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Using the BCG vaccine to understand tuberculosis infection

Submission date	Recruitment status	[X] Prospectively registered
16/03/2023	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
29/03/2023	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
28/01/2025	Infections and Infestations	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Tuberculosis (TB) is a disease that usually causes an infection in the lungs but can also affect other parts of the body. The only vaccine available to prevent TB is called BCG (Bacillus Calmette–Guérin). The BCG vaccine contains a live germ similar to, but weaker than, Mycobacterium tuberculosis, the germ that causes TB infection. BCG has been around for over 100 years but unfortunately, it does not work very well, and TB remains the most common cause of death caused by infection worldwide. Human challenge models involve exposing healthy volunteers to an infectious disease in a safe and carefully controlled way. This can help researchers understand more about an infectious disease and the body's response. It can also help develop new vaccines and treatments. The purpose of this study is to set up a human challenge model using BCG to understand how the body responds to this existing vaccine. It is hoped that if the human challenge model works well it may be used to help researchers to develop new vaccines and new tablets to treat TB in the future.

Who can participate?
Healthy volunteers aged 18-50 years with no previous history of tuberculosis or a recent TB contact and no previous vaccination with the BCG or a tuberculosis trial vaccine

What does the study involve?
The first part of the study (phase A) will recruit 10 participants. The participants in phase A will receive an intradermal injection with BCG vaccine into the upper arm at three times the usual dose given to children. On day 14 after the BCG injection the following skin samples will be taken from the BCG injection site with the use of local anaesthetic: skin swab, microbiopsy, skin scrape and punch biopsy. Participants in this phase of the study will also have blood tests to ensure they are safe to take part and to monitor the immune response to BCG. The overall aim of this part of the study will be to ensure BCG can be isolated (grown in culture and by molecular techniques) from the participants' BCG injection site at 14 days after the injection. The researchers will test whether BCG can be isolated in comparable amounts by punch biopsy and minimally invasive techniques (microbiopsy, skin scrape and skin swab). If BCG can be isolated successfully using the minimally invasive methods of skin sampling and the participants have not experienced any serious adverse events, the researchers can then proceed to the next phase of the study (phase B).

In the second phase of the study (phase B) 20 participants will be recruited. These participants will receive the BCG vaccine as described for phase A. They will then have serial skin samples taken using either microbiopsy, skin scrape or skin swab (depending on which method was most successful in phase A) on days 0, 2, 7, 14 and 28. The focus of this phase of the study is to assess immune responses to intradermal injection at the local (skin), systemic (blood) and respiratory mucosal (nose) compartments. This will involve taking blood samples, skin samples, and nasal samples to measure how the BCG grows over time and the immune response over time. It will be particularly important to see the immune response to the BCG in the respiratory mucosa, given this is the area usually affected by tuberculosis disease.

What are the possible benefits and risks of participating?
The main benefit to participants is participating in research which could help improve vaccinations and treatments against tuberculosis. Participants may gain some protection against tuberculosis, although the BCG vaccine is not very effective against TB of the lungs in adults. An additional benefit is receiving a general health check as part of the screening process and having regular contact with medical doctors and nurses during the study.
Reactions to the BCG vaccine are uncommon and generally mild. The expected reaction to the vaccination is swelling, redness, and pain followed by the development of a small ulcer which heals to leave a scar. A swelling of lymph nodes in the armpit is also common. Uncommon side effects include headache, painful tender lymph nodes, fever, and a discharging ulcer. Rare side effects include an abscess, infection in the body, or an allergic reaction such as anaphylaxis.
Mild stinging on local anaesthetic is usual. Numbness of the area after the procedure can occur. Serious complications are very rare with a local anaesthetic. Allergic reactions may rarely occur, this may just be a localised itchy rash over the injection site or an unexpected severe allergic reaction such as anaphylaxis, but this is very rare.
A punch biopsy is a safe procedure and complications are uncommon. Pain after the procedure is common and usually mild. Bleeding will occur during the procedure, but it is uncommon for participants to get continued bleeding after the procedure. Participants will usually be left with a small faint scar. Infection is uncommon and occurs in around 1 in 500.
The risks of microbiopsy are minimal. There may be mild pain and a small drop of blood, any small wound usually heals within 24 hours. Stitches are not required.
The skin scrape may cause some mild pain or discomfort and occasionally some mild bleeding.
Blood sampling may cause temporary pain, bruising and/or bleeding to the participant's arm.
Throat swabs/COVID throat/nose swabs/nasal samples may make participants feel some discomfort, gag a little, and there may be a small amount of nasal bleeding.

Where is the study run from?
Liverpool School of Tropical Medicine (UK)

When is the study starting and how long is it expected to run for?
July 2022 to March 2025

Who is funding the study?
United Kingdom Research and Innovation (UKRI)

Who is the main contact?
Ben Morton, ben.morton@lstmed.ac.uk

Contact information

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Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)

321376

ClinicalTrials.gov (NCT)
NCT05820594

Protocol serial number
IRAS 321376, CPMS 55553

Study information

Scientific Title
A feasibility study of controlled human infection with intradermal Bacillus Calmette–Guérin injection

Acronym
Pilot BCG CHIM

Study objectives
1. The researchers hypothesise that they will recover the BCG SSI strain by tissue biopsy 14 days after intradermal injection by both classical microbiological and molecular diagnostic techniques.
2. The researchers hypothesise that quantified BCG recovery (molecular techniques) by minimally invasive skin biopsy will be at least 90% as good as gold standard punch biopsy and will offer a more acceptable method for participants in the future.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 18/01/2023, North West - Liverpool Central Research Ethics Committee (3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)2071048118; liverpoolcentral.rec@hra.nhs.uk), ref: 22/NW/0373

Study design
Single-centre prospective longitudinal controlled human infection study

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
The use of a human challenge model for tuberculosis using BCG, which could be used to test vaccines and therapeutics

Interventions
Participants will receive an intradermal BCG challenge with three times the usual dose of the vaccine on day 0. Participants will undergo a skin punch biopsy at day 14 with parallel minimally invasive skin sampling techniques (skin microbiopsy, skin scrape, skin swab) in phase A of the study, these samples will be processed for mycobacterial culture and PCR. In phase B of the

study, participants will undergo serial skin sampling with the minimally invasive technique selected from phase A for mycobacterial isolation as well as single-cell immunological techniques. In phase B participants will have parallel nasal samples taken (nasal wash, nasal cell, nasosorption), for monitoring the respiratory mucosal immune response, and cytokine production. In both phases of the study blood tests will be performed for RNA and peripheral blood mononuclear cells (PBMCs) to investigate the systemic immune response to BCG.

Intervention Type
Biological/Vaccine

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Bacillus Calmette-Guerin, Danish strain 1331, live attenuated

Primary outcome(s)
BCG recovered from the intradermal BCG challenge site quantified using culture and PCR of punch biopsy on day 14, Phase A

Key secondary outcome(s))
1. Safety and tolerability of study procedures in participants, confirmed using actively (solicited) and passively collected data on adverse events and daily symptom diary for 14 days, reviewed on days 2, 7, 14, 21 and 28
2. Agreement of BCG recovery between punch biopsy and minimally invasive skin biopsy, quantified using culture and PCR on day 14, Phase A
3. Agreement of BCG recovery between punch biopsy and minimally invasive skin scrape, quantified using culture and PCR on day 14, Phase A
4. Longitudinal quantification of BCG recovery from the intradermal BCG challenge site using culture and PCR of non-invasive skin swabs at 2, 7, 14, 21 and 28 days, Phase B
5. Laboratory assays for immune response to BCG at intradermal injection site, confirmed by examining punch biopsy cell pellet for immune cell differentiation and antigen stimulation on days 2, 7, 14, 21, 28, Phase B
6. Laboratory assays for immune response to BCG in systemic circulation, confirmed using immune cell activation and functional assays and cytokine levels in blood samples on days 2, 7, 14, 21, 28, Phase B
7. Immune response to BCG injection in respiratory mucosa measured using nasal scrape pellet examined for cell differentiation and activation on days 2, 7, 14, 21, 28, Phase B

Completion date
31/03/2025

Eligibility

Key inclusion criteria
1. Healthy adults aged 18-50 years (inclusive)
2. Resident near Liverpool School of Tropical Medicine (LSTM) (<1 h drive) for the duration of the study period
3. Allows the investigators to discuss the volunteer’s medical history with their GP
4. Females of childbearing potential with a negative urine pregnancy test at screening and willing to practice adequate birth control measures during the study.

5. Fluent spoken English - to ensure a comprehensive understanding of the research project and their proposed involvement
6. Capacity to provide written informed consent
7. Able and willing (in the investigator's opinion) to comply with all the study requirements

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
50 years

Sex
All

Total final enrolment
30

Key exclusion criteria
1. Laboratory evidence at screening of latent M. tb infection as indicated by a positive ELISPOT response to ESAT6 or CFP10 antigens
2. Clinical, radiological, or laboratory evidence of current active TB disease
3. Previous vaccination with BCG, or any candidate TB vaccine
4. Within the last year had close household contact with an individual with smear-positive pulmonary tuberculosis
5. Clinically significant history of skin disorder, allergy, immunodeficiency (including HIV), cancer, cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder, neurological illness or psychiatric disorder
6. Current medical issues:
6.1. Acute respiratory tract infection in the 4 weeks preceding recruitment
6.2. Any uncontrolled medical or surgical condition at the discretion of the study doctor
7. Maternal:
7.1. Female participants who are pregnant
7.2. Female participants who are lactating
7.3. Female participants who intend to become pregnant during the study
7.4. Female participants who are unable to take contraception measures during the study
8. Smoking:
8.1. Current (defined as ≥5/week) or ex-smoker (cigarettes/cigars/e-cigarette /vaping/smoking of recreational drugs) in the last 6 months
8.2. Previous significant smoking history (more than 20 cigarettes per day for 20 years or the equivalent [>20 pack years])
9. Current alcohol and recreational drug use
9.1. Regularly drinks ≥3 units/day (male) or ≥2 units/day (female)

9.2. Uses recreational drugs
9.3. Participants may be excluded at the discretion of the research clinician
10. Concurrent oral or systemic steroid medication or the concurrent use of other immunosuppressive agents
11. History of anaphylaxis to vaccination or any allergy likely to be exacerbated by any component of the challenge agent
12. Has received any vaccination within one month of the screening visit
13. Has not completed at least two COVID-19 vaccination doses
14. Any abnormality of screening blood or urine tests that is deemed to be clinically significant or that may compromise the safety of the volunteer in the study
15. Positive HBsAg, HCV or HIV antibodies
16. Current involvement in another trial that involves regular blood tests or an investigational medicinal product
17. Use of an investigational medicinal product or non-registered drug, live vaccine, or investigational medical device for 4 weeks prior to dosing with the study challenge agent
18. Administration of immunoglobulins and/or any blood products within the three months preceding the planned challenge date
19. Participants who meet STOP criteria at the time of screening
20. Any other issue which, in the opinion of the study staff, may:
20.1. Put the participant or their contacts at risk because of participation in the study
20.2. Adversely affect the interpretation of the study results
20.3. Impair the participant's ability to participate in the study

Date of first enrolment
30/06/2023

Date of final enrolment
23/01/2025

Locations

Countries of recruitment
United Kingdom

England

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Sponsor information

Organisation

Liverpool School of Tropical Medicine

ROR
https://ror.org/03svjbs84

Funder(s)

Funder type
Research organisation

Funder Name
UK Research and Innovation

Alternative Name(s)
UKRI

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		05/06/2024	02/09/2024	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes