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Trials

STUDY PROTOCOL

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Community and Universal Testing for TB among close contacts of microbiologically confirmed pulmonary TB patients in two high TB burden countries: a protocol for a pragmatic cluster-randomised control trial

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Abstract

Background Tuberculosis (TB) symptom screening and testing using either smear microscopy or GeneXpert MTB/RIF Ultra (Xpert Ultra) have been the mainstay for diagnosing TB disease in case finding. Reliance on symptom-based TB screening results in missed TB cases, and universal TB testing approach might be more suitable to find missing TB cases in high-risk populations. Universal TB testing involves testing for TB disease regardless of TB symptoms in those at risk of TB. However, limited evidence exists to support its adoption including cost-effectiveness. In this study, we will evaluate the effectiveness of universal TB testing for detection of TB and uptake of TB preventive therapy (TPT) among eligible household and community contacts in high TB settings as per country guidelines.

Methods This is a pragmatic cluster-randomised trial conducted in Lesotho and Tanzania. Drug-sensitive TB (DS-TB) index patients aged ≥ 18 years, who have at least one contact, will be enrolled if they are microbiologically confirmed with TB within ≤ 6 weeks of diagnosis at the time of recruitment by study team at health facilities in selected districts or regions. Each TB index patient and their contact(s) will be randomised into either universal TB testing or standard TB screening arms. Household and community contacts listed by each TB index case will be enumerated and invited to participate in the study after providing informed consent or assent during household visits. The study has four sub-studies including health economics and modelling, paediatrics, microbiology, and socio-behavioural. A preparatory cross-sectional study will be conducted before delivery of the pragmatic cluster-randomised trial. It will determine the prevalence of TB infection (TBI), TPT eligibility in household contacts (HHCs), and compare the performance of QuantiFERON-TB-Gold-Plus (QFT-Plus) and QIAreach for diagnosing TBI among HHCs of TB index patients. Cluster-randomised trial and community contact tracing will be conducted in phase II.

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Significance This trial will provide evidence for a more intensive approach which is hypothesised to increase cost-effectiveness of TB case finding. In addition, it will provide evidence for high TB burden countries with inherently different cost structures compared to intermediate and low burden settings where previous cost-effectiveness analyses have been undertaken.

Clinical trial registration number BMC Trial Registry ISRCTN10003903. Registered on December 22, 2020.

Protocol version number and date.

Version 1.2, dated 15 January 2023.

Date recruitment began.

1 March 2022.

Estimated date of recruitment completion.

31 July 2025.

Keywords Tuberculosis, Universal TB testing, Household contacts, Household contact tracing, TB preventive therapy, Tuberculosis infection, High TB burden

Introduction

Tuberculosis (TB) is a communicable disease caused by *Mycobacterium tuberculosis* [1]. Despite being curable and preventable, TB remains one of the deadliest infectious diseases worldwide [1]. In 2023, 10.8 million people fell ill with TB, but only 8.4 million notified, and more than 1.23 million succumbed to the disease [1]. Contacts of people diagnosed with TB are at high risk of developing TB as a result of their close proximity and persistent exposure to infectious TB at household and community levels [2]. As a result, national TB programmes have prioritised TB case detection among TB contacts to curb the ongoing transmission in this population group through active case finding methods such as household contact tracing (HHCT), TB screening or testing, and TB preventive therapy (TPT) [3–5].

HHCT is a well-established method for detecting and preventing TB transmission, through increasing the number TB cases detected for treatment and offering an opportunity for TPT. However, its programmatic adoption remains mixed [3–5]. One of the key challenges is the varying yield of TB patients reported among contacts aged ≥ 5 years, ranging from 1.5% to 7.8% [6–9]. Symptom-based screening has been most commonly used in low resource settings. However, the symptom-based screening has demonstrated sub-optimal sensitivity for identifying individuals with undiagnosed TB, leading to missed cases [10]. The universal TB testing approach, testing for TB using rapid-molecular tests regardless of symptoms, might help increase the yield and prove to be cost-effective. A trial in South Africa reported a five-fold increase in TB case detection among HIV-positive pregnant women when universal TB testing was employed [11–13]. However, there is a lack of evidence on the universal TB testing in the general population and other groups, including contacts, and its cost-effectiveness is unknown.

Moreover, it is not known how universal TB testing impacts TPT uptake in contacts. Global TPT uptake remains far from optimal. According to the 2023 World Health Organization (WHO) global TB report, only 10% (2 million) of contacts aged ≥ 5 years and 49–55% of those aged < 5 years received TPT between 2018 and 2022 [14]. One of the challenges is the need to rule out active TB and the fear of generating drug resistance. While X-ray-based screening is recommended by the WHO, its availability is limited. A simplified algorithm, employing the universal screening and TB testing, may facilitate the initiation of TPT by addressing need to rule TB and address risk of drug resistance.

We hypothesise that universal testing of high-risk populations such as contacts of TB patients will: [1] increase the number of contacts reached for TB screening; [2] increase the yield of undiagnosed TB; and [3] assist in ruling out active TB disease thereby increasing the number of contacts started on TPT. This will ultimately provide simplified algorithms for TB contact investigation.

Another knowledge gap in the implementation of contact tracing relates to defining who is deemed a significant 'contact' and the extent to which contact tracing should be conducted. The evidence for defining this threshold is limited and at times conflicting and requires further evaluation. Limited evidence has suggested that more emphasis should be placed on 'community contacts' with a higher proportion of linked transmission occurring outside than within the

household when using genotyping. Among children in the Gambia, where extended family compounds are common, nearly half of all co-prevalent TB disease diagnosed in child contacts would have been missed if contact tracing was restricted to the immediate households [8]. In contrast, a study in Vietnam did not report finding any undiagnosed TB among extended contacts of multi-drug resistant TB (MDR-TB) index patients [15]. Concerns of stigma and disclosure of TB status to community contacts also arise when extending the reach of contact tracing and thus needs additional evaluation.

We are conducting a pragmatic cluster-randomised trial with the primary objective to evaluate the effectiveness of universal TB testing compared to standard TB screening for detection of TB among household and community contacts in Lesotho and Tanzania. As the secondary objectives, the study will also compare the uptake of TPT in the households that offered universal TB testing compared to standard TB screening per country guidelines.

The study aims to enhance TB case detection among these community contacts through systematic screening and testing for TBI. One of the primary objectives is to determine the prevalence of TPT eligibility among these contacts, particularly focusing on those who are people living with HIV, children under 5 years of age in Tanzania and children under the age of 15 in Lesotho, or those who test positive on the TBI test. By including community contacts in the screening process, the study seeks to compare the uptake of TPT and the diagnostic yield of TB cases between those offered universal TB testing and those undergoing standard TB screening. This approach is expected to provide valuable insights into the effectiveness of extending TB screening beyond HHCs, ultimately contributing to improved TB control strategies in the targeted regions.

Methodology

Study design and setting

We will conduct a pragmatic cluster-randomised controlled trial, with the cluster as household, in the peri-urban communities of Lesotho (Maseru, Thaba-Tseka, Berea, and Quthing districts) and Tanzania (Songwe and Mbeya regions). The chosen study sites are situated in geographies with varying TB incidence rates, socio-economic profiles, and differing human immunodeficiency virus (HIV) prevalence [1]. The study will comprise of phase I, a preparatory study, and phase II where randomisation will occur (Fig. 1).

Study population and eligibility criteria

We will enrol drug-sensitive TB (DS-TB) index patients and their household and/or community contacts. TB index patients who: [1] are aged ≥ 18 years; [2] are microbiologically confirmed with TB within ≤ 6 weeks of diagnosis at a time of recruitment; and (3) have at least one household contact. Household contacts are defined as a person who shared the same enclosed living space for 7 nights or for frequent or extended periods during the day with the index patient during the 3 months before commencement of the current treatment episode and community contact as any individual that spends more than 1 h a day with the index patient at least 3–4 times a week (typically work colleagues, friends, school mates, caregivers).

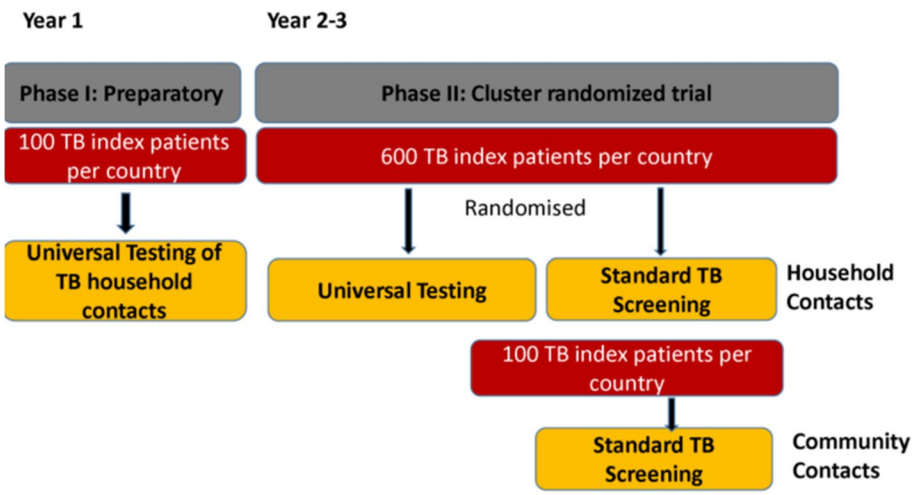


Fig. 1 Schematic representation of our study design

Description of study arms

Intervention arm

The intervention arm will be universal TB testing which will involve testing for TB of all HHCs (regardless of TB symptoms) with Xpert MTB/RIF Ultra (Xpert Ultra) and referral of TB-positive patients for TB treatment at their chosen or nearest health facility. Those that do not have symptoms or test negative on Xpert Ultra will be referred for TPT to their preferred health facilities.

Standard of care arm

The standard of care will involve standard TB screening, using WHO four-symptom screening questions (cough, fever, night sweats, or unintentional weight-loss). All HHCs who self-report one or more TB symptom will be asked to provide a spot-sputum sample for investigation using Xpert Ultra. Those who test positive with Xpert Ultra will be referred for TB treatment at their chosen or nearest health facility. HHCs that do not report symptoms or test negative on Xpert Ultra will be referred for TPT as per national guidelines.

Description of study procedures

Recruitment procedures

Recruitment of TB index patients will take place at health care facilities, through collaboration with national TB programmes in each country. HHCs will be recruited during household visits at addresses given by TB index patients. Written informed consent will be obtained from all participants prior to any study-specific procedures.

Phase I will be a cross-sectional study conducted to inform the need for and type of TBI test to be used in the pragmatic cluster-randomised trial (phase II). Phase I objectives include: [1] to determine the prevalence of TBI and TPT eligibility among TB contacts and [2] to assess the diagnostic agreement of QFT-Plus and QIAreach for diagnosing TBI among HHCs of TB index patients. In phase I, to assess TB infection status, blood samples will be collected from HHCs aged ≥ 5 years. A single lithium heparin tube will be used to collect blood sample for QuantiFERON-TB-Gold-Plus (QFT-Plus) processing, testing, and interpretation following manufacturer's guidelines. Those with positive QFT-Plus results will be considered to have TBI.

In phase II, following consent, index cases and their households will be randomised together to the same arm of the study. In the intervention arm, contacts aged ≥ 5 years will be requested to provide sputum samples for microbiological testing using the Xpert Ultra test regardless of whether they exhibit TB symptoms.

Clinical procedures

Sputum samples will be collected from TB index patients for culture (Liquid MGIT TB culture system, Becton Dickinson) testing. Among HHCs, sputum samples will be collected for Xpert Ultra testing according to their randomised arm, with additional culture testing performed only among those with positive Xpert Ultra results. Alternative sampling methods such as stool, urine, and induced sputum will be employed in children who cannot spontaneously produce sputum in Tanzania. HIV testing will be provided to HHCs who are HIV negative, have an unknown HIV status, or have not been tested in the last 6 months (3 months for Lesotho).

Household follow-up visits

A first household follow-up visit will be conducted to: (i) provide Xpert Ultra and QFT-Plus results, (ii) refer those who test positive on Xpert Ultra to start TB treatment, (iii) collect second sputum samples among those who had positive Xpert Ultra results, and (iv) refer eligible participants for TPT per country guideline and those with positive QFT-Plus results and negative Xpert Ultra results. A second household follow-up visit will be conducted: (i) to check if those who were referred at first follow-up visits went to the clinic for appropriate care and (ii) to ascertain the outcome of TB treatment or TPT initiation. Table 1 illustrates the schedule of events, procedures, and flow of participants in the different intervention arms throughout the study, while Fig. 2 shows the overview of the study project and phases.

CRF, case report form; *TB*, tuberculosis; *LTBI*, latent TB infection; *TPT*, TB preventive therapy; *Xpert*, GeneXpert MTB/RIF.

Description of substudies

Economic evaluation—health economics and modelling

We will perform a full economic costing from a societal perspective including both provider and patient costs to: (i) determine the relative cost-effectiveness in terms of incremental cost per additional case detected through a universal TB testing strategy using Xpert Ultra vs. the standard TB screening using symptoms and (ii) evaluate cost-effectiveness and model the effect on TB incidence of the interventions: universal TB testing vs. standard TB symptom screening and household testing vs. community testing. Provider costs include all resources utilised in the two contact tracing strategies. To the extent possible, patient costs of TB treatment will be based on published literature and complemented with data from local surveys as required. Modelling is an efficient means

Table 1 Schedule of study activities

Activity	Phase I				Phase II							
					Universal testing				Standard screening			
	Index	Household visit 1	Household visit 2*	Household visit 3*	Index	Household visit 1	Household visit 2*	Household visit 3*	Index	Household visit 1	Household visit 2*	Household visit 3*
Visit code	00.0	01.0	02.0	03.0	00.0	01.0	02.0	03.0	00.0	01.0	02.0	03.0
Visit day	−7	0	±7	±60	−7	0	±7	±60	−7	0	±7	±60
Informed consent	X	X			X	X			X	X		
Randomisation					X				X			
Enrolment CRFs	X	X			X	X			X	X		
Symptom screening	X	X			X	X			X	X		
TB stigma score	X											
Economic questions***		X				X			X			
Sputum collection—TB culture	X (5 ml)				X (5 ml)				X (5 ml)			
LTBI test (QFT-Plus)**		X (7 ml)										
Xpert Ultra test		X (5 ml)				X (5 ml)						
Xpert Ultra (only if symptomatic)										X		
TPT referral (if asymptomatic)										X		
TB culture (if Xpert Ultra positive)			X				X				X	
TB treatment referral (if Xpert Ultra positive)			X				X				X	
TPT referral (if Xpert Ultra negative)			X				X				X	
Multimorbidity screening**** Blood glucose—2 ml fluoride tube HbA1c—4 ml EDTA Creatinine/cholesterol—5 ml serum separating tube		X (20 ml)										
Blood ml collected per visit		(27 ml)				(7 ml)				(7 ml)		

*Could be a number of different visits but all procedures should be complete

**Dependent on whether it is deemed necessary for TPT implementation following results from phase I

***For adult contacts only

****For adult contacts in South Africa and Tanzania only

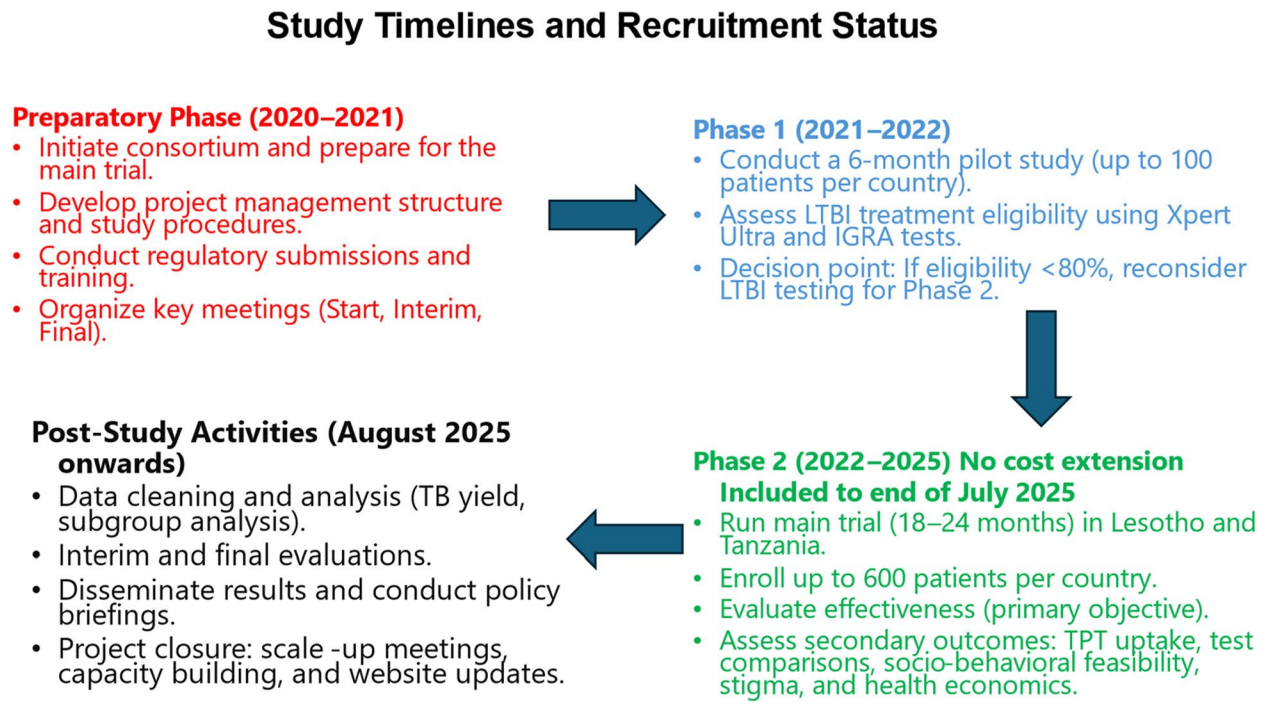


Fig. 2 Overview of the study project and phases

of testing different combinations of innovations to project their potential impact, thus reducing the need for costly, large-scale primary research studies. We will build a Markov model with activation to active TB as the main outcome. TPT uptake (for a specific subset of children in Tanzania) will be based on empirical data generated within the project.

Paediatric evaluation

All child contacts will be evaluated for TB to improve TB screening and uptake of TPT in child contacts. Informed consent will be obtained from parents or legal guardians in preferred local languages in addition to English. The assent form will be used when the child age is 7–17 years.

Child contacts will be screened as per country specific guidelines; however, specific screening approaches will be implemented for child contacts < 10 years who are typically unable to expectorate sputum. In children < 10 years, sputum will not be collected if they are asymptomatic and cannot spontaneously produce sputum. In children < 10 years in Tanzania, only those who are symptomatic will be invited at the childhood TB clinic for sputum induction, and in addition stool for Xpert Ultra and urine for LAM will be collected.

Microbiology methods

The study aims to understand transmission dynamics using next generation whole genome sequencing (NG-WGS) between TB index patients and their household and community contacts. We will do this to determine what proportion of co-prevalent TB cases identified among household and community contacts are related to the index TB patient.

Qualitative evaluation—socio-behavioural component

A descriptive qualitative study design will be used for this study. In-depth interviews will be the key method of data collection to understand how drivers, facilitators, stigma marking, experiences, and practices influence implementation of TB case finding and TPT uptake for HHC and community contacts of index cases. The study will also aim to understand the caregivers' (parents and legal guardians) experiences of caring for children on TPT. As secondary objectives, this component will seek to describe the stigmatisation process across a socio-ecological spectrum in the context of TB testing and treatment, specifically universal TB testing and TPT. In addition, we will explore stigma that intersect with TB, such as HIV co-infection, symptoms of TB, age, race, gender, and poverty. Lastly, we will assess barriers to TB screening, as well as initiation of TPT in child TB contacts.

The study population will consist of participants recruited in the main cluster-randomised trial in Tanzania and Lesotho, as well as TB index patients accessing treatment from the study facility. We will interview at least 75 participants per country: 20 TB index patients, 15 caregivers of children on TPT, 20 HHCs, and 20 community contacts. We will assess the data for saturation of themes and if convergence has not been attained then we will continue with the interviews to a maximum of 105 participants per country: 30 TB index patients, 15 caregivers of children on TPT, 30 HHCs, and 30 community contacts. We will ensure that there is a variation in gender and age within and across countries.

Trial outcomes

For the preparatory study (phase I), the key outcomes will be: [1] prevalence of TBI, defined as proportion of HHCs with a positive QFT-Plus test; [2] TPT eligibility among HHCs, defined as proportion of HHCs with a positive TBI test, or HIV positive or child less than 5 years of age in Tanzania and less than 15 years in Lesotho; and (3) diagnostic concordance of QIAreach compared against QFT-Plus.

For phase II, the primary endpoint is TB case finding yield which will be measured as the proportion of new microbiologically confirmed TB patients (positive on smear, Xpert Ultra, or culture) identified among contacts screened for TB comparing universal TB testing and standard TB symptom screening. The secondary endpoints of the trial will be: [1] the uptake of TPT, defined as the proportion of eligible HHCs (adults or children) started on TPT in accordance with country specific national guidelines, and [2] TB treatment uptake, defined as proportion of HHCs (adults or children) diagnosed with microbiologically confirmed TB initiated or started on TB treatment in accordance with country specific national guidelines.

For the community contact tracing component, TB case finding yield will be the key endpoint, defined as the proportion of new microbiologically confirmed TB patients (positive on smear, Xpert Ultra, or culture) identified among community contacts screened for TB, comparing universal TB testing (intervention) and standard TB screening.

For economic evaluation (health economics and modelling), the outcome will be the cost-effectiveness of the effect of the intervention on TB incidence: universal TB testing vs. standard TB screening. For paediatric evaluation sub-study, the outcome will be the proportion of child contacts under 10 years of age who start TPT. For the microbiology component, the outcome will be TB transmission dynamics by determining genomic relationship between TB diagnosed among household and community contacts to the TB index patients using NGWGS. Qualitative outcomes will be perceived barriers and facilitators to universal TB testing, TPT initiation and completion. These will also include universal TB testing and impact on stigma that affects TB case finding and uptake of TPT. Stigma and caregivers' experiences with children on TPT will also form part of our qualitative outcomes.

Sample size considerations

For the cluster-randomised trial (phase II), we aim to enrol 600 TB index patients in each of the two countries. Among these patients, 300 will be assigned to the standard TB screening arm, while the remaining 300 will be allocated to the universal TB testing arm. In addition to this among 100 index cases from each arm, community contacts will be screened.

The total number of community contacts to be screened per country in the CUT-TB study is approximately 3 community contacts per TB index patient. Given that the study plans to enrol around 100 TB index patients per country, this results in a total of about 300 community contacts per country to be screened. Community contacts are defined as individuals who have close interactions with TB index patients but do not reside in the same household.

It is anticipated that there will be 3 to 5 HHCs per TB index patient, resulting in a total of 900 to 1500 HHCs per country per arm. The chosen sample size ensures good precision for estimating the difference in TB yield between the two arms specifically 6% and 3% in intervention arm and the standard of care arm, respectively. Specifically, the effective sample size (ESS) per arm for Tanzania and Lesotho will be approximately 923 and 1071, respectively. Consequently, the expected precision for the difference in yield is approximately ± 1.9% and ± 1.8%, respectively.

Data management and analyses

Data management

In this study, REDCap is utilised as the database for collecting and managing data, with a structured questionnaire tool designed and tested before deployment. Research assistants will administer the REDCap survey to collect data, utilising its features for defining study attributes, managing user access, and facilitating data extraction. The platform allows data entry and cleaning within the system, accessible via web or mobile app. Health economics, microbiology, and paediatrics data

will be integrated, with a focus on data quality and secure input processes.

The analysis plan for phase I study will focus on the prevalence of criteria for treatment of TBI, expected to be around 80%, with a precision of 5% (95% confidence interval of 75–85%). The data will be analysed to determine the proportion of contacts eligible for TPT based on their test results and demographic factors. This phase will also assess the feasibility of including TBI testing in the main trial, depending on the eligibility rates observed. Statistical methods will include logistic regression to evaluate the outcomes and adjust for potential confounders, ensuring robust findings that can inform the subsequent phases of the study.

Data analysis principles

The study design for the phase II, cluster-randomised trial focuses on defining primary and secondary outcomes related to TB screening and treatment. The primary outcome is determined for all HHCs who consent, even though not all contacts are part of the intention-to-treat (ITT) population due to randomisation methods. The analysis considers that the trial arm should not influence the proportion of contacts agreeing to screen. TB detection is a secondary outcome among all HHCs, seen as the ITT population.

Per-protocol analysis will be used for TPT uptake, TB treatment uptake, and TB treatment outcomes. Results will be reported for both standard TB screening and universal TB testing arms, with further stratification by TB symptoms in the universal testing arm. Community contacts are excluded from the primary analysis but will be considered in secondary analyses for TB yield, TPT eligibility, and initiation. These outcomes, however, will not be included in the primary results publication.

The study design for the cluster-randomised trial is meticulously planned, focusing on key aspects such as confidence intervals, p values, baseline factors, and comparability between randomisation arms. Adjustment for design and baseline factors is carefully considered, with a weighting method as a sensitivity analysis to achieve balance between arms. Anticipated low levels of missing data for main outcomes will allow for available case analyses, and effect measures will be expressed as adjusted odds ratios with 95% confidence intervals. The conduct of a pooled analysis across countries will provide a comprehensive overview, with comparisons between household and community contacts to assess TB prevalence and intervention effectiveness.

Detailed analysis plans encompass recruitment, intervention uptake, and follow-up procedures following CONSORT guidelines. Sensitivity analyses and subgroup analyses by country and age groups will be conducted to ensure robust results. Sensitivity analyses will explore how results might change with different diagnostic thresholds or methods, while subgroup analyses will break down the population into specific age groups (e.g. children under 5 and those aged 5–10) and countries (like Tanzania and Lesotho) to identify trends and differences in TB screening and treatment efficacy. This dual approach is crucial for ensuring that the study's conclusions are valid across diverse populations, allowing for the development of tailored public health strategies that effectively address the unique characteristics and needs of each subgroup affected by TB.

Regression diagnostics will help diagnose model fit issues, with analysis checking procedures in place to verify primary outcome results. The thorough approach to data analysis and reporting in this trial aims to provide reliable insights into TB screening and treatment outcomes across different settings and populations. The Technical Data Manager at The Aurum Institute will manage the final data set, while other staff such as investigators will have role-based access to REDCap data system specific to the site. Predefined permissions will ensure confidentiality and compliance with ethical standards.

Ethics considerations

The study obtained ethical clearance from Johns Hopkins Bloomberg School of Public Health's Institutional Review Board (Ref: 16,967) and Lesotho National Health Research Ethics Committee (Ref: 37–2021) in Lesotho. In Tanzania, ethical clearance was received from Tanzania Medical Research Coordinating Committee (Ref: NIMR/HQ/R.8a/Vol.IX/3799) and Mbeya Medical Research and Ethics Review Committee (Ref: SZEC-2439/R.C/V.1/55).

Prior to commencement of study procedures, we will seek informed consent from all study participants using written informed consent and information sheet available in the commonly used local languages. Assent will be obtained from participants aged 7–17 years. An impartial witness is used to witness the verbal consent for illiterate participants. Privacy and confidentiality will be maintained throughout the study. Every attempt will be made to ensure that the study procedures are conducted in a safe, secure, and private environment to ensure confidentiality and dignity of all study participants.

Participants will be informed that the study has minimal risks associated with participation, and that no post care will be offered by protocol except routine care as guided by national TB treatment guidelines. No formal compensation is planned except that participants will retain the right to withdraw consent at any point in the study. Electronic database will be password protected and only the designated researchers and regulatory bodies

will have access to the database. In addition, study personnel will be trained on ethical processes and practices through good clinical practice course. All paper-based documents with personal identifiers will be kept under lock and key. Lastly, the study has a trial steering committee that meets biannually to discuss study progress.

Discussion

This study aims to evaluate the effectiveness of universal TB testing in increasing the detection of new microbiologically confirmed TB cases among household and community contacts in Lesotho and Tanzania. The researchers highlight the importance of HHCT as an effective strategy, which can identify significantly more undiagnosed TB cases compared to passive case finding [5, 16]. Evidence from other high TB prevalence settings, such as Vietnam, supports the cost-effectiveness of contact tracing when combined with passive case finding [16]. The study hypothesises that universal TB testing will increase the number of contacts screened, yield more undiagnosed TB cases, and help rule out active TB, ultimately reducing transmission.

However, there are counterarguments to the implementation of universal TB testing. Symptom screening, the current standard, has shown sub-optimal sensitivity and missed cases, leading to the exploration of universal testing [10]. But the reliance on advanced genomic techniques for TB transmission dynamics and drug resistance analysis may limit feasibility in resource-limited settings. Additionally, the complexity and resource demands of genomic data analysis could delay the practical application of findings. Economic evaluations using models may not fully capture real-world variability, potentially affecting the accuracy of cost-effectiveness analyses.

The study also consists of four sub-studies. Firstly, a paediatric TB screening and preventive therapy, aiming to improve outcomes for children under 10 years. A second sub-study will be a health economic cost-effectiveness evaluation of universal TB testing relative to symptom based TB testing. Thirdly, a socio-behavioural sub-study will assess drivers, facilitators, stigma markings, experiences and practices that influence TPT uptake. Lastly, the microbiology sub-study will evaluate the genomic co-prevalence dynamics between household transmission and community transmission. The multifaceted nature of the research activities in the protocol highlights the need for careful planning and consideration for the implementation of the study.

Strengths and limitations

The study will be implemented as a pragmatic trial in two countries with differing epidemics and socio-economic profiles, using existing processes for TB contact tracing. This is a strength of the study as it ensures that we can generalise our findings to similar settings and also measure the true impact of introducing universal TB testing within the routine programme, rather than under clinical trial conditions, which are often not reproducible in programmes. As the trial is pragmatic, it will rely on routine systems for sample collection, laboratory processing, and accessing results. We will also rely on routine systems to ensure that contacts are started on TPT, and follow-up of persons diagnosed with TB. This is a strength in that using the available non-experimental real-world resources captures the effectiveness of the intervention without confounding through experimental manipulation. In addition, the sub-studies ensure a comprehensive approach that includes economic, paediatric, microbiology, and qualitative components to bring about a holistic conclusion on the effectiveness of the two interventions.

Other limitations are a high probability of low sputum MTB load and quality in asymptomatic participants, rendering some tests not effectively usable. Some HHCs may not be contacted by random chance, as these are socio-economically active people or children at school who might not be available for study procedures. Finally, other limitations are in relation to existing known limitations of Xpert Ultra testing, such as availability, cost, electricity dependence, and cartridge shelf life. Ultimately, the goal of our intervention is to reduce TB incidence both within households and to reduce transmission to communities. Lastly, although the study will be conducted in multiple regions in each of the two countries, the sample size will be relatively smaller and therefore will make it difficult to generalise our findings to other regions.

Dissemination

The plan involves the development of a communication strategy through formative activities, network meetings, and community engagement to ensure wide visibility and maximise the impact of the project outcomes. The dissemination and publication of results will entail submission to peer-reviewed journals, engagement with local and international civil society and community groups, communication and dissemination strategies, presentations at local, national, and international conferences, and networking. The plan also includes the development of information materials and the use of media, the introduction of the project to relevant regional and global initiatives, networks, and groups, as well as the dissemination of results to health care workers involved in the trial, national governments, WHO, and other international agencies and organisations.

Trial status

The study is currently in its final stages of implementation, with a projected completion date of 31 July 2025. Year 1 activities included contract management, preparatory tasks, and the phase I component, while years 2 and 3 focused on the enrolment and follow-up of phase II, the cluster-randomised trial. Years 4 and 5 will be dedicated to completing all work packages, data cleaning, analysis, and write-up.

Appendix

Table 2 SPIRIT checklist

		Reporting item	Page and line number	Reason if not applicable
Administrative information				
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1	
Trial registration	#2a	Trial identifier and registry name. If not yet registered, the name of the intended registry	Page 3	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A	No data from WHO data set was used
Protocol version	#3	Date and version identifier	Page 3	
Funding	#4	Sources and types of financial, material, and other support	25	
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	26	
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Page 24	
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	26	Sponsor had the following roles: Design Data collection Management Data analysis Results interpretation Report writing Decision to submit for publication Funder had no role in the above
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see item 21a for data monitoring committee)	24	Coordinating centre Steering committee Endpoint adjudication committee Data management team
Introduction			Page 4	
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 4	

		Reporting item	Page and line number	Reason if not applicable
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Page 4	
Objectives	#7	Specific objectives or hypotheses	Page 5 and 6	
Trial design	#8	Description of trial design including type of trial (e.g. parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g. superiority, equivalence, non-inferiority, exploratory)	Page 7 and 8	
Methods: participants, interventions, and outcomes				
Study setting	#9	Description of study settings (e.g. community clinic, academic hospital) and list of countries where data will be collected. Reference to where the list of study sites can be obtained	Page 3	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g. surgeons, psychotherapists)	Page 9	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 9 to 11	
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g. drug dose change in response to harms, participant request, or improving/worsening disease)	In this version of the protocol, there was no further change in interventions	
Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g. drug tablet return; laboratory tests)	Page 9, 10, and 21	The discussion points out that the study uses routine systems for adherence to procedures of TB treatment
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A	The study is not a medical drug comparative interventional study. Participants are randomised into different screening arms not medical interventions
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (e.g. systolic blood pressure), analysis metric (e.g. change from baseline, final value, time to event), method of aggregation (e.g. median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14 and 15	

		Reporting item	Page and line number	Reason if not applicable
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and wash-outs), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11	
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15 and 16	Version after SA is removed—does it specify how many ppts in Lesotho and Tanzania?
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9	
Methods: assignment of interventions (for controlled trials)				
Allocation: sequence generation	#16a	Method of generating the allocation sequence (e.g. computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g. blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (e.g. central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9	Randomisation will occur at the household level of the index patient
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (e.g. trial participants, care providers, outcome assessors, data analysts), and how	N/A	The trial is not a blinded design
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A	The study is a cluster-randomised unblinded design

		Reporting item	Page and line number	Reason if not applicable
Methods: data collection, management, and analysis				
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g. duplicate measurements, training of assessors) and a description of study instruments (e.g. questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 16–17	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 16–17	
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g. double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 16–17	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 16–17	
Statistics: additional analyses	#20b	Methods for any additional analyses (e.g. subgroup and adjusted analyses)	Page 16–17	
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (e.g. as randomised analysis), and any statistical methods to handle missing data (e.g. multiple imputation)	Page 16–17	
Methods: monitoring				
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A	The CUT-TB trial will not establish a data monitoring committee (DMC), as the study is considered low risk. Instead, oversight will be provided by an independent trial steering committee (TSC), which will meet biannually to review progress and includes external experts with no competing interests

		Reporting item	Page and line number	Reason if not applicable
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A	The protocol does not include plans for interim analyses or stopping guidelines. No procedures will be outlined for early trial termination, and no roles will be assigned for reviewing interim results or making decisions to stop the trial early
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A	The interventions are low risk, such as preventive therapy and standard of care tuberculosis treatment
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A	The study only has steering committee that meets biannually
Ethics and dissemination				
Research ethics approval	#24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	N/A	Approval from ethics was obtained
Protocol amendments	#25	Plans for communicating important protocol modifications (e.g. changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g. investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A	No protocol amendment
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see item 32)	12	
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	12	
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18–19	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	24	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18	
Ancillary and post-trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	19	

		Reporting item	Page and line number	Reason if not applicable
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g. via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	22	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	22	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	22	
Appendices				
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Page 2	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Page 12	

Abbreviations

CI	Confidence interval
CUT-TB	Community and Universal Testing for TB among Contacts
DS-TB	Drug-sensitive tuberculosis
EDCTP	European & Developing Countries Clinical Trials Partnership
ESS	Effective sample size
HHC	Household contact
HHCT	Household contact tracing
HIV	Human immunodeficiency virus
ITT	Intention-to-treat
MDR-TB	Multi-drug resistant tuberculosis
MTB	*Mycobacterium tuberculosis*
NG-WGS	Next generation whole genome sequencing
NTP	National TB programme
QFT-Plus	QuantiFERON-TB-Gold-Plus
TB	Tuberculosis
TBI	Tuberculosis infection
TPT	Tuberculosis preventive therapy
WHO	World Health Organization
Xpert Ultra	GeneXpert MTB/RIF Ultra

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-08978-5.

Supplementary Material 1.
Supplementary Material 2.
Supplementary Material 3.
Supplementary Material 4.
Supplementary Material 5.
Supplementary Material 6.
Supplementary Material 7.
Supplementary Material 8.
Supplementary Material 9.

Acknowledgements
We thank the thousands of participants who consented to taking part in the study. We are thankful to the many stakeholders for their support for the study to be implemented: Ministries of Health in Lesotho and Tanzania, District and Region health authorities, and health facilities for their support to make this study a success. We appreciate the commitment and efforts of the CUT-TB team in enrolling and interviewing participants.

Trial sponsor
The Aurum Institute.

Authors' contributions
Funding acquisition, supervision, methodology: YH, AC, SS, IS, ENN, JL, LTM, TC, KL, SN, MM, MR, SC, KV. Conceptualisation, project administration, writing original draft, review, reading, and editing: MM, TN, YH, AC, SS, IS, ENN, JL, MM, GK, KN, IM, MN, LT, RM, DM, LTM, TC, TC, KL, SN, MR, SC, KV.

Funding
The study results will be generated with the assistance of financial support from The European and Developing Countries Clinical Trials Partnership 2 (EDCTP2) programme supported by the European Union with following project code: RIA2019IR-2877. The funder had no role in study design, data collection and analysis, decision to publish, or preparation manuscript.

Data availability
Not applicable.

Declarations

Competing interests
Staff and authors, in particular investigators, had no interests declared before the initiation of the CUT-TB trial.

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Received: 10 April 2025 Accepted: 14 July 2025
Published online: 11 August 2025

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