

# Using the BCG vaccine to understand tuberculosis infection

<b>Submission date</b>	<b>Recruitment status</b>	<input checked="" type="checkbox"/> Prospectively registered
16/03/2023	No longer recruiting	<input checked="" type="checkbox"/> Protocol
<b>Registration date</b>	<b>Overall study status</b>	<input type="checkbox"/> Statistical analysis plan
29/03/2023	Completed	<input type="checkbox"/> Results
<b>Last Edited</b>	<b>Condition category</b>	<input type="checkbox"/> Individual participant data
28/01/2025	Infections and Infestations	<input type="checkbox"/> 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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## 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  $\geq 5/\text{week}$ ) 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 [ $>20 \text{ pack years}$ ])
9. Current alcohol and recreational drug use
  - 9.1. Regularly drinks  $\geq 3$  units/day (male) or  $\geq 2$  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

#### **Study participating centre**

**Liverpool School of Tropical Medicine**

Pembroke Place

Liverpool

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L3 5QA

## **Sponsor information**

#### **Organisation**

## 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?
<a href="#">Protocol article</a>		05/06/2024	02/09/2024	Yes	No
<a href="#">HRA research summary</a>			28/06/2023	No	No
<a href="#">Participant information sheet</a>	Participant information sheet	11/11/2025	11/11/2025	No	Yes