ISRCTN21883784 https://doi.org/10.1186/ISRCTN21883784

Asymptomatic TB transmission in Indonesia and South Africa

Submission date	Recruitment status	[X] Prospectively registered
11/12/2025	Not yet recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
05/02/2026	Ongoing	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
05/02/2026	Infections and Infestations	[X] Record updated in last year

Plain English summary of protocol

Background and study aims

Tuberculosis (TB) remains one of the leading infectious diseases globally, causing significant morbidity and mortality each year. Despite decades of control efforts, TB continues to pose a major public health challenge, particularly in low- and middle-income countries. Traditionally, TB control strategies have focused on identifying and treating individuals who present with symptoms such as persistent cough, fever, and weight loss. However, emerging evidence indicates that a substantial proportion of people infected with TB bacteria exhibit no symptoms a condition referred to as asymptomatic TB (aTB).

This silent form of TB is particularly concerning because individuals with aTB can still harbor infectious bacteria and contribute to ongoing transmission within communities. The presence of undetected people with TB creates a critical gap in current TB programs, which largely rely on symptom-based screening. As a result, many people with TB remain unidentified, possibly perpetuating the cycle of infection and undermining global TB elimination goals.

The ATTIS study (Asymptomatic TB Transmission in Indonesia and South Africa) seeks to address this gap by quantifying the role of aTB in TB transmission dynamics. By conducting detailed investigations in households across South Africa and Indonesia, two countries with high TB burdens the study aims to generate robust data on the prevalence, infectiousness, and transmission potential of asymptomatic people with TB. These insights will inform the development of more comprehensive screening strategies that go beyond symptom-based approaches, ensuring earlier detection and treatment.

Understanding and addressing asymptomatic TB is essential for accelerating progress towards global TB targets. Closing this detection gap, especially if people with aTB transmit TB, could significantly reduce TB incidence, prevent new infections, and ultimately save millions of lives worldwide. The findings from ATTIS have the potential to reshape TB control policies and strengthen public health interventions at both national and global levels.

Who can participate?

The study will include adults and adolescents aged 15 years and older living in selected communities in South Africa and Indonesia. In the selected communities, only households with children aged 2 to 14 years will be part of the study, as these children will be tested for TB infection. Pregnant women can participate. All participants must provide informed consent prior to any study procedures. People who cannot understand the study or give consent will not be

included. Prisoners and individuals lacking mental capacity will not take part. The goal is to involve a broad range of community members to understand TB transmission in real-life settings.

What does the study involve?
Participants will first be screened in their households. Adults will answer health questions, undergo symptom checks, and provide sputum samples for TB testing. If sputum cannot be collected, a tongue swab may be used. A chest X-ray will also be done for all adults as part of the screening. Children in the household will have blood tests to check for TB infection and may be tested again after 8 to 10 weeks. Some participants will visit clinics for more detailed tests, including blood draws and new diagnostic tools like breath sampling. All results will be shared with participants, and anyone diagnosed with TB will be referred for treatment. Those that are contacts of a person with TB will be referred for TB preventative therapy.

What are the possible risks and benefits of participating?
The study involves minimal risks. Sputum collection is safe but requires precautions to prevent infection spread. Chest X-rays use very low radiation and are considered safe, even for pregnant women with proper shielding. Blood draws may cause slight pain, bruising, or dizziness, but these effects are short-lived. Learning about a new TB or HIV diagnosis can be stressful, so counselling will be provided by the study staff. Strict confidentiality will be maintained to protect personal information. Benefits for participating in the ATTIS study include free TB and HIV screening, early diagnosis, and referral for treatment. Participants also contribute to research that could improve TB control in their communities and globally.

Where is the study being run from?
The study will take place in two countries: South Africa and Indonesia. In South Africa, it will be conducted in KwaZulu-Natal Province, King Cetshwayo and Umkhanyakude districts. In Indonesia, the study will run in Bandung City, West Java Province. These locations were chosen because they have high TB rates but different patterns of disease. South Africa has a high HIV and TB co-infection rate, while Indonesia faces challenges like smoking and undernutrition. Studying these diverse settings will help researchers understand TB transmission better and develop strategies that work in different environments.

When is the study starting and how long is it expected to run for?
The study will commence in February 2026 and will run for 3 years, to December 2028.

Who is funding the study?
Wellcome Trust (UK)
Gates Foundation (USA)

Who is the main contact person?
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Additional identifiers

Wellcome Trust grant code
331594/Z/25/Z

Study information

Scientific Title
Asymptomatic TB transmission in Indonesia and South Africa

Acronym
ATTIS Study

Study objectives
The co-primary objectives of the study are to compare Mtb infection, as defined by interferon release assay (IGRA) positivity, in child (2-14 years) household contacts of adults with bacteriologically-confirmed asymptomatic TB (aTB-C), with:
1. children in households with no adult with TB
2. children who are household contacts of adults with bacteriologically-confirmed symptomatic TB (sTB-C)
The secondary objectives are to:
1. Evaluate the diagnostic performance, feasibility, and acceptability of current tools for detecting aTB, including digital chest X-ray with computer-aided diagnosis (dCXR/CAD) and sputum Xpert, and sputum Mycobacteria Growth Indicator Tube (MGIT)
2. Evaluate the performance of novel diagnostic and screening tools to detect aTB including tongue swab NAAT, bioaerosol NAAT, exhaled breath condensate for lipoarabinomannan, cell free Mtb DNA and Mtb-specific T cell activation.
3. Characterize the features and longitudinal outcomes of sub-groups of people with aTB, including those with dCXR/CAD findings suggestive of TB but who are sputum Xpert & culture negative.
4. Establish a biobank and conduct studies of immune responses to understand the biology of aTB and define correlates of progression and resolution.
5. Model the contributions of aTB to global TB transmission and incidence and the potential impact of interventions to detect and treat this disease phenotype
6. Evaluate the proportion of child household contacts who convert from baseline negative to positive IGRA at 10-week visit or have a positive blood biomarker (including cell free DNA assay or positive Mtb-specific T cell activation assay).
7. Define the proportion of participants with TB screening results consistent with sTB-U who have a subsequent positive sputum Xpert, sputum MGIT, tongue swab NAAT or facemask NAAT.
8. Identification of transmission clusters using whole genome sequencing of Mtb strains obtained from participants with aTB-C, sTB-C and their household contacts.

Ethics approval required
Ethics approval required

Ethics approval(s)
submitted 09/10/2025, University of KwaZulu Natal Biomedical Research Ethics Committee (Westville Campus Govan Mbeki Building Private Bag X 54001 Durban 4000, Durban, 4000, South Africa; +27 31 260 4709; BREC@ukzn.ac.za), ref: BREC/00009530/2025

Primary study design
Observational

Secondary study design
Epidemiological study

Study type(s)

Health condition(s) or problem(s) studied
Asymptomatic TB transmission in Indonesia and South Africa

Interventions
This is a multi-country, cross-sectional study designed to assess household Mtb infection and transmission among asymptomatic (aTB) and symptomatic TB (sTB) cases and their household

contacts. Community-based screening will be implemented across contiguous geographic areas within each participating country. It is estimated that approximately 60,000 adults in Indonesia and 30,000 adults in South Africa will undergo screening. Eligible participants identified through community screening will be enrolled into the core study and related sub-studies for further diagnostic evaluation, clinical phenotyping, and biobanking. The core study is a cross-sectional study comparing the Mtb infection status in child household contacts of people with aTB-C, sTB-C and community controls (randomly selected noTB). These households will be identified through community-based TB screening.
The case-control phenotyping study (sub-study 1) will be conducted in people with asymptomatic TB symptomatic TB and identified controls in the core study and will comprise additional diagnostic tests, clinical phenotyping and biobanking.
A TB-U cohort study (sub-study 2) will be conducted in individuals identified during the community screening with bacteriologically unconfirmed TB that do not meet criteria for TB treatment, and will comprise serial clinical evaluation, diagnostic testing and biobanking.
A mathematical modelling study (sub-study 3) will utilize empiric data from the study to estimate the contribution of asymptomatic TB to local and global TB transmission and incidence and the impact of potential interventions.

Intervention Type
Other

Primary outcome(s)
1. Cumulative prevalence of child household contact IGRA positivity and/or confirmed TB (TB-C) at 10 weeks after diagnosis of the index case measured using study data (percentage) at 2 and 10 weeks

2. Proportion of children that convert from negative IGRA status at baseline to a positive IGRA status at 10-week visit measured using study data (percentage) at 2 and 10 weeks

Key secondary outcome(s))
1. Proportion of children with a positive plasma cell free Mtb DNA assay and positive Mtb-specific T cell activation assay, stratified by household group measured using study data (percentage) at 2 and 10 weeks

2. Sensitivity, specificity, positive predictive value, negative predictive value, yield, feasibility, acceptability of digital chest x-ray measured using computer aided diagnosis (dCXR/CAD), sputum Nucleic Acid Amplification Test (NAAT), Mycobacteria Growth Indicator Tube (MGIT), tongue swab NAAT, and bioaerosol collection facemask mask NAAT to detect aTB-C at baseline

3. Time to event and factors associated with microbiological progression in participants with initially untreated aTB-U measured using study data (percentage) at 3, 6, 9 and 12 months

4. Plasma biomarkers that correlate with progression from aTB-U in the 12 months after TB screening measured using cell free Mtb DNA, Mtb-specific T cells, transcriptional signatures at 3, 6, 9 and 12 months

5. Proportion and characteristics of participants with TB screening results suggestive of (TB-U) who have a subsequent positive sputum Xpert, sputum MGIT, tongue swab NAAT or bioaerosol collection facemask NAAT measured using study data (percentage) at 3, 6, 9 and 12 months

Completion date

31/08/2028

Eligibility

Key inclusion criteria
Adolescent/Adult participants for community screening:
1. Age >15 years
2. Residence in the designated study area
3. Residence in a household with children (2-14 years)
2. Child household contacts

Aged 2-14 years:
1. Household residence with an adolescent/adult participant with:
1.1. aTB-C, or
1.2. sTB-C, or
1.3. An adolescent/adult participant who has been selected as a healthy control (no TB)

Adolescent/adult participant in TB screening:
1. Screening W4SS negative
2. Screening sputum Xpert positive (any grade) OR Mtb MGIT positive* OR tongue swab NAAT positive

Participants with sTB-C:
1. Adolescent/adult participant in TB screening
2. Screening W4SS positive
3. Screening sputum Xpert positive (any grade) OR Mtb MGIT positive* OR tongue swab NAAT positive

Participants selected as healthy controls:
1. Adolescent/adult participant in TB screening
2. Screening W4SS negative
3. Screening sputum Xpert negative; AND Mtb MGIT negative*
4. Selected as a healthy control in the Cross-sectional study of Mtb infection in households (see above)

1. Adolescent/adult participant in TB screening
2. All three sputa Xpert are negative/ ‘trace’ AND all three sputum are Mtb MGIT negative
3. Screening dCXR/CAD interpretation is “suggestive of TB”
4. Clinical assessment at phenotyping visit does not suggest a non-TB aetiology for dCXR/CAD findings and is consistent with TB-U
5. Participant did not commence TB treatment after phenotyping visit

Healthy volunteers allowed
Yes

Age group
Mixed

Lower age limit
2 years

Upper age limit
99 years

Sex
All

Total final enrolment
90000

Key exclusion criteria
Adolescent/Adult participants for community screening:
1. Unable or unwilling to consent (>18 years)
2. Unable to unwilling to assent (15-17 years)
3. Parent or guardian unwilling to consent (15-17 years)
4. Residence in a household with a participant in a TB vaccine trial (currently or previous 2 years)

Child household contacts:
1. Unable or unwilling to assent (>7 years)
2. Parent/guardian unable or unwilling to consent
3. Residence in household in which any resident has been diagnosed with TB within the past 2 years
4. Residence in a household with more than one adolescent/adult with current co-prevalent TB-C
1. Participants with aTB-C ; 2. Participants with sTB-C ; 3. Participants selected as healthy controls

ALL 3 groups above:
1. Unable or unwilling to consent
* MGIT results returning after enrolment may result in study group re-categorisation
2. Participants who meet the study case definition for bacteriologically-unconfirmed TB (TB-U)

1. Unable or unwilling to consent to longitudinal follow-up

Date of first enrolment
16/02/2026

Date of final enrolment
31/07/2028

Locations

Countries of recruitment
Indonesia

South Africa

Study participating centre
Africa Health Research Institute
-

-
South Africa
-

Study participating centre
RC3ID Research Center for Care and Control of Infectious Diseases
-
-
Indonesia
-

Sponsor information

Organisation
Wellcome Trust

ROR
https://ror.org/029chgv08

Organisation
Gates Foundation

ROR
https://ror.org/0456r8d26

Funder(s)

Funder type

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

Funder Name
Gates Family Foundation

Alternative Name(s)
Gates Foundation, FUNDACIÓN DE LA FAMILIA GATES, Fundación Gates, GFF

Funding Body Type
Private sector organisation

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

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan

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 file	version 1.2	05/12/2025	17/12/2025	No	No