Cover page

Official title of the study:

BCG to Reduce Absenteeism Among Health Care Workers During the COVID-19 Pandemic

NCT number:

NCT04641858 - https://clinicaltrials.gov/ct2/show/NCT04641858

Date of document:

January 20, 2022

BCG vaccine to reduce unplanned absenteeism due to illness of health care workers during the COVID-19 pandemic. A multi-center randomised controlled trial (BCG-COVID-RCT)

LIST OF ABBREVIATIONS

AEs – Adverse Events

BCG – Bacille Calmette-Guérin

CFU – Colony-Forming Units

CI – Confidence Interval

COVID-19 – Corona Virus Disease

DSMB – Data Safety and Management Board

EDCTP - European & Developing Countries Clinical Trials Partnership

HCW – Health Care Workers

HIV – Human Immunodeficiency virus

ISC – International Steering Committee

NSC – National Steering Committee

NSEs – Non-specific effects

PCR – Polymerase Chain Reaction

POC – Point Of Care

PI – Principal Investigator

RCT – Randomized Controlled Trial

RR – Relative Risk

SAEs – Serious Adverse Events

SARS-CoV2 - Severe Acute Respiratory Syndrome Coronavirus 2

ABSTRACT

The COVID-19 pandemic challenges available hospital capacity. This is augmented by absenteeism of health care workers (HCW). Strategies to protect HCW are desperately needed. Bacille Calmette-Guérin (BCG) has protective non-specific effects against other infections; a plausible immunological mechanism has been identified in terms of "trained innate immunity". European and North American trials to study if BCG can reduce the incidence and/or severity of COVID-19 have now been initiated. African studies are needed. The underlying hypothesis for this study is that BCG vaccination of HCW reduces unplanned absenteeism due to illness by 20%.

The primary objective of the study is to evaluate whether BCG can reduce unplanned absenteeism due to illness among HCW during the COVID-19 pandemic. Secondary objectives are to reduce the number of HCW that are infected with COVID-19, reduce hospital admissions of HCW during the COVID-19 pandemic and to improve the capacity for clinical research in Cape Verde and Guinea-Bissau.

Design: Single-blind, parallel-group placebo-controlled multi-centre block randomized trial including a total of 1050 HCW. The study sites will be the Manhiça District Hospital and Mavalane Hospital in Mozambique and Hospital Nacional Simão Mendes and other hospitals in the capital Bissau in Guinea-Bissau. Population: HCW (nurses/physicians/others) ≥18 years. Exclusion criteria: known allergy to (components of) BCG or serious adverse events to prior BCG administration; known previous, active or latent infection with Mycobacterium tuberculosis or other mycobacterial species, fever (>38 C) within past 24 hours; suspicion of active viral or bacterial infection, severely immunocompromised subjects, self-reported HIV infection, self-reported pregnancy; active solid or non-solid malignancy or lymphoma within the last two years; any other contraindications for live-attenuated vaccine administration fulfilled, not having a mobile phone.

Intervention: Block randomization 1:1 to intradermal standard dose (0.1 ml) of BCG vaccine or placebo (saline). Endpoints: Primary: Days of unplanned absenteeism due to illness. Secondary: Days of absenteeism because of documented COVID-19; cumulative incidence of infectious disease hospitalizations.

Baseline data collection: Enrolment data regarding chronic illnesses and treatment, lifestyle (family structure, socioeconomic factors, smoking), vaccination history including previous BCG vaccination. Blood sample for SARS-CoV-2 serology. Follow-up: mobile phone interviews every second week, regarding symptoms, absenteeism and causes, COVID-19 testing (if done) and their results. Supplemented by daily workplace presence registry information (where present).

Statistical analysis: Total number of unplanned days of absenteeism analysed using Bayesian negative binomial regression with a fixed effect for BCG, hospital, professional category, observation week, number of average workdays per week. Monthly interim analyses.

Adaptive design with frequent interim analyses will allow results to inform policy-makers during the ongoing pandemic.

Perspectives: If BCG can reduce HCW absenteeism it has global implications. The intervention can quickly be scaled up all over the world.

ADMINISTRATIVE INFORMATION

Trial registration

The trial is registered at clinicaltrials.gov. (https://clinicaltrials.gov/ct2/show/NCT04641858)

Data category	Information
Primary registry and trial identifying number	https://clinicaltrials.gov/ct2/show/NCT04641858
Date of registration in primary registry	November 24, 2020
Secondary identifying numbers	NA
Source(s) of monetary or material support	EDCTP
Primary sponsor	EDCTP
Secondary sponsor(s)	Institute of Hygiene and Tropical Medicine, NOVA University Lisbon University of Southern Denmark
Contact for public queries	Christine Stabell Benn
Contact for scientific queries	Christine Stabell Benn
Public title	
Scientific title	BCG vaccine to reduce unplanned absenteeism due to illness of health care workers during the COVID-19 pandemic. A multi-centre randomised controlled trial (BCG-COVID-RCT)
Countries of recruitment	Guinea-Bissau, Mozambique
Health condition(s) or problem(s) studied	BCG vaccine, absenteeism, COVID-19
Intervention(s)	Active comparator: intradermal standard 0.1 ml dose of attenuated Mycobacterium bovis BCG (Bacillus Calmette-Guerin), Danish strain 1331, 2-8 × 105 CFU Placebo comparator: intradermal standard 0.1 ml saline solution (NaCl 0.9%)
Key inclusion and exclusion criteria	Population: Health care workers (physicians, nurses, and others), ≥18 years. Exclusion if known allergy or previous adverse events to BCG; previous/active infection with M. tuberculosis; Fever (>38 C) within past 24 hours; Suspicion of active viral/bacterial/HIV infection; Pregnancy; Being immunocompromised; Not having mobile phone.
Study type	Single-blind, parallel-group placebo-controlled adaptive multi-centre block-randomised trial including a total of 1050 HCW with two arms (BCG arm and placebo arm).
Date of first enrolment	
Target sample size	1050
Primary outcome(s)	Days of unplanned absenteeism due to illness
Key secondary outcomes	Days of unplanned absenteeism due to documented COVID-19; Cumulative incidence of hospitalisations

Funding

EDCTP is funding the run-in costs for the BCG-COVID-RCT, including trials in the respective countries and for training and management. The budget of each RCT site covers costs related to regulatory and ethical approval, clinical and supervisory personnel, field workers (enrolment of study subjects and data collection, including biological samples), costs of communication, cost of materials (offices, electricity, vaccines) and costs of communication (follow up will be by telephone).

The collaboration of the tenured staff members of the Cape Verdean, Danish and Portuguese Institutions (University of Cape Verde, National Institute of Public Health of Cape Verde, University of Southern Denmark, NOVA University Lisbon, Portugal) will be fully supported by their own institutions.

TECHNICAL INFORMATION

Background and rationale

The COVID-19 pandemic reflects a serious threat to hospital personnel capacity as the number of COVID-19 infected patients that require hospital care may well exceed the capacity of hospital personnel. Furthermore, healthcare workers (HCW) face an elevated risk of exposure to - and infection with - SARS-CoV-2. Even if further mobilisation of hospital personnel is possible to some extent, it is imperative to ensure the safety, health and fitness of hospital personnel, not only for moral and professional reasons, but also in order to safeguard continuous patient care and to prevent health care systems from collapsing. Strategies to prevent COVID-19 infection or to mitigate its clinical consequences among HCW are therefore desperately needed.

To date, treatment therapies for COVID-19 has been of supportive nature, and no curative or protective treatment has been identified yet, despite many ongoing trials. Particularly, there are no interventions specifically targeting HCW, apart from adequate personal protective equipment and sound professional practices.

Bacillus Calmette-Guérin (BCG) was developed as a vaccine against tuberculosis, but it has been shown that it can protect against death from other infections - it has so-called *non-specific effects* (NSEs) (1-3). In clinical studies, BCG vaccination was associated with reduced infant mortality, mainly as a result of fewer cases of neonatal sepsis and respiratory infections (4-6). NSEs of BCG are not limited to infants (7,8). For instance, an Indonesian trial showed that consecutive BCG vaccination for 3 months reduced the incidence of acute upper tract respiratory infections by 80% (95%CI=22% to 95%) (8), and in a South African trial among adolescents, the risk of upper respiratory tract infections was 2.1% in the BCG revaccination group but 7.9% in the placebo group (P<0.001) (9).

It has recently been demonstrated that the beneficial NSEs of BCG vaccination are due to epigenetic and metabolic reprogramming of innate immune cells leading to an increased antimicrobial activity, a process termed "trained immunity" (10). Upon stimulation with a pathogen, the innate immune system becomes primed and can react faster and more efficiently to a secondary (and non-related) stimulus. These effects lasts for at least one year (10). There is proof-of-principle that this will affect the course of a viral challenge; in a human experimental study randomising adult volunteers to BCG vs. placebo 4 weeks prior to a yellow fever vaccine challenge, those who had received BCG had a lower yellow fever viral load, and improved anti-viral responses (11).

Boosting with BCG (revaccination) may enhance these beneficial NSEs (12). This has been shown for children in an RCT of BCG revaccination (13). Also, the therapeutic effect of BCG for bladder cancer is higher for patients that had previously been vaccinated with BCG (14). It was recently demonstrated in a pilot study of 40 Guineans above 50 years of age, that BCG revaccination was associated with "innate training", and this was most pronounced in individuals who had a positive IGRA test (submitted). In the proposed trial, boosting may be important, as many HCW are expected to have been BCG vaccinated previously.

BCG vaccine in immunocompetent adults is considered safe, also for persons with prior BCG vaccination and even in latently infected adults (15). In a randomised controlled trial (RCT) that compared revaccination with BCG versus placebo, no vaccine-related serious adverse events were observed in the 312 patients in the BCG arm (9).

Research hypothesis

The COVID-19 pandemic in Africa challenges available hospital capacity. This is augmented by unplanned absenteeism of HCW. Strategies to prevent their absenteeism are needed. BCG has

protective NSEs against other infections and a plausible immunological mechanism, "trained innate immunity", has been identified.

Based on the capacity of BCG to: 1) reduce the incidence of respiratory tract infections and mortality in children and perhaps in the elderly; 2) exert antiviral effects and reduce viremia in an experimental human model of viral infection, we hypothesize that BCG vaccination may induce partial protection against susceptibility to and/or severity of COVID-19 and associated complications which might result in a reduction in the number of days of unplanned absenteeism from work for HCW.

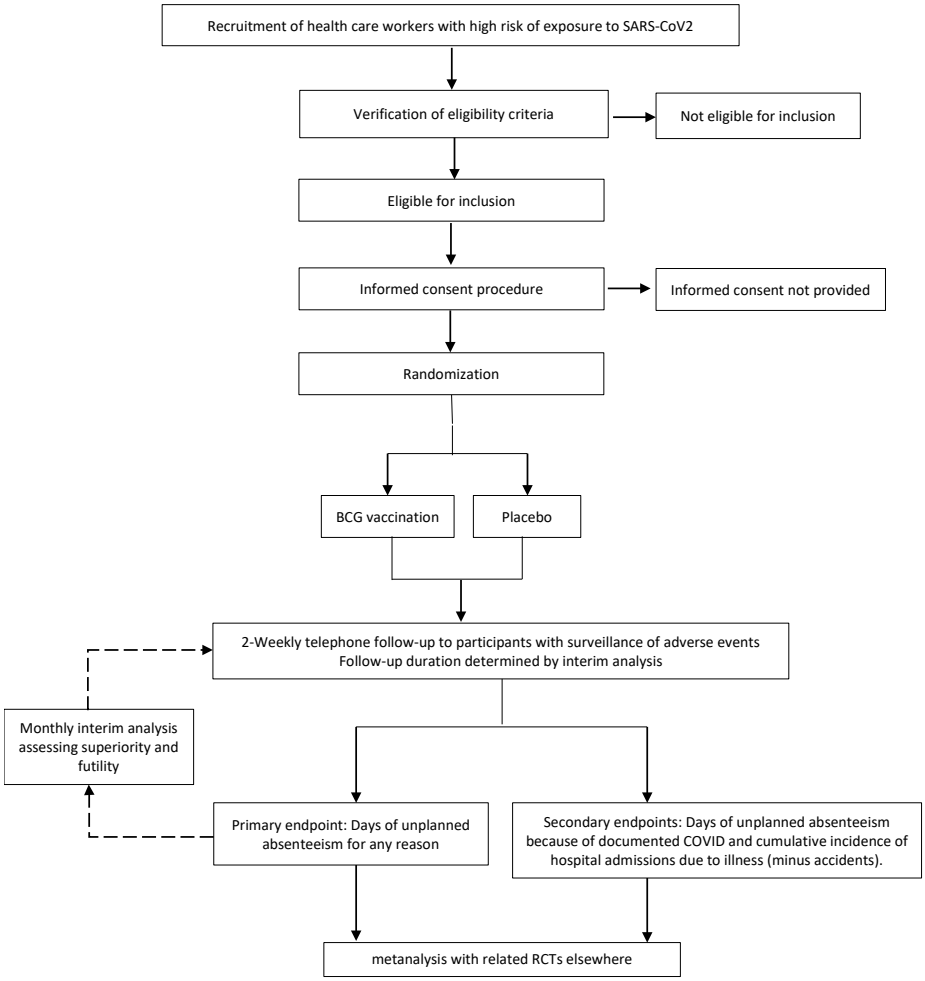
Objectives

Primary: Test the capability of BCG to reduce absenteeism among HCW working at a health care facility that treats patients who could suffer from COVID during the COVID-19 pandemic. Secondary: reduce number of HCW that develop COVID-19; ii) reduce number of hospital admissions due to illness of HCW during the COVID-19 pandemic; iii) improve capacity for clinical research in Guinea-Bissau.

Trial design

Single-blind, parallel-group placebo-controlled adaptive multi-centre trial, with block-randomisation 1:1 to intradermal standard 0.1 ml dose of BCG vaccine or placebo (saline) including a total of 1050 HCW (BCG arm and placebo arm).

Figure 1 – Trial design and flowchart



Study population

Health Care Workers defined as a person who delivers care and services to the sick and ailing either directly as doctors and nurses or indirectly as aides, helpers, laboratory technicians, or even medical waste handlers.

Inclusion and exclusion criteria for participants

Participants must provide written, informed consent before any study procedures occur (see ethics section).

Inclusion criteria

Participants eligible for the trial must comply with all of the following at randomization:

- health care worker (physician, nurse, or other) based at one of the research hospitals.
- age ≥18 years

Exclusion criteria

- known allergy to (components of) BCG or serious adverse events to prior BCG administration;

- known previous, active or latent infection with Mycobacterium tuberculosis or other mycobacterial species
- fever (>38 C) within past 24 hours;
- suspicion of active viral or bacterial infection
- severely immunocompromised subjects
- self-reported HIV infection or a positive HIV test at inclusion
- self-reported pregnancy;
- active solid or non-solid malignancy or lymphoma within the prior two years;
- contraindications for live attenuated vaccine administration.
- not having a mobile phone.

Intervention

The intervention will consist of the administration of an intradermal injection of a standard 0.1 ml adult dose of attenuated *Mycobacterium bovis* BCG (Bacillus Calmette-Guerin), Danish strain 1331, 2-8 × 10^5 CFU or the placebo comparator: intradermal standard 0.1 ml saline solution (NaCl 0.9%). Both BCG and saline solution will be injected in the skin over the upper deltoid muscle.

Product name	Manufacturer	Details of product
BCG	AJ vaccines (first market authorization 1993 - marketing authorization number 14762)	Attenuated Mycobacterium bovis BCG (Bacillus Calmette-Guerin), Danish strain 1331, 2-8 × 10^5 cfu (Approval for use No 08731) http://www.produktresume.dk/AppBuilder/search?utf8=%E2%9C%93&id=&type=&q=bcg&button=S%C3%B8g
Saline Solution (NaCl 0.9%)	NA	NA

The BCG vaccine has been commercialized since the 1930s and the current stock is sufficient to meet the study needs. BCG vaccines from different manufacturers are not identical. The results from this clinical trial will therefore be applicable for BCG Vaccine AJV and not necessarily to other BCG vaccine strains.

The expected local reaction after successful vaccination with BCG Vaccine "AJ Vaccines" is injection site swelling followed by a local lesion that can form an ulcer after 2-4 weeks and heal after a few months, leaving a small flat scar. Redness and tenderness may occur at the injection site. Regional swelling of the lymph node <1 cm may also occur. Not common (≥1/1,000 to <1/100) and rare (≥1/10,000 to 1/1,000) adverse reactions:

- Blood and lymphatic system - Regional swelling of lymph nodes> 1 cm
- Nervous system disorders - Headache
- Bones, joints, muscles and connective tissue - Osteitis
- Infections and parasitic diseases - Suppurative lymphadenitis, osteomyelitis, BCGitis
- Abscess at the injection site

We will specifically enquire about adverse events at the biweekly interviews and in the end questionnaire.

Outcomes

Primary outcome measures

Difference between the two treatment arms in the numbers of days of unplanned absenteeism due to illness.

Secondary outcome measures

Days of unplanned absenteeism because of documented COVID-19 and cumulative incidence of hospital admissions due to illness (minus accidents).

Unplanned absenteeism is defined by being absent from work due to causes other than holidays, parental leave, and other planned leaves, family assistance (including mourning leave) and quarantine measures.

Hospital admissions involves staying at a hospital for at least one night or more for medical reasons. It includes admissions to hospital wards and overnight stays in emergency departments.

Sample size

The sample size was calculated on the basis of the primary hypothesis. A total of 1050 HCW randomized with an estimated loss to follow-up of 5%, and a mean number of days off work due to illness in the control group of 5 days (SD=5) over a 6-month period will demonstrate a reduction among BCG vaccinated of 20% for a mean absence of 4 days (80% power and alpha 0.05). The estimated loss to follow-up (5%) was based on past telephone-based surveys conducted in Mozambique and Bissau.

Assignment of interventions

Randomization

All participants who give consent for participation and who fulfil the inclusion criteria will be randomly assigned to either placebo or BCG group with a 1:1 (treatment:placebo) allocation in blocks of 4 to 6 within strata defined by gender (male/female) and occupational group (doctors/ nurses/other).

Blinding

The BCG vaccine will be administered by study physicians/nurses, who are not blinded but also not involved in the data collection. Participants, data collectors and data entry clerks will be blinded to the treatment allocation. In case of serious adverse events, the participant can be unblinded after consultation with the investigator or the vaccinating physician/nurse.

When the study has ended, all participants will receive information about the intervention that they received.

Data collection

Data collection instruments include: consent form, inclusion/exclusion criteria form, baseline questionnaire, follow-up questionnaire, and end questionnaire.

Variables

The endpoint variables are described in

Table 1.

Table 1 – Definition of end-point variables

Variables	Definition	Type	Scale	Domain
Absenteeism	Refers to the total number of days absent from work due to illness	Quantitative	Numeric	In days

Variables	Definition	Type	Scale	Domain
Absenteeism for COVID-19	Refers to the number of days absent from work due to COVID-19	Quantitative	Numeric	In days
Absenteeism besides COVID-19	Refers to the number of days absent from work due to diseases /illness besides COVID-19	Quantitative	Numeric	In days
Absenteeism for infections	Refers to the number of days (unplanned) absent from work due to infections	Quantitative	Numeric	In days
Absenteeism for respiratory infections	Refers to the number of days (unplanned) absent from work due to respiratory infections	Quantitative	Numeric	In days
COVID-19 infection	Describes if the participant is positive for SARS-CoV2 or has had COVID-19	Qualitative	Nominal	No Yes
Death	Whether the participant died during follow-up	Qualitative	Nominal	No Yes
Cumulative incidence of infectious disease episodes	Cumulative incidence of infectious disease episodes	Quantitative	Numeric	Episodes
Cumulative incidence of respiratory infectious disease episodes	Cumulative incidence of respiratory infectious disease episodes	Quantitative	Numeric	Episodes
Cumulative incidence of hospital admissions	Cumulative incidence of hospital admissions	Quantitative	Numeric	Admissions
Cumulative incidence of infectious disease hospital admissions	Cumulative incidence of infectious hospital admissions	Quantitative	Numeric	Admissions
Cumulative incidence of respiratory infectious hospital admissions	Cumulative incidence of respiratory infectious hospital admissions	Quantitative	Numeric	Admissions
Cumulative incidence of hospital admissions due to documented COVID-19	Cumulative incidence of hospital admissions due to documented COVID-19	Quantitative	Numeric	Admissions
Cumulative incidence all-cause and infectious intensive care admission	Cumulative incidence all-cause and infectious intensive care admission	Quantitative	Numeric	Nights
Cumulative incidence of intensive care admission due to	Cumulative incidence all-cause and infectious intensive care admission	Quantitative	Numeric	Nights

Variables	Definition	Type	Scale	Domain
documented COVID-19 infection				

Statistical methods

The responsible for statistical analyses in the consortium will be Sebastian Nielsen affiliated with the University of Southern Denmark.

Data analysis:

Data will be reported quantitatively. All analyses will be performed from the intention-to-treat principle. Missing data on background variables will be dealt with by multiple imputation. Final data analysis will begin when the last participant in the multicentric RCT has completed the follow-up period. The primary endpoint, work absenteeism due to illness, will be reported as the total number of sick days with standard deviation. Total days of absenteeism will be analysed using a Bayesian negative binomial regression with a fixed effect for BCG, hospital, professional category, age, enrolment week and number of average workdays per week. The brm function from the R package "brms" will be used for fitting the negative binomial model. The effect will be reported as a relative risk with 95% confidence interval (CI). Please refer to section interim analysis for type-1 error control and power.

Similar regression models will be used for secondary endpoints. Cumulative incidence outcomes will primarily be analysed using Cox Proportional Hazard Regression.

Continuous baseline characteristics will be reported as means with the standard deviation or medians with the inter-quartile range, as appropriate. Categorical baseline characteristics will be reported as count and percentage. No statistical testing for baseline characteristics will be reported.

Please refer to the Data Analysis Plan for more details.

Interim analysis

Every month, an interim analysis will be conducted for each study site and of the combined dataset. Interim analyses will start after the 200th participant has been recruited across the two sites. The primary endpoint will be analysed as described above. The Bayesian model yields a posterior distribution of the relative risk (RR). The posterior probability of the superiority hypothesis (RR < 1) will be calculated. If during any of the interim analyses, the posterior probability of superiority is > 0.995, a conclusion is reached, and the trial will be stopped.

Monthly, the following secondary endpoints will be reported from the sites: hospital admissions, and deaths.

IMPLEMENTATION

Inception

The study will begin with an inception meeting to be held in Cape Verde or virtually, depending on travel and quarantine recommendations at the time. Besides administrative issues, the meeting will address:

a) Strengthening Health Care Workers knowledge on Personal Protective Measures through provision of leaflets with detailed information on reasoning the use, the best practices, and the common pitfalls to avoid getting infected by COVID-19 or any other transmissible pathogens (when dealing with endemic highly transmissible diseases and/or future outbreaks, epidemics or pandemics). The leaflets will be developed based on best evidence available by members of consortium and will be handed-out to all health care workers working at the inclusion sites.

b) Short course on Fundamentals of Epidemics and Pandemics for Health Care Workers based in hospitals with limited resources. The course will cover best available knowledge on epidemiological characteristics of epidemics and pandemics and impart abilities/skills and attitudes to deal will epidemics and pandemics based on lessons learned from previous epidemics and pandemics in last 100 years, including strategies and interventions that are possible to implement for adequate containment and mitigation of epidemics and pandemics. We expect to develop the curriculum for the training and implement in all study sites. The initial training will be for 20 to 25 participants who will be trained in order to themselves be trainers and therefore replicate to their fellow colleagues along the time in their own Districts/Regions and elsewhere in their respective countries;

c) Short course on fundamentals of clinical research and RCT management - Training of research staff will include obtaining a certification in good clinical practice (GCP) and in the appropriate field procedures for all researchers involved in the study. GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials, whose principles help assure the safety, integrity, and quality of clinical trials. The GCP training aims to ensure that the rights, safety, and well-being of human subjects are protected and that clinical trials are conducted in accordance with approved plans with rigor, and that data with integrity derived from clinical trials is reliable. GCP certification will be done online. Several certified online courses are currently available. We will prefer those recommended by the NHI.

See also study management, monitoring and quality control and Gantt chart.

Study setting

The study will be conducted in two different African countries: Guinea-Bissau and Mozambique. These countries were selected because they 1) are both Portuguese Speaking; and 2) have a low amount of HCW per population ratio which, in the scenario of the COVID-19 pandemic, places them in a fragile situation in terms of health care system capacity to respond to the pandemic; 3) have long-standing research/academic working relationships, namely with the European partners; and 4) belong to EDCTP supported networks of excellence.

The sites in the two countries were selected because they all provide care for COVID patients and have well established research capacity.

In Guinea-Bissau, the study site will be Hospital Simão Mendes and other hospitals located in the capital city. Hospital Simão Mendes is the national hospital of reference and the leading public health institution in the provision of care to COVID-19 patients.

The same criteria apply to Mozambique (Manhiça Hospital) (Table 2).

Table 2 – Participating hospitals and anticipated number of participants

Country	**Participating hospitals**	**Hospital collaborator**	**Anticipated number of eligible participants**
Guinea-Bissau	Hospital Simão Mendes	Dr. Agostinho Pedro Semedo	1050
Mozambique	Hospital Distrital da Manhiça	Dr. Flezer Tomadote	100
	Hospital Geral de Mavalane	Dra. Marlene Tovele	150

Recruitment

Prior to the initiation of the trial, the hospital director will inform the department heads about the trial. Each department head will be provided with written material about the trial, its objectives and the practicalities. A telephone number will be provided, to which HCW can address potential questions. After a week (where presumably all staff has rotated and been informed about the upcoming trial), enrolment dates will be arranged with the department heads and communicated to staff. Enrolment will take place at a designated room at the hospital. A point-of-care (POC) test will be done for antibodies anti-SARS-CoV2.

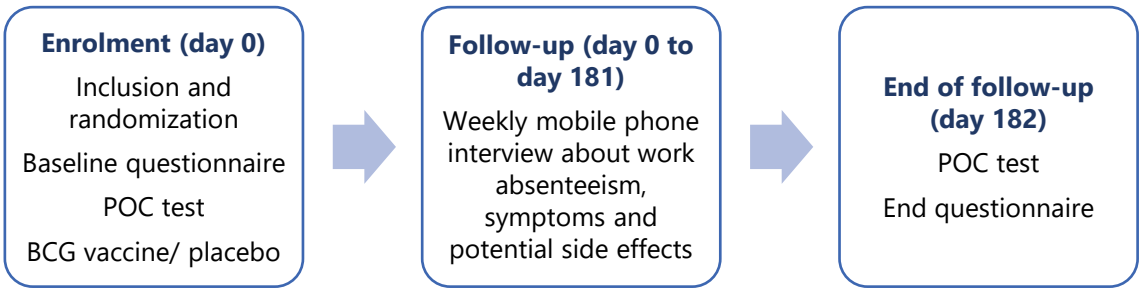
BCG will be given by people trained to administer vaccines by the intradermal technique. The injection site should be clean and dry. The vaccine should be injected intradermally on the outer side of the upper arm, corresponding to the area of the distal insertion of the deltoid muscle (about one-third down the upper arm), as follows:

- The skin is stretched between the thumb and index finger.
- The injection needle is held almost parallel to the skin surface and inserted slowly with the oblique edge pointing upwards, approx. 2 mm down into the upper skin layer.
- The needle should be visible through the epidermis at insertion.
- Vaccination should be performed slowly.
- The appearance of a pale bladder is evidence of proper injection technique.
- The injection site should be uncovered to promote healing.
- The administration of the saline solution will follow the exact same procedure.

Follow-up

Follow-up will last for 6 months (182 days). Every second week, participants will be contacted over telephone and interviewed for symptoms and absenteeism from work. By the end of follow-up, participants will be invited for another POC test for COVID-19 serology.

Figure 2 - Flowchart



In case of not answering the telephone call and questionnaire for ≥18 days, information on the participant will be retrieved from hospital registries for absenteeism and hospital admission registries, ICU admission and outcomes. An explicit permission for this procedure will be requested from the participant during informed consent procedures at enrolment.

Participant timeline

	Staff member	Enrolment	Follow-up	End of Follow-up

		(W1)	(W2 to W25)	(W26)
Consent form	Research assistant	x		
Inclusion/exclusion criteria form	Research assistant	x		
POC test for COVID antibodies	Study nurse	x		
Randomization	Study nurse	x		
Administration of intervention	Study nurse	x		
Baseline questionnaire	Research assistant	x		
Follow-up Interview	Research assistant		x	
End questionnaire	Research assistant			x

Data management

The researchers will archive the published articles and the final peer-reviewed manuscripts in an online repository before, if feasible, at the same time as, or after publication in open access mode. The researchers will also make their data available according to the Open Research Data Pilot (ORD pilot) of the Horizon 2020 program.

Study management, monitoring and quality control

The project will be led by an International Steering Committee (ISC) consisting of PIs in each of the five countries involved: Amabelia Rodrigues, PI from Guinea-Bissau; Christine Stabell Benn (international coordinator), PI from Denmark; Inês Fronteira, PI from Portugal; Isabel Inês Araújo, PI from Cape Verde; and Pedro Aide, PI from Mozambique.

Figure 3 - Organogram of management structures

Overall coordination will be with the Danish partner. The leader has extensive leadership experience from heading a Center of Excellence in Denmark and the Bandim Health Project research group in Bissau for many years. Bandim Health Project has a history of past collaboration with the Portuguese partner.

The ISC will have telemeetings, at least once a week, with a formal pre-arranged agenda on training, enrolment, follow up, losses to follow up, staff turn-over, vaccine logistics, quality control of data collection, data entry and database management, interim analysis, communication and dissemination activities, other risks. Decisions of each meeting will be recorded by the coordinator.

Co-PIs in each one of the hospitals involved as study sites will constitute a National Steering Committee (NSC) coordinated by the country's PI. Meeting frequency will depend on project needs, but the NSC will interact at least once a week before ISC telemeetings. The agenda will be of a more operational nature.

The NSC should provide country PIs with information relevant to the agenda of fortnightly telemeeting of ISC and will also address other site relevant issues. Decisions of each meeting will be recorded by the country PI.

Structure	Membership		Functions	Description
	Name	Affiliation		
Data Safety and Monitoring Board (DSMB)	António Pedro de Sá	NOVA-IHMT	Member	Quality management activities include recruitment of a Data Safety and Monitoring Board, who are actively involved in the project, approving the quality of the project outputs, including deliverables and dissemination, and supporting the consortium in key decisions taken within the project, while maintaining their independence. Furthermore, each site will recruit an internal monitor, who will conduct at least two monitoring visits during the conduct of the trial.
	Mariza Morgado	Fundação Oswaldo Cruz	Member	
	Poul-Erik Kofoed	Lillebaelt Hospital	President	
	Jahit Sacarlal	Eduardo Mondlane Med School	Member	
	Zacarias da Silva	National Institute of Health, Guinea-Bissau	Member	
International Trial Steering Committee (ITSC)	Christine S Benn	Southern Denmark University	Presides, Danish PI	The project will be led by an International Steering Committee (ISC) consisting of PIs in each one of the five countries involved. Overall coordination will be with the Danish partner. The leader has extensive leadership experience from heading a Center of Excellence in Denmark and the Bandim Health Project research group for many years. Bandim Health Project has a history of past collaboration with the Portuguese partner.
	Amabélia Rodrigues	Bandim Health Project	Guinean-Bissau PI	
	Inês Fronteira	Universidade Nova de Lisboa	Portuguese PI	
	Isabel Araújo	Universidade de Cabo Verde	Cape Verdean PI	The ISC will have at least once a week telemeetings with a formal pre-arranged agenda on training, enrolment, follow up, losses to follow up, staff turn-over, vaccine logistics, quality control of data collection, data entry and database management, interim analysis, communication and dissemination activities, other risks. Decisions of each meeting will be recorded by the coordinator.
	Pedro Aide	Centro de Investigação em Saúde da Manhiça	Mozambican PI	
Guinea-Bissau Trial Steering Committee (GBTSC)	Amabélia Rodrigues	Bandim Health Project	Guinean-Bissau PI	Co-PIs in each one of the hospitals involved as study sites will constitute a National Steering Committee coordinated by the country's PI. Meeting frequency will depend on project needs, but the NSC will interact at least once a week before telemeeting of ISC. The agenda will be of a more operational nature. This should provide the country PI with information relevant to the agenda of weekly telemeeting of ISC and will also address other site relevant issues. Decisions of each meeting will be recorded by the country PI.
	Christine Benn	Researchers coordinating field work at Hospital Nacional Simão Mendes and other participating hospitals.	Members	
	Sebastian Nielsen			
	Frederik Schaltz-Buchholzer			
	Elsi Ca			

Structure	Membership		Functions	Description
	Name	Affiliation		
	Isaquel da Silva			
Mozambique Trial Steering Committee (MZSC)	Pedro Aide	Centro de Investigação em Saúde da Manhiça	Mozambican PI	

Critical risks

The critical risks for implementation are

- Negative effect of the intervention - negative BCG effect on COVID cannot be excluded. It is reassuring that other trials are already ongoing and are likely to detect if BCG, against all indications, should have a harmful effect in HCW, before we have enrolled a lot of participants. Hence, we would limit any harm of participants. BCG has been used for 100 years, and it is considered a very safe vaccine. We have no reason to believe that it causes harm, rather the contrary.
- Lack of clinical research experience is variable among sites and unsatisfactory compliance with requirements for data collection – the workplan contemplates: training of researchers and data collectors; pre-testing data collection tools, repeat 10% of data collection interviews by different interviewer, data entry from early on with ongoing validation. Both Mozambique and Guinea-Bissau have well established, experienced cadres of field research workers.
- Study sites with insufficient staff to perform all tasks required - Staff will either be hospital-based or working from home. Quarantine is not likely to affect health workers unless they are infected or symptomatic. That is precisely the main outcome we want to study. Collaborators doing phone calls for follow-up will be working from home/project offices.
- Hospital staff lacks interest in participating in trial - The participating hospitals anticipate having enough eligible participants between them. Should we face a situation where we cannot recruit the anticipated 1050 participants, other hospitals expressed interest in participating, but were not able to confirm participation before the grant deadline.
- Enrolment is too slow - Good management and monitoring of recruitment and follow-up.
- Recruitment is too fast and outstrips capacity of data collection team - Good management and monitoring of recruitment and follow-up.
- High volumes of data queries and re-queries - Once again good data management and monitoring.
- Staff carrying out follow-up leaves the project and needs to be replaced without losing efficiency - Both Mozambique and Guinea-Bissau have well established, experienced cadres of field research workers.
- Limited capacity for COVID-testing - If point-of-care tests are not available, we may have to collect capillary blood samples for later serology. This analysis is not central for the main objective of the RCT (absenteeism).
- Ensuring vaccine supply - We will procure vaccines locally, rather than relying on flying in vaccines specifically for the trial. This may give variability in vaccine type available (supply can be from several UNICEF-pre-qualified producers). However, in the current situation with limited shipping possibilities for research, we find this the best, pragmatic solution. If producers are different in the different sites, this will be noted, and we will scrutinize data for signs of differences in effect by producer. Essentially, this trial will address the research question of relevance for Africa now: can we use the BCG available to mitigate the pandemic.

Quality management

Quality management activities include recruitment of a Data Safety and Monitoring Board (DSMB), who are actively involved in the project, approving the quality of the project outputs, including deliverables and dissemination, and supporting the consortium in key decisions taken within the project, while maintaining their independence. Furthermore, each site will recruit an internal monitor, who will conduct at least two monitoring visits during the conduct of the trial.

ETHICS

The protocol for this study follows standard clinical trials ethical approval procedures for each country. In Mozambique, the study protocol was first approved by the CISM Committee for Bioethics in Health on the 26th of October 2021, approval number CIBS-CISM/079/2020. Approval by the National Committee on Bioethics in Health (Comité Nacional de Bioética para a Saúde), was given on March 11 2021 with approval number Ref: 115/CNBS/21. A protocol amendment regarding changes in inclusion criteria was approved on June 21, 2021 with approval number Ref: 347/CNBS/21. In Guinea-Bissau, the study protocol was approved by the Ethics Committee for Research (Comité Nacional de Ética na Saúde) on November 3 2020 with approval number 119/CNES/INASA/2020.

In Denmark, the study protocol was given consultative approval by the National Ethics Committee on November 2, 2020, approval number 2015556. In Portugal and Denmark, no local ethical approval is required as long as the study protocol is approved by the Ethics Committees of the countries where the study is to be conducted.

Ethical approval and legal documentation will be kept by the PI of the respective country.

Recruitment, inclusion and exclusion criteria and informed consent procedures.

The RCT involves healthy, volunteer human participants able to give informed consent to participate in an interventional trial consisting in the intradermal administration of BCG vaccine standard dose or placebo (saline).

The participants of this research will be health care workers defined as nurses, physicians and other health workers, including students and auxiliary staff.

Prior to the initiation of the trial, the hospital director will inform the department heads about the trial. Each department head will be provided with written material about the trial, its objectives and the practicalities. A telephone number will be provided, to which HCW can address potential questions. After a week (where presumably all staff has rotated and been informed about the upcoming trial), inclusion dates will be arranged with the department heads and communicated to staff. To avoid queuing and to ensure privacy, staff interested in participating will be asked to come one-by-one for enrolment. Whenever possible, a separate cabinet will be allocated to the study, in each study site to keep the HCW privacy.

All HCW who are 18 or older that present themselves to inclusion sites will be considered as potential participants. Those with known allergy to (components of) BCG or serious adverse events to prior BCG administration; known previous, active or latent infection with *Mycobacterium tuberculosis* or other mycobacterial species; fever (>38 C) within the past 24 hours; suspicion of active viral or bacterial infection; pregnancy; and severe immunocompromised subjects; active solid or non-solid malignancy or lymphoma within the prior two years; or with contraindication for live attenuated vaccine administration, will be excluded.

Participants will be asked about their HIV status and a HIV test will be performed before enrolment. Because they are HCW, we believe that most of them are aware of their HIV status, especially in high prevalence settings as is the case of Mozambique. Participants who report that they are HIV-positive and those that test positive with the point-of-care HIV test will be excluded from the study; the latter will be referred for confirmatory testing.

Eligible participants will be invited to participate in the study after being informed thoroughly about the intervention and having been given the opportunity to discuss the main features of the study with the research team and having the possibility to ask questions. The discussion will include the aims, methods and implications of the research, the nature of the participation, potential benefits, risks or discomfort that might ensue as well as the voluntary nature of their participation and the right to withdraw from the study.

After information of the main features of the study, participants will be asked to sign the information sheets, containing all information in writing plus the e-mail and telephonic contacts of the research team, procedures to withdraw from the study and informed consent. The informed consent will comprise 1) consent to have either BCG or saline water administered by intradermal injection; 2) consent to collect personal data as determined in the study protocol; 3) consent to do POC testing for SARS-CoV2 antibodies at the beginning and end of the study; and 4) consent to be contacted through mobile calls biweekly during follow-up procedures conducted by the research team.

Each participant will be given a copy of the signed informed consent and information sheets and a second copy will be kept by the research team in each study site. Informed consent for all study sites will be kept by the country research team in a locked room where only research team personnel will have access.

Risk assessment for intervention

Based on previous experience and randomized controlled trials in adult and elderly individuals, the risks of BCG vaccination are considered low. It is common and not treatment-demanding that, following BCG vaccination, redness, swelling and ulceration of the skin where the vaccine is given will occur. There may be swollen lymph nodes in the area some weeks after the vaccine is given, and in the longer term, a small ~5 mm diameter scar will appear where the vaccine was given. In case these appear, we will follow the recommendations of the National Immunization plan. Severe but very rare side effects are injection site abscesses, BCG lymphadenitis, disseminated BCG diseases, osteitis, osteomyelitis, anaphylaxis, formation of keloid/lupoid and suppurative lymphadenitis. In case these adverse events occur, the participant will be provided with medical assistance.

An insurance for the clinical trial participants will be contracted. This insurance provides cover for damage to research subjects through injury or death caused by the study. Participants will not be compensated for participating in this study. Damage to subjects through injury or death, caused by the study or negligence of local study investigators, is not accountable to the principle investigator.

Follow-up

Follow-up will take place every second week through telephone interview and by checking register of attendance at the worksite (where available). 6 months after recruitment, the participant will be invited to the study site for a new POC test for SARS-CoV2 antibodies and to answer an end-questionnaire. The participant will be informed of the result of the test. The participant will also be informed of the intervention he/she received.

The telephone contact information of the participant will be shared only with the research assistant responsible for doing the follow-up.

Protection of personal data

This research involves data collection and processing of sensitive personal data, tracking of participants and further processing of previously collected personal data (data on immunization).

Because the study comprises follow-up of participants after administration of the intervention, data cannot be anonymised. As so, data pertaining to participants will be stored in a locked room in the institution responsible for the RCT in each country (ICSM in Mozambique and Bandim Health Project in Guinea-Bissau) in one computer not connected to the internet and protected by a password. The password will be only known by the PI, Co-PI and the study supervisors.

Data analysis will be conducted by the IHMT. Personal data include: eligibility criteria, baseline characteristics, adverse events of intervention, work absenteeism and reasons, hospitalization.

Several investigators across the world have set up trials of BCG vaccination among health care workers. Until today, >20 trials are ongoing or in preparation.

Spearheaded by the Dutch group, a platform is now being established for a meta-analysis to be done immediately (i.e. within one week) after the first trial yields a significant result. The meta-analysis will include all ongoing trials except for the one yielding the significant result. If the meta-analysis confirms the effect (i.e. statistically significant difference at a two-sided p-value < 0.05) the recommendation will be to offer BCG to HCW or to stop trials. If it is not confirmed, the recommendation will be to continue all trials. The result of the interim analysis will be made public to inform health authorities.

A Data Transfer Agreement has been established to allow anonymous sharing of our data to contribute to this meta-analysis.

Safety

Intervention consist of intradermal administration of a standard dose of BCG vaccine or placebo (saline). Based on previous experience and randomized controlled trials in adult and elderly individuals, the risks of BCG vaccination are considered low. It is common and not treatment-demanding that, following BCG vaccination, redness, swelling and ulceration of the skin where the vaccine is given will occur. There may be swollen lymph nodes in the area some weeks after the vaccine is given, and in the longer term, a small ~5 mm diameter scar will appear where the vaccine was given.

Severe but very rare side effects are injection site abscesses, BCG lymphadenitis (simple or suppurative, disseminated BCG disease, osteitis, osteomyelitis, anaphylaxis, formation of keloid/lupoid. They are so rare that it would be unlikely with cases in the present trial of 1050 participants, but we will specifically enquire about adverse events at the weekly interviews and in the end questionnaire. In the case of adverse events they will be reported to the vaccine producer and the patient will be receive treatment.

Temporary halt for reasons of subject safety: In accordance to section 10, subsection 4, of the Medical Research Involving Human Subjects Act (WMO), the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety.

The sponsor will notify the EC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the EC and the DKMA. The investigator will take care that all subjects are kept informed.

Adverse events (AEs): defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product, the placebo or the trial procedures, will be biweekly assessed during the mobile phone interviews. All adverse events will be reported to the relevant authorities according to existing national notification procedures.

Serious adverse events (SAEs) is any untoward medical occurrence or effect that results in death, is life threatening or requires hospitalization or prolongation of existing inpatients' hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect or any other important medical event due to the intervention based upon appropriate judgement by the investigator. An elective hospital admission will not be considered as a serious adverse event.

Participants will be asked about the occurrence of SAE's biweekly in the questionnaire. In case of a SAE, dependent on the symptoms of the participant, he/she will be contacted by the investigator and if necessary, admitted to the hospital. The condition of the participant will be evaluated by the investigator, who can decide to un-blind if deemed necessary.

The investigator will notify sponsor and DSMB within 24 hours after first knowledge of any SAEs, in order for DSMB and sponsor to assess whether it is a suspected unexpected serious adverse reactions (SUSAR).

Unexpected adverse reactions are SUSARs if the event is serious, if there is a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose and it is unexpected, that is to say, the nature and severity of the adverse reaction is not in agreement with the product information as recorded in the summary product characteristics.

The investigator and the sponsor will report to the EC and competent national authorities.

Beneficence

It is clear that we need better tools against emerging pandemic threats. In the current approach we can first act only once we have identified the new pathogen; then we can start to develop new vaccines or new forms of treatment. This may take a long time before such measures are approved. If this RCT provides us with evidence of protective NSEs against COVID-19, we will not only have a tool against COVID-19, but likely also a tool that may help protect against other emerging pandemics in the future.

The current pandemic, COVID-19, seriously challenges the available hospital capacity and this is augmented by absenteeism of HCWs. HCWs are at high risk, as they constitute over 20% of all the COVID-19 cases in countries with available data. Strategies to prevent absenteeism of HCW are therefore desperately needed. This study contributes to that goal.

Elderly are another vulnerable group of the COVID-19 pandemic. If BCG protects COVID-19 in HCW, it will be an obvious next step to expand its use to other population groups.

Additionally, if BCG proves useful against COVID-19 it would be yet another confirmation that it strengthens the immune system against unrelated pathogens. While it is not a given that it will work against any kind of pathogen, we have so far seen BCG protects against viruses, bacteria as well as parasite infections.

Hence, there is reason to believe that it works against a large range of pathogens. Our results will provide further scientific evidence of these non-specific effects of BCG with relation to our central hypothesis that BCG (re)vaccination may induce (partial) protection against susceptibility to and/or severity of COVID-19.

Withdrawal from the study

Subjects can leave the study at any time for any reason if they wish to do so, without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

COVID-19 diagnosis and treatment

In case of suspicion of COVID-19, the national guidelines for testing and treatment of patients will be followed.

Public disclosure and publication policy:

The results of this study will be disclosed unreservedly at the end of the study. Results that are important for public health will be notified to the competent authorities as swiftly as possible. The trial will be registered in a public trial registry before the first patient is recruited.

REFERENCES

1. Aaby P, Kollmann TR, Benn CS. Nonspecific effects of neonatal and infant vaccination: public-health, immunological and conceptual challenges. Nat Immunol 2014; 15(10): 895-9

2. Aaby P, Benn CS. Developing the concept of beneficial nonspecific effect of live vaccines with epidemiological studies. Clin Microbiol Infect. 2019 Aug 23. pii: S1198-743X(19)30452-5. doi: 10.1016/j.cmi.2019.08.011. Review.

3. Benn CS, Fisker AB, Rieckmann A, Sørup S, Aaby P. Vaccinology: Time to change paradigm? Lancet Inf Dis 2020 (in press)

4. Aaby, P. et al. Randomized trial of BCG vaccination at birth to low-birth-weight children: Beneficial nonspecific effects in the neonatal period? J. Infect. Dis. (2011) doi:10.1093/infdis/jir240.

5. Biering-Sørensen S, Aaby P, Lund N, Monteiro I, Jensen K, Eriksen HB, Schaltz-Buchholzer F, Jørgensen ASP, Rodrigues A, Fisker AB, Benn CB. Early BCG and neonatal mortality among low-birth-weight infants: A randomised controlled trial. Clin Inf Dis 2017, 65: 1183-1190

6. Higgins JP, Soares-Weiser K, Lopez-Lopez JA, et al. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. BMJ 2016; 355: i5170.

7. Rieckmann A, Villumsen M, Sørup S, Haugaard LK, Ravn H, Roth A, Baker JL, Benn CS, Aaby P. Vaccinations against smallpox and tuberculosis are associated with better long-term survival: a Danish case-cohort study 1971- 2010. Int J Epidemiol 2017;46:695-705

8. Wardhana, Datau, E. A., Sultana, A., Mandang, V. V. & Jim, E. The efficacy of Bacillus Calmette-Guerin vaccinations for the prevention of acute upper respiratory tract infection in the elderly. Acta Med. Indones. (2011).

9. Nemes, E. et al. Prevention of M. Tuberculosis infection with H4:IC31 vaccine or BCG revaccination. N. Engl. J. Med. (2018) doi:10.1056/NEJMoa1714021.

10. Netea, M. G. et al. Trained immunity: A program of innate immune memory in health and disease. Science (2016) doi:10.1126/science.aaf1098.

11. Arts, R. J. W. et al. BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity. Cell Host Microbe (2018) doi:10.1016/j.chom.2017.12.010.

12. Benn CS, Fisker AB, Whittle HC, Aaby P. Revaccination with Live Attenuated Vaccines Confer Additional Beneficial Nonspecific Effects on Overall Survival: A Review. EBioMedicine 2016; 10: 312-7.

13. Roth AE, Benn CS, Ravn H, et al. Effect of revaccination with BCG in early childhood on mortality: randomised trial in Guinea-Bissau. BMJ 2010; 340: c671

14. Biot C, Rentsch CA, Gsponer JR, et al. Preexisting BCG-specific T Cells Improve Intravesical Immunotherapy for Bladder Cancer. Science Translational Med 2012;4:137ra72

15. Hatherill, M. et al. Safety and reactogenicity of BCG revaccination with isoniazid pretreatment in TST positive adults. Vaccine (2014). doi:10.1016/j.vaccine.2014.04.084.