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Active close contact investigation of tuberculosis through computer-aided detection and stool Xpert MTB/RIF among people living in Oromia Region, Ethiopia (CADOOL Study): protocol for a prospective, cross-sectional study

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ABSTRACT

Introduction Pulmonary tuberculosis (TB) is an infectious disease with high incidence in low-income countries (LICs); it remains one of the infectious diseases with the highest mortality in the world, especially in LICs. It is crucial to recognise and diagnose TB as soon as possible, but microbiological tests on sputum are not always sensitive enough. New methods for an early diagnosis of TB are needed. In this study, we will investigate the role of two different tests to detect TB in Ethiopia (where the prevalence of TB is high): molecular search for TB in stool samples with Xpert assay and detection of pulmonary TB signs on chest X-rays with CAD4TB technology.

Methods and analysis A prospective diagnostic test accuracy study during TB active contact investigation will be conducted. In the referral hospital in Southwest Shoa Zone, Oromia Region, Ethiopia, patients with pulmonary TB and a sputum sample positive for *Mycobacterium tuberculosis* and household contacts of at least 4 years of age will be enrolled, with a target sample size of 231 patients. Trained staff will label household contacts as 'possible TB' cases or not according to their symptoms; when TB is possible, a stool Xpert and computer-aided detection on chest X-ray will be performed, alongside standard diagnostic methods, assessing the diagnostic accuracy of CAD4TB compared with Xpert MTB/RIF during TB contact investigation and the accuracy of stool Xpert compared with sputum Xpert.

Ethics and dissemination This study has been approved by the Oromia Health Bureau Research Ethics Committee (ref no BFO/MBTFH/1-16/100023). All information obtained will be kept confidential. Selected investigators will have access to data, while international partners will sign a dedicated data protection agreement. Eligible participants will receive brief information about the study before being asked to participate and they will provide written informed consent. Results will be disseminated through peer-reviewed journals.

Trial registration number NCT05818059.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The prospective design of a diagnostic test accuracy study allows for the collection of more accurate and complete data.
⇒ Study instruments are based on validated tools.
⇒ Involvement of tuberculosis (TB) close contacts.
⇒ Reference standard is a molecular TB test rather than culture.
⇒ The investigation of the diagnostic accuracy within strata may be limited by the sample size and the number of TB cases in each stratum.

INTRODUCTION

Tuberculosis global burden and epidemiology

Before the advent of COVID-19, tuberculosis (TB) was the leading cause of death from a single infectious agent and the 13th cause of death from all causes.[1] TB is caused by a bacterium, *Mycobacterium tuberculosis* (MTB) that, although it commonly affects the lungs, can cause disease throughout the body and with a broad spectrum of clinical manifestations.[2]

Despite being a preventable and treatable disease, TB infects roughly 25% of the world population, causing an estimated 1.4 million deaths among HIV-negative people (95% uncertainty interval (UI): 1.3 to 1.5 million) and 187 000 deaths (95% UI: 158 000 to 218 000) among people living with HIV.[3] Globally, an estimated 10.6 million people fell ill with TB only in 2021, increasing from the 10.1 million cases estimated for 2020, thus reversing a long-lasting decreasing trend. TB is a disease of poverty, as 87% of all incident

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cases of TB were registered in the 30 high-burden countries, mainly low-income countries from WHO regions of South-East Asia and Africa. In this regard, the relationship between TB burden and commonly used indicators of underdevelopment is well established. Widely recognised TB determinants include gross domestic product and prevalence of undernourishment, the latter alone being accountable for an estimated 2 million new TB cases in 2021.[3] Other risk factors for TB include HIV infection, diabetes, smoking habits and alcohol use disorders, all conditions which are highly prevalent among vulnerable populations. Hence, in the context of the COVID-19 pandemic and of the global food crisis triggered by both the war in Ukraine[4] and climate change,[5] it is likely that overall efforts towards TB eradication will be heavily affected.

As reported by the WHO, the immediate consequence of the COVID-19 pandemic was a large fall in the number of newly reported TB cases and an estimated increase in incident cases of rifampicin-resistant TB, all indicators that represent a relevant drawback in the pursuit of the 2025 End TB Milestones.[6] These gaps in TB diagnosis include both people who are diagnosed but not reported to local public health authorities and people who are not diagnosed and thus have not entered into care.

Chest X-ray and computer-aided detection for TB

Detection of radiographic abnormalities through chest X-rays (CXRs) is the preferred tool recommended by the WHO for the screening of TB in general and high-risk populations.[7] Pooled data show that CXR set as 'any abnormality', has sensitivity and specificity of, respectively, 94% and 89%, whereas when set at detection for abnormalities 'suggestive of TB', sensitivity and specificity are, respectively, 85% and 96%. Along with screening, CXR is used as the preferred diagnostic tool for triaging people presenting to emergency department with signs or symptoms suggestive of TB.

Limitations of CXR-based screening implementation are the need for radiological equipment, not always available in resource-limited settings and the need to expose subjects to a small amount of ionising radiation. Radiation exposure may increase the risk of cancer, especially in vulnerable populations such as children—who have a longer life expectancy and have more time to develop radiation-associated side effects—and pregnant women. However, when good practices are observed, CXR exposes the patient to an average of 0.1 mSv, which is the amount of radiation that is commonly received from the environment in the course of 10 days.[8] Also, another major limitation to the use of CXR as a screening tool for TB is the fact that, in high-burden countries, health personnel trained to interpret radiography images are not always available, and that intrareader and inter-reader accuracy is highly variable.[9]

In recent years, computer-aided detection (CAD), artificial intelligence-based software, has been developed with the aim to offer automated interpretation of digital CXR images. In broad terms, CAD programmes produce a numerical score that interprets CXR alterations in order to quantify the probability of TB. When diagnostic accuracy is assessed against bacteriologically confirmed TB, CAD software sensitivity ranges from 90% to 92%, and specificity ranges from 23% to 66%, thus fulfilling the minimal sensitivity required by the WHO for a screening test. These diagnostic performances were confirmed by several prospective studies conducted in low-income and middle-income countries,[9 10] systematic reviews[11 12] and one patient-level meta-analysis,[13] thus leading to the endorsement of CAD technologies by current WHO-consolidated TB guidelines for the screening of individuals aged 15 years or older belonging to selected high-risk populations.[7]

Among the CAD software packages commercially available, CAD4TB platform V.6 (Delft Imaging Systems, the Netherlands), developed using deep learning technologies—a type of machine learning technology based on artificial neural networks—releases results in few seconds and was designed to work on patients from 4 years of age. In a recent study conducted by Murphy *et al*,[14] when compared with a microbiological Xpert reference standard, CAD4TB V.7 has been shown to have both high efficiency and cost-effectiveness in high-burden settings, being able to process 132 images per day at the cost of less than US$6 per person. Even if the technology is validated for use in individuals aged 4 years or older, very few data exist on the clinical utility of this technology among children.

Xpert MTB/RIF on stool samples

Since mortality of untreated TB approaches 50%, and cure rates associated are high,[3] overall disease burden is strictly dependent on diagnostic capacity. In sub-Saharan Africa, microbiological diagnosis of TB is generally based on Xpert MTB/RIF (Cepheid, USA), an automated, PCR-based assay able to detect mycobacterial DNA on respiratory samples. However, in those settings, good-quality sputum samples are often difficult to obtain, leading clinicians to rely on more invasive procedures for diagnosis, such as nasogastric aspirates, sputum induction and pleural or abdominal aspirates, that are both painful and not routinely available in low-resource settings. MTB detection on respiratory samples is further challenged by extrapulmonary TB,[15] smear-negative pulmonary TB (PTB) and paucibacillary TB,[16] and sputum sample collection may put healthcare workers at risk of infection due to exposure to MTB-infected aerosols.[17]

In recent years, attention has been attracted by Xpert MTB/RIF on stool samples, since mycobacteria-containing sputum may be swallowed and then be available for molecular testing. Similarly to Xpert on sputum samples, stool Xpert is able to detect both the presence of mycobacterial DNA and mutations associated with rifampin resistance. Two meta-analyses conducted in 2019 have demonstrated that both Xpert and Xpert Ultra might be used to detect MTB bacilli with high

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specificity.[18 19] On a practical standpoint, several techniques have been proposed to process stool samples for GeneXpert testing. In 2021, de Haas *et al*[20] validated a simple, one-step, gravity-based method that requires the same laboratory equipment used for sputum samples and provides valid results without needing for bead-beating, dilution and filtration steps. Details of this procedure have been illustrated in a dedicated handbook.[21]

The use of Xpert MTB/RIF on stool samples has been introduced in the 2020 WHO guidelines as a possible initial diagnostic test for children with signs and symptoms of PTB.[22] However, this recommendation is based on low certainty of evidence. Due to a lack of available evidence, no recommendation has been issued so far about the use of Xpert on stool samples in the adult population.

Justification for the study

Ethiopia is listed among the 30 high-burden countries both for TB and for HIV/TB, transitioning out, in the last Global Tuberculosis Report,[3] from the list of the high-burden countries for multidrug-resistant or rifampicin-resistant TB. Annual TB incidence is 132 cases per 100 000 people (95% CI 92 to 178), with a case fatality ratio of 15% and most of the cases attributable to undernourishment.[23]

As in most of low-resource, high-burden countries, provider-initiated contact investigation is rarely carried out in Ethiopia,[24] although contact tracing and evaluation of all persons who have been in contact with an active case of TB are recommended by the latest national guidelines.[25] The WHO recently updated its screening guidelines, putting emphasis on the importance of active, provider-initiated screening of at-risk populations, especially households of index patients with TB.[26] Epidemiological data about active TB among household contacts are limited but, when reported, prevalence rates are high.[27] Also, a meta-analysis conducted by Gamtesa *et al*[28] found that healthcare-seeking behaviour in Ethiopia is low even in patients showing signs and symptoms of TB.

Provider-initiated screening of selected, high-risk populations is a key strategy in the fight towards TB eradication. According to the WHO, this approach should entail systematic identification of people with possible TB disease with tests, examinations or other procedures that can be applied rapidly. In this context, data about the clinical impact of the use of CAD technologies in Ethiopia are lacking. Also, data about diagnostic performances of, respectively, CAD software and stool Xpert MTB/RIF in the paediatric population and adult population are needed.

Objectives of the research project

General objective

To assess the role of CAD and stool Xpert MTB/RIF in improving the diagnostic process during TB active contact investigation in Ethiopia.

Primary objective

To assess the diagnostic accuracy of CAD4TB compared with sputum and stool Xpert MTB/RIF during TB contact investigation.

Secondary objectives

- To assess the diagnostic accuracy of stool Xpert compared with sputum Xpert in adult population.
- To assess the diagnostic accuracy of CAD4TB within strata (paediatric/adult subjects, HIV status, subjects, sex, smear status, history of TB, malnutrition status, smoking status) against sputum and stool Xpert.
- To provide an estimation of TB prevalence among contacts.

Additional objectives

- To assess if the identification of positive cases can be increased when information from CAD4TB is available to the clinician.
- To assess the occurrence of cases inappropriately labelled by the attending physician as ‘possible TB’ with and without the information provided by CAD4TB.
- To compare physician self-confidence in identifying possible TB cases based on whether CAD4TB information was available or not.
- To compare CAD4TB score and clinician’s confidence on his/her identification of a ‘possible case’ of TB when not using CAD4TB.
- To assess the association between CAD4TB score and clinician’s identification of a ‘possible case’ of TB when information from CAD4TB is available.
- Identify barriers to healthcare access among TB household contacts.

METHODS AND ANALYSIS

Study design

A prospective diagnostic test accuracy study will be conducted during TB active contact investigation.

Study setting

The study will be carried out in St Luke Catholic Hospital, Wolisso, Ethiopia.

St Luke Catholic Hospital is the referral hospital in Southwest Shoa Zone, Oromia Region, between Addis Ababa and Jimma covering 400 km distance. St Luke Catholic Hospital serves a population from a catchment area of roughly 1.4 million people. As of today, the hospital bed capacity is 208, while mean outpatient department visits are 350 patients per day.[29]

Routine TB screening in St Luke Catholic Hospital is based on patient-initiated pathway with assessment of signs and symptoms suggestive of TB. Possible TB cases are identified through a clinical visit that may include CXR evaluation. When performed, CXR images are evaluated by on-duty clinicians in digital format.

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Eligibility criteria

Eligibility and inclusion criteria

All patients diagnosed with PTB and at least one sputum sample positive for acid-fast bacilli on sputum smear or MTB on sputum Xpert or smear will be eligible for inclusion as index cases. Index cases will be recruited both among hospitalised patients and patients followed in outpatient department clinics for completion of TB treatment.

All household contacts of at least 4 years of age will be eligible for inclusion if they lived in the same dwelling as the index patient during the 2 months prior to the diagnosis of the index patient. Pregnant women are eligible for the inclusion but to minimise radiation exposure risk to the fetus, CXR will not be offered.

Exclusion criteria

Household contacts already receiving treatment for active or latent TB will be excluded from the study.

Criteria for withdrawal or discontinuation

Participants can withdraw from the study at any time without the need of a rationale and without compromising their future medical care. All participants will receive the same standard of care.

Procedures before the study

CAD4TB cloud demo sessions

Few weeks before project implementation, clinicians working in Wolisso Hospital will be trained for the use of 'CAD4TB cloud' software (V.6) by partners from Delft Imaging Systems, the Netherlands. Demo sessions will be held through online meetings and will include supervised exercise and skill acquisition testing. Demo sessions will provide a basic introduction and information about interpretation and performance. Furthermore, during demo sessions, a brief CAD4TB cloud manual will be provided.

Stool Xpert MTB/RIF procedure

Prior to the start of data collection, an expert microbiologist will provide full training on the procedures for stool sample processing with Xpert MTB/RIF to St Luke Catholic Hospital laboratory staff. This experienced microbiologist will then be available, in case of need, for the whole duration of the study.

Research training

Before protocol implementation, local research assistants will be identified and specific training meetings will be organised in Wolisso. Training meetings will (1) allow research assistants to settle quickly and become productive and efficient members of data collection; (2) reinforce understanding of the theoretical background behind the research protocol, including the review of local[25] and international TB guidelines[8 15 22]; (3) ensure full understanding of all protocol procedures and design; (4) enhance teamwork within the involved facilities; (5) ensure understanding of data collection platforms and how to use them; (6) strengthen the importance of data protection and consent acquisition; and (7) provide information about principles of research ethics.

Procedures during the study

Close contact recruitment

Close contacts will be identified via administration of a screening questionnaire to index cases. Close contacts will be defined as all people living in the same dwelling of the index case or living in close contact with the index case for the period of infectivity, that is, from up to 2 months before TB diagnosis. To minimise recruitment losses, close contacts will be approached by research assistants and will be offered transportation to St Luke Catholic Hospital to enter the screening programme. Once in the hospital and prior to study entry, all close contacts will be asked for informed consent to be enrolled in the study.

Sequence randomisation

After enrolment, each subject will be assessed according to sequence AB (assessment by clinician #1 without CAD and assessment by clinician #2 with CAD) or sequence BA (assessment by clinician #1 with CAD and assessment by clinician #2 without CAD). Allocation to sequence AB or sequence BA will be performed through randomisation (see the Allocation section).

Close contact screening

St Luke Catholic Hospital is provided with a digital radiograph system capable of delivering digital CXR and compatible with the CAD4TB cloud system. Once enrolled, all patients will be screened for the presence of any CXR abnormality and any symptom suggestive of TB, that is:

- Cough of any duration.
- Haemoptysis.
- Fever.
- Poor weight gain or weight loss.
- Night sweats.
- Chest pain.
- Shortness of breath.

Chest radiography will be performed only by posteroanterior imaging, following the procedures detailed by local and international guidelines in order to minimise radiation exposure.[29–31] Images will be then uploaded on the CAD4TB cloud system. The CAD4TB system starts with a quick inspection of the X-ray image. To detect possible TB-related abnormalities, CAD4TB relies on state-of-the-art machine learning techniques based on deep learning technology. The output of CAD4TB is a score between 0 and 100 (0=normal, 100=very abnormal) indicating the likelihood that the person on the image has TB. Besides the abnormality score, a heatmap indicating the position of the potential TB abnormalities is produced. This heatmap is shown as a colour overlay on top of the original CXR.

A participant will be labelled as 'possible TB' case according to the clinical judgement of the attending physician. Labelling will be informed by all available

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data coming from symptom assessment and radiological abnormalities detected with or without CAD use. During assessment of 'possible TB' cases, clinicians will be asked to grade their level of confidence over the likelihood of TB on a 5-point Likert scale. However, all contacts, both 'possible TB cases' and people who tested negative at initial screening, will be referred for microbiological testing.

Microbiological diagnosis with Xpert MTB/RIF on stool and sputum samples

All contacts will be referred for microbiological diagnosis of TB. Patients will be asked to provide sputum for smear microscopy and Xpert MTB/RIF and stool sample for testing with Xpert MTB/RIF.

The Xpert MTB/RIF assay is an automated cartridge-based, real-time test that can detect both MTB DNA and polymorphisms associated with resistance to rifampicin in less than 2 hours, and it is listed among the WHO-endorsed automated platforms for molecular diagnosis.

For the purposes of the present study, stool samples will be processed according to the one-step technique developed by de Haas *et al*.[20] Sputum samples will be processed for Xpert and smear microscopy according to routine local procedures and Ethiopian national guidelines.[25]

Follow-up of screening negative participants

All participants who will result negative to screening by symptoms and/or CXR abnormalities (with or without CAD) and to sputum/stool Xpert will be reassessed at 6, 12 and 18 months post-exposure. This is done primarily for ethical reasons, on the assumption that the first 2 years after TB exposure are at greatest risk of active disease.

A graphical representation of study procedures is provided in figure 1.

Other study variables

Other variables that will be collected are as follows: demographics, HIV status, malnutrition status, history of TB, smoking status and questionnaire about perceived barriers towards access to care.

Criteria for discontinuing or modifying allocated procedures

The participants will not be exposed to any harm or different benefits caused by the study procedures; hence, there are no reasons for discontinuing the study for safety or ethical reasons.

Strategies to improve adherence to intervention protocols

Face-to-face adherence reminder sessions for healthcare staff will occur regularly during the study period. This session will remind them of the purpose of the study and focus on the importance of following study guidelines.

Outcomes

Primary outcome measure

The common accuracy metrics (sensitivity, specificity, positive and negative predictive values) when assessing the accuracy of CAD4TB compared with Xpert MTB/RIF.

Secondary outcome measures

- The concordance between stool Xpert and sputum Xpert.
- The common accuracy metrics (sensitivity, specificity, positive and negative predictive values) when assessing the accuracy of stool Xpert compared with sputum Xpert.
- The common accuracy metrics (sensitivity, specificity, positive and negative predictive values) when assessing the accuracy of CAD4TB compared with Xpert MTB/RIF within the strata.

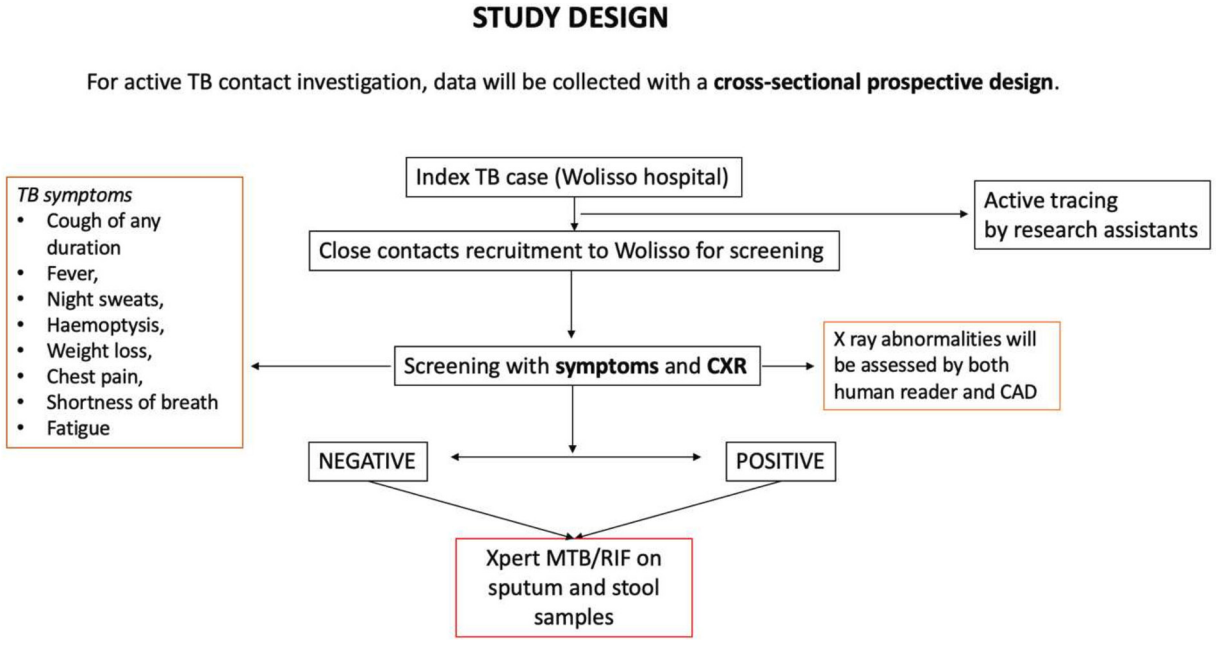

Figure 1 Study design and procedures. CAD, computer-aided detection; CXR, chest X-ray; TB, tuberculosis.

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- The incidence of new TB cases among participants during the study period.

Additional outcome measures

- The additional positive cases when information from CAD4TB is available to the clinician.
- The false-positive cases when information from CAD is available to the clinician.
- The number and type of discordant cases in CAD4TB versus clinician CXR evaluation.
- The association between CAD4TB score and clinician's confidence on his/her assessment when CAD4TB information is not available.
- The association between CAD4TB score and clinician's identification of a 'possible case' of TB when information from CAD4TB is available.

Sample size

We assume to confirm TB diagnosis in 90% of possible TB cases when using current standard assessment (without CAD4TB). Around 34 subjects are needed to be 95% confident that our estimate is within 10% of the true value in the population. As we expect to identify a possible TB case in 15% of TB contacts, then 231 TB contacts need to be enrolled in the study.

Allocation

After enrolment, each subject will be assessed according to sequence AB or sequence BA. Allocation to sequence AB or BA will be performed using a computer-generated random assignment list (with a 1:1 ratio), and assignments will be included in sealed opaque envelopes sequentially numbered.

Clinicians cannot be blinded to the assessment method (with or without CAD) and cannot be blinded to the further assessment (referral for microbiological diagnosis with stool and sputum Xpert) due to care process. However, the statistician will be blinded to the assessment during data analysis.

Data collection

Data will be collected using structured questionnaires and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Catholic University of the Sacred Heart, Rome, Italy.[32 33] REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources.

Statistical analysis

Categorical data will be summarised using absolute and relative frequencies. Numerical data will be summarised using mean and SD, or median and IQR. Estimates will be reported with 95% CIs. In accuracy investigation, the standard measures will be calculated (sensitivity, specificity, positive predictive value, negative predictive value). Concordance between stool GeneXpert and sputum GeneXpert will be assessed using Cohen's kappa and Gwet's AC1. Association between numerical data will be evaluated using Pearson's or Spearman's correlation coefficient. Additional comparisons between subgroups may be performed using Student's t-test, Mann-Whitney test, χ^2 test or Fisher's test, as appropriate. A sensitivity analysis including only subjects with available data from GeneXpert on sputum will be considered. Statistical significance will be set at 5%. The statistical analysis will be carried out using R V.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Interim analyses

Interim assessments are planned at 3, 6 and 12 months from data collection start. The analyses will assess the number of participants, the proportion of participants among eligible subjects and the proportion of possible TB cases among the participants. The purpose is to check if the magnitude of participants and TB cases is in agreement with those expected during the study design. Adjustments to sample size and duration of enrolment period may be made according to the indications from the interim assessments.

There are no stopping guidelines for harm and/or futility as none are expected.

Biological specimens

Stool

Stool samples will be handled and processed as described on the SOS stoolbox guide (KNCV Tuberculosis Foundation).[21]

Sputum

A volume of 5–10 mL is adequate and there is no advantage in collecting a larger volume. The sample should contain recently discharged material from the bronchial tree with minimal saliva content. Samples will be handled as per local routine laboratory procedures and will not be stored for research purposes.

Project time frame

- Submission of the protocol proposal to Ethics Committee: January 2023.
- Ethics Committee approval: March–April 2023.
- Research assistant's inception and training meeting: March–April 2023.
- CAD4TB demo session: March–April 2023.
- Enrolment and data collection: April 2023–December 2024 (duration of data collection will be reassessed after interim analysis results).
- Data entry and cleaning: April 2023–December 2024 (duration of data collection will be reassessed after interim analysis results).
- Interim analysis: June 2023, September 2023, April 2024.

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- Study coordination and progress monitoring: April 2023–December 2024 (duration of data collection will be reassessed after interim analysis results).
- Final data analysis: December 2024 (duration of data collection will be reassessed after interim analysis results).
- Dissemination of study findings: December 2024–January 2025 (duration of data collection will be reassessed after interim analysis results).

Patient and public involvement

The development of the research question and outcome measures were informed by patients. Patients were not involved in protocol development, nor involved in study design, recruitment or conduct of the study. Results will not be disseminated directly to study participants; the burden of the intervention was not assessed by patients.

ETHICS AND DISSEMINATION

Research ethics approval

Approval to carry out this study was received from the Oromia Health Bureau Research Ethics Committee (reference number BFO/MBTFH/1-16/100023).

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects, will require a formal amendment to the protocol and approval by the Institutional Review Board (IRB).

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These changes will be documented in a memorandum and notified to the IRB.

Confidentiality and protection of data

All information obtained will be kept confidential. Selected investigators will have access to the data. All records containing personal identifiers will be stored separately from study records identified by a code number. All case report forms and the study database will only include the study number. The database will be protected by a password and will benefit of the security features provided by REDCap.[32] International partners will sign a dedicated Data Protection Agreement. All study-related information will be stored securely at the study site. All electronic data will be secured with password-protected access systems. No information that reveals the identity of any patient will be released or published without consent.

Consent

Eligible subjects will receive brief information about the study before being asked to participate. Management of eligible subjects who decline their participation in the study will not be affected. Eligible subjects will not receive any incentives aiming at promoting the participation. Participants will provide written informed consent and will have the right to withdraw from the study at any time. All information obtained will be kept confidential.

Dissemination

The results of this study will be disseminated by publication in peer-reviewed journals and be presented at relevant conferences. The results will be shared with the community members and other relevant stakeholders and institutions through conferences and seminars.

Authorship eligibility guidelines

The guidelines for authorship of major, international, peer-reviewed journals will be used to establish authorship of collaborative publications.[34]

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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