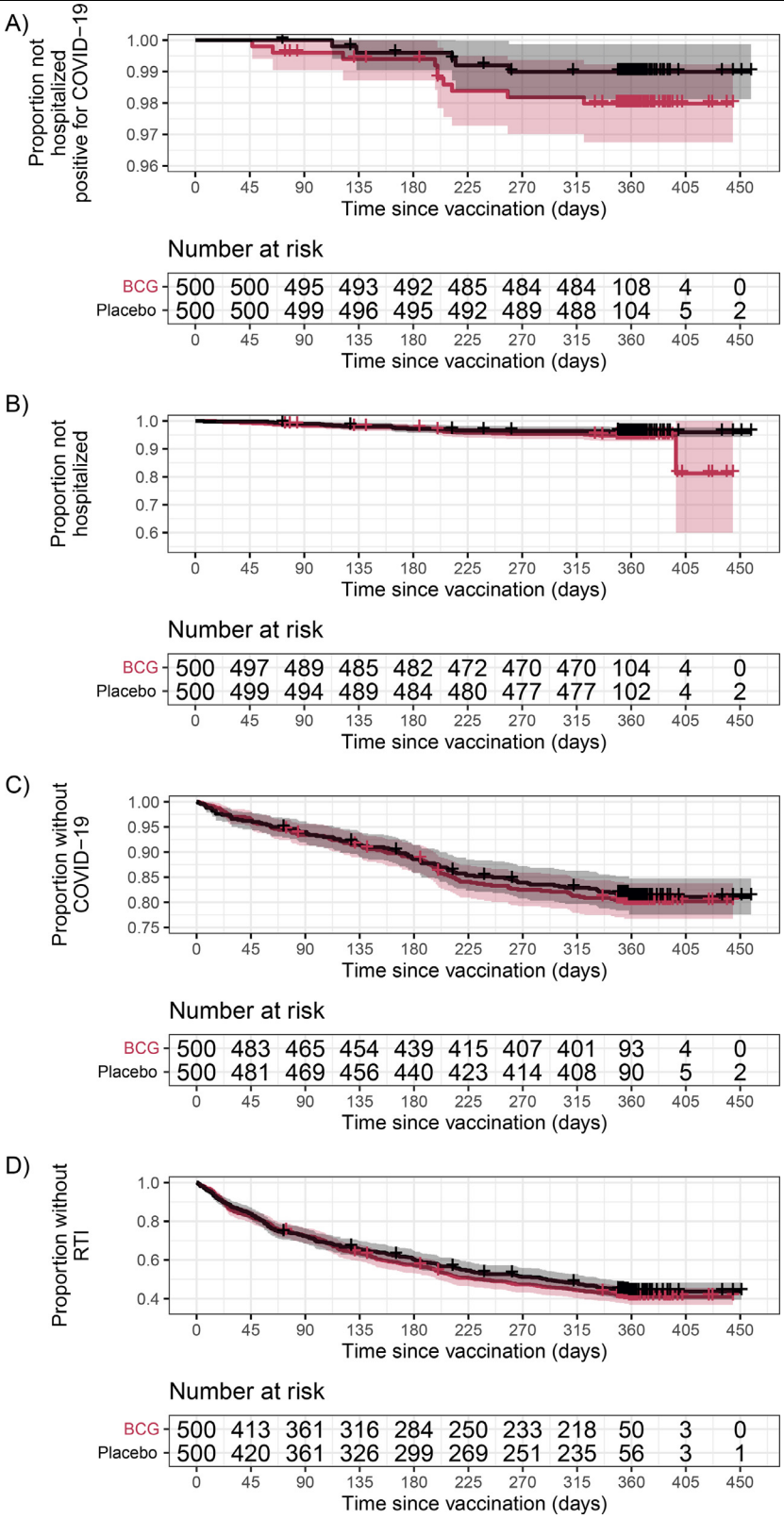

Figure 2. Kaplan-Meier plots (enhanced y-axis) for the time-to-first event for A: hospitalisation due to COVID-19 event, B: all-cause hospitalisation event, C: COVID-19 event, and D: RTI event.

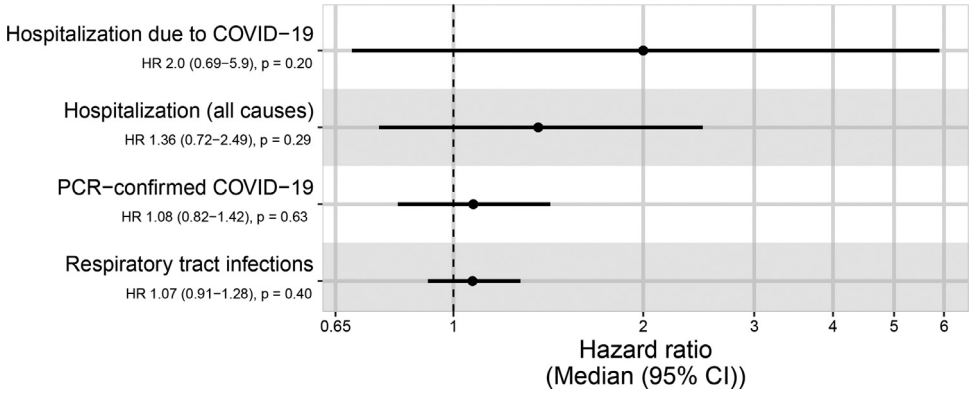

Figure 3. Forest plots for the effect in the BCG group compared to placebo (reference) on COVID-19 hospitalisation, all-cause hospitalisation, PCR confirmed COVID-19, and RTI.

Represented as a median hazard ratio (circle) and 95% confidence interval (whiskers).

COVID-19 = coronavirus disease 2019, PCR = polymerase chain reaction, HR = hazard ratio, CI = confidence interval.

considerable evidence over the last 20 years.[2,14] The negative results of our study are therefore unexpected, though in keeping with the earlier reported BCG PRIME study on prevention of COVID-19 conducted in an elderly, largely BCG naÿve population in the Netherlands. However, our results contrast the statistically significant 68% risk reduction for COVID-19 in the ACTIVATEII trial of revaccination of an elderly Greek population.[15,16] The vast majority of prior studies support a substantial reduction in RTIs across all ages. There are several population and immunological factors that may provide an explanation of why our study findings contrasted with the existing literature. This includes latent TB infection, age-related differences in immune function, and pathogen specificity.

About half of our participants had latent TB infection, which is increasingly recognized to be a continuum between immune-memory and actively-replicating mycobacteria where infection has profound effects on monocyte activation and polarization, as well as lymphocyte number and activity, while its modulating effect on the non-specific effects of BCG is unknown.[17–19] Indeed, a recent experimental study in mice has shown that TB infection inhibits trained immunity processes in the bone marrow.[20] Thus, it may be that latent TB infection either blocks or masks the non-specific effects of BCG. This same mechanism is thought to be the basis behind the decreased BCG vaccine efficacy for adult pulmonary TB related to higher non-tuberculous mycobacterial exposures in tropical low and middle income countries.[21] The non-specific immune benefits of BCG may only be of clinical importance in the very young or old where T- and B-cell compartments, proliferative capacity, and sensitivity to activation and survival signals differ profoundly.[22–24] Also, the non-specific effects of BCG may be pathogen-specific and perhaps there are no BCG-induced cross-reactive T-cells to SARS-CoV-2. Dosage and route of administration may be important, as a murine model of SARS-CoV-2 infection showed beneficial effects of BCG only when given intravenously and not intradermally.[25] Thus this may be a quirk of SARS-CoV-2, where intradermal administration was sufficient for protection from other pathogens. Notably, the lack of a BCG benefit for all RTIs may signal a specific lack of benefit for SARS-CoV-2, alongside a dramatic decrease in other circulating respiratory viruses since March 2020 due to non-pharmacological interventions such as masks, physical distancing, improved ventilation, and hand hygiene.[26]

In summary, BCG revaccination failed to protect healthcare workers in South Africa from SARS-CoV-2 infection, severe COVID-19, hospitalization and RTIs. This suggests that non-specific immune effects of BCG revaccination may be population-, age- and pathogen-specific. These results will be added to the currently more than 20 randomized-controlled studies in diverse populations investigating the effect of BCG vaccination against COVID-19. We recommend that BCG not be

Shaded area around each curve represents the standard error, computed using the Greenwood method.[27] Vertical dashes represent censoring, while downward steps represent events. Number at risk table represent the total number of participants without event or censoring. Some participants were followed up beyond 1 year due to ongoing events or challenges in contacting the participant.

COVID-19 = coronavirus disease 2019, RTI = respiratory tract infection, BCG = Bacillus Calmette–Guérin.

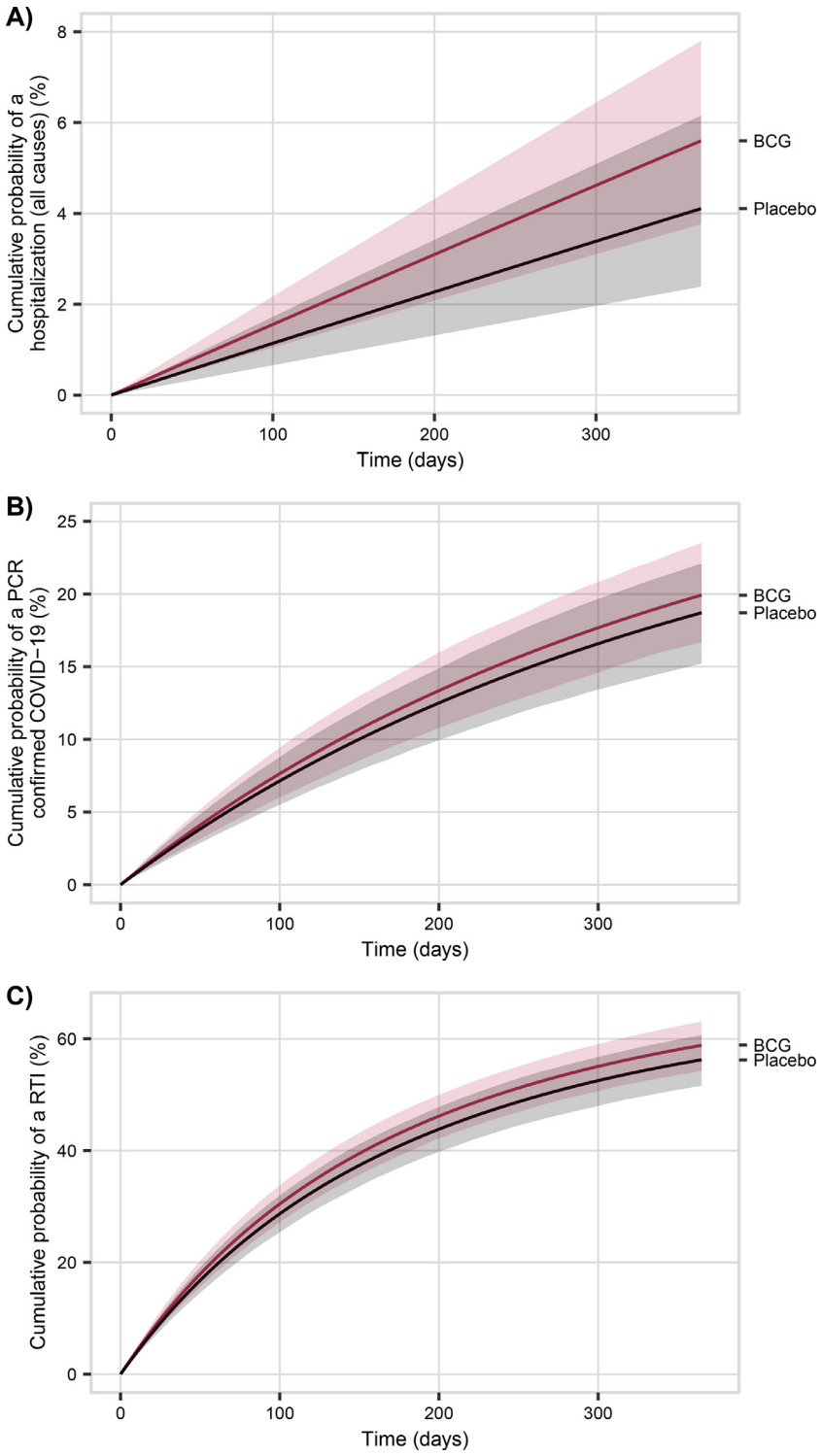

Figure 4. Cumulative probability plots of the effect in the BCG group on A: all-cause hospitalisation, B: COVID-19, and C: RTI events.

Represented as the median (solid line) and 95% confidence interval (shaded area). No statistical difference was seen between the two groups ($p > 0{\cdot}05$).

BCG = Bacillus Calmette—Guérin, COVID-19 = coronavirus disease 2019, RTI = respiratory tract infection, PCR = polymerase chain reaction.

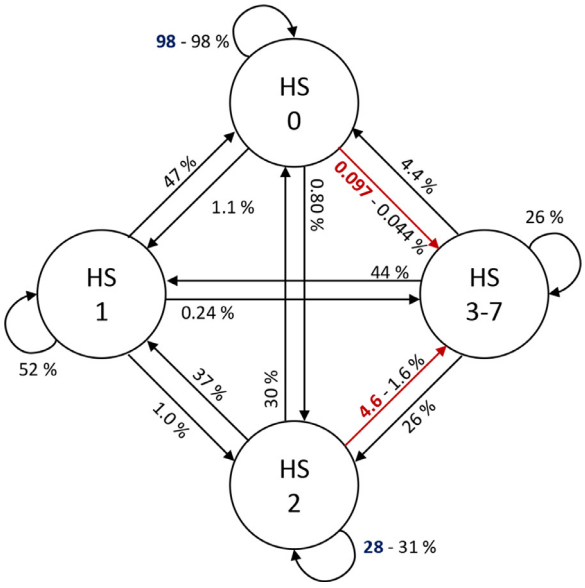

Figure 5. Probabilities of remaining in or transitioning between health status (HS) as predicted by the post hoc Markov Chain model for respiratory tract infections (RTIs). Because the majority of 958 RTIs (925, 97·0%) did not exceed HS 2 we grouped all remaining HS into HS 3–7. Participants without RTI remain in HS 0. Circles depict HS scores, arrows depict the transition from one HS to another, or remaining in the same HS for the curved arrows, with the corresponding probability noted. Dark red arrows and probabilities show the statistically significantly higher probabilities for participants on BCG to transit from HS 0 to HS 3–7 (2-fold increase, $p = 0{\cdot}02$) and from HS 2 to HS 3–7 (2·9-fold increase, $p = 0{\cdot}02$). Correspondingly, the probabilities of remaining in HS 0 and HS 2, respectively, decrease as shown in blue, as the probabilities of transitions originating from, and of remaining in each state sum up to 100% per state. BCG = Bacillus Calmette–Guérin.

used for the prevention or mitigation of COVID-19 outside of a clinical trial until we have a deeper understanding of the host and pathogen mechanisms at play that make SARS-CoV-2 unique from other respiratory pathogens.

Contributors

All authors meet the International Committee of Medical Journal Editors criteria for authorship for this Article, take responsibility for the integrity of the work as a whole, were involved in drafting and critical review of the manuscript, and approved the final version for submission. All authors agree to be accountable for all aspects of the work and attest to the accuracy and integrity of the work. CMU, AHD, RvC, GvH, AvD, US designed and conceived the study. GW, PB, JP contributed to the design of trial sub-studies. CMU, AHD, US, RvW, LM, GvH, JP, CM, KMH, GW acquired and analysed the data. CMU, AHD, US, RvW, LM, JP, RvC, GvH, AvD, HMW, GW, and PB interpreted the data. All authors reviewed the manuscript and supplementary material including tables and figures several times and contributed in writing to the interpretation and discussion of the data and to the presentation of findings. US, RvW, LM, GvH accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing

Study data will be shared in an open access data repository on completion of all secondary analyses. Deidentified participant data that underlie the results reported in this article, will be shared within 6 months of publication and available indefinitely. The study protocol and statistical analysis plan are available in Supplementary Materials.

Declaration of interests

We declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101414.

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