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Characteristics of the early immune response in airway and blood in people with latent tuberculosis (TB) infection and active TB disease.

Submission date
01/09/2021

Recruitment status
No longer recruiting

Registration date
10/09/2021

Overall study status
Ongoing

Last Edited
19/04/2024

Condition category
Infections and Infestations

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Tuberculosis (TB) is a disease caused by bacteria called Mycobacterium tuberculosis (M. tuberculosis). TB usually affects the lungs and is increasing in the UK. It can result in serious illness and remains a major cause of death in the world. However, not everyone infected with M. tuberculosis becomes sick and exhibits features of active TB disease. Thus, there are two TB-related conditions:
•Active TB disease and
•Latent TB infection (LTBI)

Those with LTBI do not feel sick and do not have any symptoms, they are infected but not clinically affected. Currently, the diagnosis of LTBI is based solely on evidence of immune reaction, usually by positive blood test (QuantiFERON--TB Gold In--Tube). Overall, without treatment, about 10--20% of LTBI patients will develop active TB disease at some point in their lives, with most developing TB disease in the first two years of infection.

Clinically, there is no current test that can:
•differentiate active TB disease from LTBI or
•identify those with LTBI who may progress to active TB disease

Identification of those LTBI individuals most at risk of developing active TB disease would help clinicians to target preventative therapy. This is an important issue as disease treatment is lengthy with potentially toxic drugs.

To improve the detection and treatment of LTBI, we need a better understanding of how the immune system responds to it. This study aims to identify the patterns of gene activity that represent the immune response of patients with active TB disease and LTBI both systemically (from blood) and locally (from samples taken from the lungs).

Who can participate?
Persons aged 18 to 84 years who have engagement with the Leicester Clinical TB Service with either suspected active TB disease or as a recent contact of active TB disease.

What does the study involve?
If you are found to have latent TB infection, you will attend a maximum of eleven visits over two years. Each visit will take no longer than 1 hour (unless you are having an additional bronchoscopy which will take longer). At each visit you will be met by one of our Research Team and they will collect the samples needed. We will be as flexible as possible in arranging these visits so that they are mutually convenient. We have linked most of the visits to the clinical appointments that are usually needed as part of your routine medical care. If you are unable to attend the research unit for your visits, we may be able to undertake some of the testing at your home. If you decide to take part in research bronchoscopy, you will attend maximum two bronchoscopy (at baseline and at 3 month) and wash sample will be obtained during the procedure. You will also attend PET-CT scan prior to each bronchoscopy. If you develop active TB disease during the study, you will attend further PET-CT scan and may attend another bronchoscopy if this is required as part of clinical care.
If you are found to have active TB disease, then you will have one visit which will be linked to your clinical appointment. At the visit, you will meet our research team and they will collect the samples needed. If you need bronchoscopy as part of your clinical investigation, additional wash samples will be collected for the study during bronchoscopy.

What are the possible benefits and risks of participating?
You will be monitored regularly and receive prompt assessment should you become unwell. Additionally, the information we get from this study may help people with active TB disease and LTBI in the future.
There are minimal risks associated with study procedures. Common side effects from bronchoscopy include a small amount of blood from the nostril or on coughing, a sore throat or a hoarse voice for up to a few days following the test. Less common side effects may be due to the effect of sedation, which can affect the breathing or cause excessive sleepiness. After the bronchoscopy, you will be monitored for 1-2 hours in the Endoscopy Department, Glenfield Hospital.
If you take part in this study you will have x-rays of your chest and possibly PET-CT scans. Some of these will be extra to those that you would have if you did not take part in the trial. These procedures use ionising radiation to form images of your body and provide your doctor with other clinical information. Ionising radiation may cause cancer many years or decades after the exposure. We are all at risk of developing cancer during our lifetime. 50% of the population is likely to develop one of the many forms of cancer at some stage during our lifetime. Taking part in this study may increase the chances of this happening to you to about 0.2% (without PET-CT scans) to 0.24% (with PET-CT scans).

Where is the study run from?
University of Leicester (UK)

When is the study starting and how long is it expected to run for?
July 2021 to August 2026

Who is funding the study?
Wellcome Trust (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
277963

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number

CPMS 49593, WT 215628/Z/19/Z, IRAS 277963

Study information

Scientific Title
Investigating early immunological EVENTs in active TB disease and latent TB infection (EVENT TB)

Acronym
EVENT TB

Study objectives
The main hypothesis for this study is that the cellular and airway samples taken from patients who have Latent TB infection (LTBI) will show common and unique features in their immune response when compared to the blood and airway samples taken from those with active TB disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 23/07/2021, East Midlands – Nottingham 1 Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 (0)207104 8036; Nottingham1.rec@hra.nhs.uk), ref: 21/EM/0139

Study design
Observational cohort study

Primary study design
Observational

Study type(s)
Other

Health condition(s) or problem(s) studied
Tuberculosis

Interventions
This study design is based on a longitudinal observational setting using the same methods for patients in the different groups – LTBI, active TB disease, and a healthy control group (no LTBI but exposed to active TB disease). The methodology employed for analysing the immune response will be the same as previously used by our collaborators (Anne O'Garra, Head of Division of Immunoregulation, The Francis Crick Institute, London). Blood samples for QuantiFERONGold TB InTube testing will be analysed using the current laboratory based methods established within the University Hospitals of Leicester NHS Trust. Most of the samples will be stored at the NIHR Leicester Respiratory Biomedical Research Centre as some of the sputum samples may be stored at the University of Leicester (in accordance with infection control procedures). The samples taken from the airways at the time of bronchoscopy will be transferred the same day to The Francis Crick Institute, London.

There are three main groups to this study:
1. “Active TB Group”: Subjects identified with and treated for active TB disease:
a. Clinical symptoms of TB AND
b. Positive culture for Mtb OR
c. Positive PCR with Genexpert

2. “LTBI Group”: Subjects attending TB services with no evidence of active TB disease but a positive IGRA test, using QuantiFERONGold TB InTube (QFT):
a. No clinical symptoms
b. No features of active TB on serial radiological imaging
c. Positive QFT 2-3 months after index notification if screened as a recent contact of active TB disease
d. declined chemoprophylaxis (a combination of two antituberculous drugs for 3 months offered to some LTBI patients as a potential protective treatment against the development of active TB disease for the immediate TB exposure that they have just experienced. It should be noted that chemoprophylaxis does not necessarily protect a LTBI individual from developing active TB disease from future new TB exposures)
3. “Control Group”: Subjects attending TB services with no evidence of active TB disease but a negative IGRA test, using QuantiFERONGold TB InTube (QFT):
a. No clinical symptoms
b. No features of active TB on radiological imaging
c. Negative QFT 2-3 months after index notification if screened as a recent contact of active TB disease

ACTIVE TB DISEASE GROUP visits:
Visit 1 (baseline)

LTBI GROUP & CONTROL GROUP visits:
These sub-groups have a common investigative and follow-up pathway. This pathway is divided into two phases for clarity:
Phase 1 (investigative, Visit 1 (baseline) to Visit 4 (3 months)): This represents the recruitment stage (where they undergo screening with QuantiFERONGold TB InTube) to identify if they have LTBI.
Phase 2 (follow-up, Visit 5 (6 months from visit 1) to Visit 11 (24 months from Visit 1)): This focuses on the longitudinal monitoring of LTBI Group to capture anyone developing clinical features of active TB disease at the earliest opportunity.
Control Arm
Controls are needed to minimise unintended influences such as researcher bias, experimental bias and biological variation.

Broad Timetable
This study is expected to span 5 years. The first 2.5 years will concentrate on recruitment and the following 2.5 years will be used to complete the observational periods for the participants and analyse the findings. Throughout the study, regular group steering committee meetings within Leicester and with our collaborators will be held to ensure the study is progressing as planned.

Intervention Type
Other

Primary outcome(s)

Early immune response in the airway of patients with latent TB infection is determined using cellular and transcriptional profiling (flow cytometry and RNA sequencing) at baseline and 3 months.

Key secondary outcome(s))
1. Early immune response in the airway of patients with Active TB infection and LTBI progressors are determined using the cellular and transcriptional profiling at baseline.
2. Longitudinal changes in immune response in latent TB infection is determined by assessing changes in the transcriptional gene signatures
(bioinformatics analyses to identify signatures from RNA seq data) over 2 years.
3. Comparison of blood and airway transcriptional profiles (RNA sequencing) in active TB and latent TB infection.

Completion date
01/08/2026

Eligibility

Key inclusion criteria
Current inclusion criteria as of 02/11/2023:

1. Provision of informed consent.
2. Aged 16 years or older.
3. Engagement with the Leicester Clinical TB service with either suspected TB or as a recent contact of active TB disease.
4. Healthy controls with no evidence of active TB disease or LTBI.

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Previous inclusion criteria:

1. Provision of informed consent.
2. Aged 18 to 84 years.
3. Engagement with the Leicester Clinical TB Service with either suspected active TB disease or as a recent contact of active TB disease.
4. Healthy controls will be recruited from the same cohort after investigations have identified no evidence for active TB disease or LTBI.

Participant type(s)
Mixed

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
16 years

Upper age limit

94 years

Sex
All

Key exclusion criteria
Current exclusion criteria as of 02/11/2023:

1. Any chronic medical disorder which, in the opinion of the investigator, may either put the subject at risk (because of participating in the study) or may influence the results of the study or the subjects' ability to participate in the study.
2. Donation of blood >450ml within 3 months of study commencement or during the study (other than for study purposes).
3. Pregnancy or lactation.
4. Participation in an interventional clinical study in the 3 months prior to of Visit 1 or participation in a study using interventional medicinal products in the previous 6 months.
5. Proven immunosuppression, including diagnosed immunodeficiency disorders and treatment with immunosuppressive medication, including oral corticosteroids at any dose.
6. Previous chemotherapy for LTBI in the last 5 year.
7. Previous treatment for active TB disease in the last 2 year.

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Previous exclusion criteria:

1. History of any acute infection in the previous 4-6 weeks
2. Any chronic medical disorder which, in the opinion of the investigator, may either put the subject at risk (because of participating in the study) or may influence the results of the study or the subjects' ability to participate in the study.
3. Donation of blood > 450ml within 3 months of study commencement or during the study (other than for study purposes).
4. Pregnancy or lactation.
5. Participation in an interventional clinical study in the 3 months prior to Visit 1 or participation in a study using interventional medicinal products in the previous 6 months.
6. Proven immunosuppression, including diagnosed immunodeficiency disorders and treatment with immunosuppressive medication, including oral corticosteroids at any dose.
7. Previous chemotherapy for LTBI.
8. Previous treatment for active TB disease.
9. Aged 85 or over

Date of first enrolment
07/09/2021

Date of final enrolment
20/05/2024

Locations

Countries of recruitment
United Kingdom

Study participating centre
Glenfield Hospital
NIHR Respiratory Biomedical Research Centre
University Hospitals of Leicester
Groby Road
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Sponsor information

Organisation
University of Leicester

ROR
https://ror.org/04h699437

Funder(s)

Funder type
Charity

Funder Name
Wellcome Trust

Alternative Name(s)
Wellcome, WT

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

All data generated or analysed during this study will be included in the subsequent results publication.

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Protocol file	version 1.1	21/06/2021	07/09/2021	No	No