“Institution logo”

Evaluating the performance, feasibility, acceptability and impact of treatment-decision algorithms for pulmonary tuberculosis in children in “country name”

**TDA4Child** study

(**T**B treatment **D**ecision **A**lgorithmsfor **Child**ren)

Version: 1 – April 2023

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# Abbreviations and acronyms

|  |  |
| --- | --- |
| **ETAT** | Emergency Triage and Treatment |
| **GDG** | Guideline Development Group |
| **HIV** | Human Immunodeficiency Virus |
| **ICF** | Informed consent form |
| **IMCI** | Integrated Management of Childhood Illnesses |
| **IPD** | Individual patient data |
| **LF-LAM** | Lateral Flow Lipoarabinomannan Assay |
| **MUAC** | Mid-Upper Arm Circumference |
| **mWRD** | Molecular WHO-recommended diagnostic test |
| **NPA** | Nasopharyngeal aspirate |
| **NTP** | National TB programme |
| **PHC** | Primary Health Centre |
| **SAM** | Severe Acute Malnutrition |
| **TB** | Tuberculosis |
| **TDA** | Treatment decision algorithm |
| **TPT** | Tuberculosis preventive treatment |
| **WHO** | World Health Organization |

# About this protocol

This protocol has been developed to harmonise research efforts to externally validate two treatment decision algorithms (TDAs) for the detection of pulmonary TB in children which are included in the 2022 WHO operational handbook on the management of TB in children and adolescents. WHO made an interim general conditional recommendation relating to the use of integrated TDAs for childhood TB treatment decision-making in their WHO consolidated guidelines on the management of TB in children and adolescents in 2022 (1). Two newly developed algorithms (2) were included in an accompanying operational handbook (3) as examples. Parts of this protocol are based on these 2022 consolidated guidelines and the accompanying operational handbook.

Black text represents generic text proposed for inclusion in the protocol. Guidance to investigators to adapt the protocol for the local context are written in red.

The rationale for this protocol was discussed and agreed with the Global TB Programme at the World Health Organization (WHO). Development of this document was led by the Special Programme for Research and Training in Tropical Diseases (TDR) of WHO (Corinne Merle and Jay Achar).

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# Protocol synopsis

|  |  |
| --- | --- |
| Title | Evaluating the performance, feasibility, acceptability, and impact of treatment-decision algorithms for pulmonary tuberculosis in children |
| Investigator/study location | To be added by investigators |
| Primary objectives | To describe the diagnostic accuracy (sensitivity, specificity, negative and positive predictive values) of TDAs for pulmonary TB in children under 10 years old in [[ name of country ]]. |
| Study design | a single/multi-centre interventional single-arm diagnostic evaluation |
| Study population | The study population includes children under 10 years old. |
| Inclusion criteria | Presenting to a study site with features of presumptive TB |
| Exclusion criteria | Diagnosed with and on treatment for TB disease at the time of evaluation,  No informed consent from parent or guardian,  Where applicable, the child declines to participate |
| Diagnostic intervention | Two diagnostic algorithms are defined in the protocol for evaluation based on previously published studies. While both use clinical and laboratory findings to guide treatment decision making, one is designed for sites where x-ray is available. |
| Comparator | The reference standard has been adapted from a consensus case definition proposed by an international panel of experts. It uses clinical, laboratory and x-ray findings along with a 2-month response to treatment assessment. |
| Outcome measurement and endpoints | The sensitivity, specificity, negative and positive predictive values will be calculated for per-protocol and modified intention to treat cohorts:  **Sensitivity**: the number of children who are recommended to start TB treatment by the algorithm divided by the number of children classified as suffering from pulmonary TB by the reference definition (confirmed or unconfirmed pulmonary TB).  **Specificity**: the number of children who are not recommended to start TB treatment by the algorithm divided by the number of children classified as unlikely to be suffering from TB by the consensus definition.  **Positive predictive value**: the number of children who are recommended to start TB treatment by the algorithm **and** are classified as suffering from pulmonary TB by the consensus definition (confirmed or unconfirmed pulmonary TB - true positives), divided by the number of children who are recommended to start treatment by the algorithm.  **Negative predictive value**: the number of children who are **not** recommended to start TB treatment by the algorithm and are not classified as suffering from pulmonary TB by the consensus definition (true negatives), divided by the number of children who are not recommended to start treatment by the algorithm. |
| Study duration | 6-12 months |
| Anticipated study dates | To be added by investigators |

# Background

Each year an estimated 1.1 million children and adolescents under 15 years old become sick due to tuberculosis (TB). Despite TB being preventable and curable, in 2021, approximately 200 000 children died from the disease (4). While treatment is both effective and tolerable, case detection continues to challenge many national TB programmes (NTPs), particularly in children under 5 years old. Less than half of children and young adolescents with TB are diagnosed and notified each year.

## Diagnostic gaps

The reasons for this large gap in case detection are multiple. Specimen collection, particularly in younger children requires trained and experienced staff. Bacteriological confirmation is less frequent due to the paucibacillary nature of disease in children and the resultant reduction in sensitivity when using available diagnostic tests. Clinical syndromes can be non-specific and rapidly progressive, resulting in early mortality and frequent clinical misdiagnosis. To overcome some of these barriers, health systems often require referral of children suspected of suffering with symptoms of TB to secondary or tertiary health centres so that expert staff can be consulted, and relevant specimens taken. This may result in additional cost, cause further delays in diagnosis and treatment initiation, and may ultimately result in greater morbidity and mortality.

To reduce the case detection gap and to avoid diagnostic delays, policymakers and programme implementers have promoted child and adolescent TB assessment at primary health (PHC) or child health centres, often through integration into existing child services diagnosing similar conditions. While child TB case notifications prior to the COVID-19 pandemic had been increasing, they declined sharply between 2019 and 2020 due to COVID (5). Childhood notifications recovered more slowly compared to adults in 2021, and efforts continue to be hampered by limited PHC staff expertise, poor access to diagnostic tests including chest x-ray and a lack of dedicated time for over-burdened health care staff.

## Childhood TB epidemiology in [[ name of country ]]

* This section should include information about the childhood TB epidemiology in the country and setting in which the study will be implemented. Where possible epidemiological information should be disaggregated by age (0-4 and 5-9 years). Investigators should include the following information for each of the previous 5 years – additional relevant information may be added:
* The number of children under 10 years old (or combined with young adolescents, e.g. below 15 years if applicable) diagnosed and notified with pulmonary TB, the proportion that started treatment and their treatment outcomes. Include a brief description on any significant trends that were noted during this period.
* The proportion of pulmonary TB cases in children under 10 that are bacteriologically confirmed
* The TB-attributed mortality amongst children under 10 years old
* The prevalence of human immunodeficiency virus (HIV) in adults and children under 10 if known
* The prevalence of severe acute malnutrition in children under 10 years old diagnosed with pulmonary TB
* Describe the current approach to the diagnosis of childhood TB in country, including the level(s) at which screening, diagnosis and treatment services are available and the steps of any diagnostic algorithm which is used (e.g., requirement for x-ray and bacteriological testing).

## WHO recommendation

To improve case detection in children, the World Health Organization (WHO), in their 2022 TB guideline update, included an interim general recommendation on the use of integrated TDAs (1). An individual patient data (IPD) set was established from several studies implemented in a range of high-TB burden countries. The IPD included the records of 4811 children with a median age of 26 months (1). Data from 13 studies representing 5 of the 6 WHO regions were included (2). Thirty eight percent of included children had TB of which 30% were bacteriologically confirmed.

The Union Desk Guide Algorithm (6), which sought to operationalise previous recommended best-practices was used as a reference-standard for comparison. Seven TDAs were evaluated, and pooled estimates of the sensitivity and specificity were compared. For the overall population of children under the age of 10 years, the pooled sensitivity of the seven TDAs or scoring systems ranged from 16% to 95%, while the pooled specificity ranged from 9% to 89%.

The Guideline Development Group (GDG) agreed that while none of the evaluated TDAs were optimal in their performance, there was a need for further work on TDAs to improve the gaps in TB case detection in children. Algorithms including clinical criteria have an important role in the decision to initiate treatment, particularly in PHCs where clinical expertise may be lacking.

Given the fact that high specificity of an algorithm results in low sensitivity and vice versa, the GDG agreed that treatment decision algorithms should prioritise sensitivity, to minimise the risk of missed cases of TB while accepting the risk of over-diagnosis and unnecessary treatment in some children.

Ultimately, an interim conditional recommendation (below) was included in the WHO consolidated guidelines on the management of TB in children and adolescents, with a 24-month validity period after which new evidence would need to be reviewed.

|  |
| --- |
| “In children with presumptive pulmonary TB attending health care facilities, integrated treatment decision algorithms may be used to diagnose pulmonary TB.” |

WHO interim conditional recommendation (1)

Following the GDG recommendation, two treatment decision algorithms were developed to serve as examples for implementation (2). These algorithms were optimised from the IPD data set used in the GDG evidence review. The scoring systems embedded within each algorithm have a sensitivity of approximately 85% and a specificity between 30-37%. Additional evaluation steps were added to the algorithms to improve their accuracy. External validation of these algorithms from a variety of implementation contexts is an important step to better understanding their role in the programmatic diagnosis and treatment of pulmonary TB in children. This generic protocol aims to harmonize research methods for the generation of data towards this external validation.

# Aim and objectives

## Aim

To describe the diagnostic performance, feasibility, healthcare worker acceptability and effect on case notifications of the study TDAs for pulmonary TB in children under 10 years old under programmatic conditions in [[ **name of country** ]]

## Primary objective

1. To describe the diagnostic accuracy (sensitivity, specificity, negative and positive predictive values) of TDAs for pulmonary TB in children under 10 years old in [[ **name of country** ]].

## Secondary objectives

Investigators who wish to compare the study TDAs with those that are already in use at study sites may add secondary objectives – for example, “To compare the diagnostic accuracy of the study TDA with historically implemented algorithms”.

Investigators may wish to describe the experience of caregivers when implementing the TDA. This would require defining a secondary objective, describing and implementing a dedicated consent process and the development of a structured questionnaire for data collection.

1. To record the number and proportion of children who completed the study TDA assessment, and the time elapsed from algorithm initiation through each step of the study algorithm.
2. To report the number and proportion of children lost to follow-up at each step of the study algorithm.
3. To report the number and proportion of children who die during the first 2 months of follow-up who are:
   * Recommended to start treatment for TB disease by the study algorithm assessment
   * Not recommended to start treatment for TB disease by the study algorithm assessment
4. To describe the proportion of children not recommended to start treatment following study algorithm assessment who subsequently initiate treatment for TB disease in the 2 months following initial evaluation
5. To describe the proportion of children who were evaluated with a mWRD test
6. To describe the proportion of children evaluated with algorithm A who have a chest x-ray
7. To report the proportion of children recommended to start treatment for TB disease who are bacteriologically confirmed
8. To compare child and adult TB notification rates before and after study initiation
9. To report the discordance between clinician treatment initiation decision and TDA recommendation
10. To describe healthcare worker satisfaction with and feasibility of algorithm implementation
11. To report the healthcare worker fidelity in completing TDA scoring

# Outcome measure

## Primary outcomes

Performance of the treatment decision algorithm will be measured by comparing the TDA decision to initiate TB treatment with classifications based on a reference definition of pulmonary tuberculosis in children (Annex 1) (7). Since the time taken to apply the treatment-decision algorithm can vary, each participant’s result will be recorded when their follow-up schedule has been completed.

**Sensitivity:** the number of children who are recommended to start TB treatment by the algorithm divided by the number of children classified as suffering from pulmonary TB by the reference definition (confirmed or unconfirmed pulmonary TB).

**Specificity:** the number of children who are not recommended to start TB treatment by the algorithm divided by the number of children classified as unlikely to be suffering from TB by the consensus definition.

**Positive predictive value:** the number of children who are recommended to start TB treatment by the algorithm **and** are classified as suffering from pulmonary TB by the consensus definition (confirmed or unconfirmed pulmonary TB - true positives), divided by the number of children who are recommended to start treatment by the algorithm.

**Negative predictive value:** the number of children who are **not** recommended to start TB treatment by the algorithm and are not classified as suffering from pulmonary TB by the consensus definition (true negatives), divided by the number of children who are not recommended to start treatment by the algorithm.

Feasibility of algorithm implementation will be measured through the following outcomes:

## Secondary outcomes

**Completed TDA assessment:** the proportion of included children who completed all steps of the algorithm and were given a treatment-decision.

**Time from assessment initiation** to each of the following algorithm steps:

Collection of respiratory/urine/stool specimens for laboratory testing

Availability of laboratory result

Initial algorithm score (if applicable)

Final algorithm treatment recommendation

Treatment initiation (if applicable)

**Loss to follow-up at each TDA step:** the proportion of children who do not complete a given assigned step in the TDA within 2 weeks of the expected date.

**Post-assessment mortality:** proportion of children who die within 2 months of an algorithm treatment recommendation being determined.

**TB treatment initiation against algorithm treatment assessment:** the proportion of included children who initiate TB treatment within 2 months of a TDA recommendation to not start treatment.

**mWRD, LF-LAM or culture performed:** the proportion of included children who had a bacteriological test for TB.

**Chest x-ray performed:** the proportion of included children evaluated using algorithm A (see Annex 2) who are evaluated for TB with a chest x-ray.

**Laboratory confirmation:** the proportion of included children with a recommendation to start TB treatment who have laboratory confirmed TB.

**TB notification rates:** the number of people notified with TB disease within a site’s catchment area in the 24 months prior to, or the 6- or 12-months following study initiation. If possible, this outcome should be disaggregated by age (0-4, 5-9, 10-14, 15 and greater) and sex.

**Discordant TB initiation:** the proportion of children in whom the healthcare staff treatment decision is different to the recommendation from the algorithm.

**TDA scoring fidelity:** the difference between health care worker calculated TDA score and TDA score derived from recorded values expressed as a proportion.

**Healthcare worker acceptability and TDA feasibility:** the proportion of healthcare workers who respond “somewhat agree” or “strongly agree” to questions relating to acceptability and feasibility.

## Timing of outcome measurement

The allocation of an outcome from the algorithm assessment should occur after all steps of the algorithm have been completed and a valid endpoint can be assigned to a participant (see section 12.2). This will mean that the time from algorithm assessment initiation to assignment of an outcome will vary for each participant.

Diagram

Description automatically generated

Figure 1 describes a scenario where the algorithm assessment is completed and an outcome assigned. The reference standard assessment follows 2 months later (see 13.4 Post assessment follow-up)

# Study design

## Overview

This study will implement a single/multi-centre interventional single-arm diagnostic evaluation of children under 10 years old with presumptive pulmonary TB using an both the integrated treatment decision algorithm. Algorithm results will be used for patient care and will be compared with a reference standard (described below) to measure diagnostic performance.

When considering the duration of study enrolment, investigators should aim to analyse datasets approximately 12 months after study initiation. This may represent closure of the study or a pre-planned interim analysis.

## Blinding

Clinicians involved in implementing the treatment decision algorithm will not be blinded from resultant scores. An external end-point evaluation committee (see Annex 4) who will review cases where a child dies or where treatment initiation is discordant from the TDA recommendation will be blinded from results generated from the treatment decision algorithm, but not from relevant clinical information.

# Study sites

Country investigators should include a description of each proposed study site. Relevant information includes:

* On-site and off-site access to diagnostic tests and specimen collection methods within the algorithm including HIV testing, x-ray and x-ray interpretation, mWRD, *M.tuberculosis* culture, and LF-LAM. Where access is off-site, describe specimen transportation procedures and turn-around-time for results.
* Number of new pulmonary TB cases in the previous calendar year – disaggregated by age – 0-4y, 5-9y, 10-14y (or 5-14y if 5-year age groups not available), 15-19y, ≥20y.
* Experience of site health care workers – important information may include the level of formalised training, completion of TB training courses, experience in paediatrics and specimen collection in younger children.
* Estimated prevalence of HIV and severe acute malnutrition amongst eligible children
* Description of the site catchment area.
* Previous experience as a study site for diagnostic TB research

When choosing study sites, country investigators should try and include sites with a variety of contextual characteristics – e.g., experience of health care workers, on-site access to x-ray and mWRD.

# Study population

This study will recruit children under 10 years old as participants. All children under 10 years old attending a study site will be considered for inclusion.

## Inclusion criteria

A child will be eligible for inclusion if all the criteria listed below are satisfied.

1. Under 10 years old on the day of assessment
2. Fulfils the criteria of presumptive TB according to the definition 11.3.1

A healthcare worker will be eligible for inclusion in the acceptability assessment if they have evaluated at least ten children during the study period.

## Exclusion criteria

A child will be ineligible for inclusion if any of the criteria below are present.

1. Diagnosed with and on treatment for TB disease at the time of evaluation
2. Parent or guardian does not allow the child to participate in the study or declines to sign the Informed Consent Form (ICF) (Annex 3)
3. The child does not wish to participate in the study or declines to sign the Assent Form (where applicable)

A healthcare worker will be ineligible for inclusion if they refuse to participate in the study, refuse to sign the Informed Consent Form or have not evaluated any children using the algorithm during the study period (Annex 5)

# Treatment Decision Intervention

Eligible children will be assessed by study site staff according to Algorithm A or B (Annex 2) (3) depending on site access to x-ray.

## Danger signs

The first step in both algorithms is to determine whether the child has signs and symptoms that indicate an urgent health problem. In children aged under 5 years, these signs and symptoms typically refer to “danger signs”, as defined by the IMCI approach. In older children, these signs and symptoms are defined in paediatric emergency triage, assessment and treatment (ETAT) (3).

If any of these signs is present, the child should be stabilized and referred to a higher level of care whenever possible. Once stabilized, the child with presumptive TB should continue to be evaluated using Algorithm A or B. Children with presumptive TB are then stratified based on their risk of rapid TB disease progression (section 10.3).

## HIV testing

Children with unknown HIV status should be offered rapid HIV testing accompanied by pre- and post-test counselling in accordance with WHO recommendations for children with presumptive TB or TB exposure. An age-appropriate nationally approved testing approach should be used (e.g., antibody/antigen combination immunoassays for children over 18 months and virologic PCR testing in children under 18 months). This allows the child to be placed into the appropriate risk group to inform clinical management, as described below

## Risk of progression

Children at high risk of progression include those aged under 2 years, living with HIV or with severe acute malnutrition (SAM) (defined as weight-for-height Z-score less than −3 standard deviations or mid-upper arm circumference below 115 mm or with bilateral pitting oedema).

For children with high-risk characteristics, a respiratory sample (spontaneously expectorated or induced sputum, NPA sample, gastric aspirate or stool) should be collected for testing with a mWRD (e.g., Xpert MTB/RIF or Xpert Ultra) if available. For children living with HIV, a urine specimen should be collected and sent for LF-LAM testing if available. If Xpert or LF-LAM is not available, or if the result is negative, or if there will be a delay before receiving the results, high-risk children should enter the next step in either of the TDAs.

Children without high-risk characteristics should first be managed and treated for the most likely diagnosis based on the presenting signs and symptoms (e.g., asthma, pneumonia, pertussis, malaria). This would commonly include a course of broad-spectrum antibiotics and clinical review after 1–2 weeks. If the child has persistent or worsening symptoms when evaluated after 1–2 weeks, they should provide samples for testing with a mWRD. If Xpert is unavailable or negative or a delay of more than 5 days is anticipated before receiving the result, the child should enter the next step in either of the algorithms.

## TB exposure

While taking the clinical history, the health worker or clinician should identify whether the child has been exposed to a person with infectious (Xpert-, smear- or culture-positive) pulmonary TB in the previous 12 months. This might include household exposure or close exposure to a person outside the home. Children in whom TB exposure is identified but treatment of TB disease is not recommended, should be evaluated for treatment of TB infection (TPT).

## Assessment of symptoms and signs

If there is no identified TB exposure, the next step is to assess the signs and symptoms listed in the algorithm using information collected during the clinical history and physical examination of the child.

Where available (algorithm A), a chest x-ray should be performed. The presence of signs and symptoms, and x-ray features (if applicable) suggestive of pulmonary TB should be scored as described by each algorithm (Annex 2).

If the resultant score is greater than 10, the algorithm recommends the child starts TB treatment. If the score is 10 or less, the child should return in 1-2 weeks for re-assessment.

# Study definitions

## Diagnostic definitions

### Diagnostic tests

The following mWRD tests are appropriate for the TDA:

* Xpert MTB/RIF,
* Xpert MTB/RIF Ultra,
* Truenat MTB,
* Truenat MTB Plus,
* TB-LAMP tests,
* Moderate complexity automated NAATs:
  + Abbott RealTime MTB and Abbott RealTime MTB RIF/INH (Abbott),
  + FluoroType MTBDR and FluoroType MTB (Bruker/Hain Lifescience),
  + BD MAX MDR-TB (Becton Dickinson),
  + cobas MTB and cobas MTB-RIF/INH (Roche)

The following definitions refer to results from mWRD and LF-LAM tests where applicable. If initial test results are indeterminate, assays should be repeated as per manufacturer instructions. Where indeterminate results cannot be repeated, “Result not available” should be recorded.

**MTB detected**: A positive test result as defined by the manufacturer. Xpert trace results should be interpreted as MTB detected.

**MTB not detected**: A negative test result as defined by the manufacturer

**Not performed**: The test was not performed. Reasons for not performing the test when required may be included in the data collection forms.

**Result not available**: The test was performed, but the result is unavailable to the investigators, or the test gave an invalid or error result.

## Endpoint definitions

The treatment-decision algorithm includes the following endpoints:

**Initiate TB treatment:** Where the algorithmic assessment recommends treatment initiation for the child.

**Do not initiate TB treatment:** Where the final algorithmic assessment does not recommend treatment initiation for the child.

**Transferred out due to presence of danger signs:** The child is transferred to another healthcare facility due to the presence of danger signs requiring urgent medical care.

**Treated successfully for non-TB condition(s):** Two weeks after treatment for non-TB diseases, the child’s symptoms are not persistent and have not worsened. The child will not be reassessed for TB during the current episode.

**Lost to follow up during algorithm evaluation:** A participant with no danger signs who does not complete the algorithm assessment and can therefore not be assigned a final treatment recommendation.

## Reference standard evaluation

The reference standard evaluation for the detection of TB will be adapted from a consensus case definition proposed by an international panel of experts (Annex 1) (7). Each participant will be assessed and allocated an outcome 2 months after initial TDA assessment is completed (see 13.3 Follow-up during assessment).

Each participant will receive one of the following endpoints from the reference standard evaluation:

**Confirmed tuberculosis**

**Unconfirmed tuberculosis**

**Unlikely tuberculosis**

**Unclassifiable**

The external endpoint evaluation committee (see Annex 4) will review cases in which a child dies or where the treatment initiation decision from the healthcare staff is discordant from the TDA recommendation and may reallocate reference standard endpoints if required.

**True positives** will be defined as children evaluated by the reference standard as “*Confirmed*” or “*Unconfirmed*” tuberculosis cases

**True negatives** will be defined as children evaluated by the reference standard as “*Unlikely*” tuberculosis cases.

## Other definitions

### Presumptive TB

Person who presents with any unremitting symptoms or signs suggestive of TB (listed below) lasting more than 2 weeks (3).

**Cough**: persistent, unremitting cough for 2 weeks or more, or cough of any duration in children living with HIV.

**Fever**: persistent fever for 2 weeks or more (the score in the algorithm is based on the duration of fever as per the history rather than the actual temperature on examination).

**Lethargy**: persistent unexplained lethargy or decrease in playfulness or activity reported by the parent or caregiver.

**Weight loss**: more than 5% reduction in weight compared with the highest weight recorded in the past 3 months, or failure to thrive (clear deviation from previous growth trajectory, or documented crossing of percentile lines in the preceding 3 months, or WFA Z-score of −2 or less, or weight-for-height Z-score of −2 or less in the absence of information on previous or recent growth trajectory), or MUAC ≤125mm in children between 6 months and 5 years old.

### TB exposure

Close or household contact in the 12 months prior to assessment.

**Close contact:**A person who does not live in the household but who shared an enclosed space, such as a social gathering place, workplace or facility, with the index patient for extended periods during the day during the 3 months before the current disease episode commenced (8).

**Household contact:** A person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index patient during the 3 months before the start of current treatment (8).

# Investigational plan

The study is expected to be collecting data for approximately 9 months. Enrolment will be open for 6 months followed by reference standard assessments up to 2 months after cohort closure.

## Participant enrolment and timeline

Children who meet the inclusion criteria and whose caregivers provide consent will be enrolled in the study as they present to study sites during the study period (see 17.3 for a detailed description).

Children presenting with presumptive TB (defined in 1.3.1) will be screened according to the study inclusion and exclusion criteria. Written informed consent will be obtained from the caregiver before any study-specific procedures are performed.

Once the child has been found eligible, health staff will initiate the assessment based on the treatment decision algorithm being studied at the site. Caregivers will be asked for contact details for study staff to contact them if they fail to bring their child for assessment and to facilitate follow-up where treatment is not initiated.

Children and caregivers who decline participation in the study or who are not eligible will receive routine assessment and care with no negative consequences.

Six months after study initiation, all healthcare workers involved with the study will be asked to complete the semi-structured questionnaire designed to evaluate algorithm acceptance.

If investigators choose to invite a sample of healthcare workers to complete the semi-structured questionnaire, the method of sampling and a short justification should be included.

## Screening and examinations

If investigators plan to compare study TDAs with algorithms that have already been implemented at study sites, sufficient information must be collected from each child to allow comparison of all proposed algorithms.

Included children will be assessed according to the treatment-decision algorithm being studied at each site (Annex 2). As part of the study process, the information listed below will be collected from each child:

1. Demographic characteristics, medical history and TB exposure will be recorded.
2. Clinical evaluation will include:
   * Height, weight and mid-upper arm circumference (MUAC)
   * Temperature
   * Clinical examination
3. X-ray evaluation, including:
   * Presence of cavities
   * Presence of enlarged lymph nodes
   * Presence of opacities
   * Miliary pattern of lung opacification
   * Presence of pleural effusion
4. Laboratory testing, including:
   * History of HIV exposure and age-appropriate HIV counselling and testing
5. Bacteriological tests, including:
   * Respiratory specimen mWRD result, if available
   * Respiratory specimen culture, if available
   * Urine specimen LF-LAM result, if available
   * Respiratory specimen microscopy smear (x2), if available

X-ray evaluation will follow the routine process at each study site.

## Follow-up during assessment

During the TDA assessment, participants may be required to return to the study site for further evaluation, for example after the treatment of non-TB conditions. As part of the study data collection process, the date and time of key events will be recorded to help evaluate the feasibility of algorithm implementation.

Where this is required, participants and their caregiver will be given a date to return to the study site by healthcare staff. They will be advised to return earlier if symptoms worsen.

If participants fail to attend within 3 days of their return date, site staff will telephone their caregiver twice during the following 3 days to encourage them to return. If they fail to attend within 6 weeks of their return date, lost to follow-up will be recorded as their study outcome.

To reduce the risk of loss to follow-up, site investigators may conduct home visits to evaluate children. Where this option is added, the ICF should be adjusted to include the possibility of a home visit, the need to record the child’s home address and any steps taken to limit the risk of causing stigma to the child or their family.

## Study exit assessment

All participants will be followed up as they exit the study. This will occur 2 months after completion of the initial TDA assessment. Attendance between 6 weeks and 3 months after initial algorithm assessment will be accepted. During the study exit assessment, study staff will apply the criteria set out in the reference standard (Annex 1) to allocate a study outcome. Additionally, the endpoint review committee will evaluate cases where a child has died or where the TDA recommendation was different to the health staff treatment decision.

The need for a 2-month follow-up appointment, regardless of the treatment decision taken, will be explained to caregivers on study entry. They will be reminded of this appointment by healthcare staff when the treatment decision for their child is taken.

Investigators should describe any approaches used to reduce the risk of participants failing to attend the 2-month follow-up appointment.

Where participants and caregivers are unable to attend 2-month follow-up assessments in-person, healthcare staff may complete the data collection form through a telephone consultation. Funds (transportation cost) can be provided for the participants and the caregiver for the 2-month return visit.

## Measuring indirect impact

TB case notification data for children and adults at each study site for the preceding 24 months will be retrospectively collected from site registers. Similar notification data will be prospectively collected from site registers for a period of 12 months (Figure 2). The corresponding calendar months during study implementation will be compared to the mean of the previous two years.

Diagram

Description automatically generated

Figure 2. Periods of notification data collection prior to and after study initiation

# Study monitoring

As part of a quality control system, monitoring visits should be conducted to verify that the study is conducted in accordance with the protocol and principles of good clinical practice. On-site routine monitoring visits should be conducted throughout the process of a research study. These visits can be conducted either by external monitors to benefit from assessment by someone who is not involved in the research project, or by internal monitors/supervisors as part of internal quality control procedures.

In this section, investigators should describe the quality control system that will be put in place. Only critical procedures (such as the informed consent process) and critical data (such as the status of the study participants) will be checked in priority during these visits. A monitoring package will be provided to guide the study team.

# Data collection and management

Standardised data collection forms will be used. Baseline participant characteristics will be recorded immediately after informed consent has been provided. Results from each step of the treatment decision algorithm will be recorded while the child is being assessed. Final scores generated following the full assessment will be recorded by study staff when all results are available. Results of laboratory tests will be retrieved from the processing laboratory by study staff. Participants will return for assessment 2 months after their initial evaluation to define their true final diagnosis. Study staff will record final conclusions on dedicated data collection forms.

All hard copies of data will be securely stored, and all computerised information will be password protected. Study data will be pseudo-anonymised through assignment of unique identification keys.

Describe the data flow i.e., where data is generated, how study data will be recorded by study staff members then transcribed to the study database. For example, data may initially be recorded on paper data collection forms before being entered electronically into a secure database.

Describe where physical and any electronic data records will be stored and how they will be managed. Only data relevant to this study will be recorded. If necessary, merging of data for statistical analysis will be conducted using statistical software. Backups of data will be generated regularly and stored by the study data entry supervisor and the primary investigator. Access to study data will be restricted to investigators involved in data management and analysis. Following study completion, all consent forms and other data will be retained according to local record retention policies.

# Data analysis

## Sample size

The primary analysis will estimate the performance of the diagnostic algorithm in children under 10 with presumptive pulmonary TB. The sample size scenarios in Table 1 are based on the true sensitivity of the diagnostic algorithm since minimising the risk of false negative results is a priority. The estimated sample size is highly dependent on the prevalence of TB amongst the study population which is likely to vary by context.

Where the prevalence of pulmonary TB amongst eligible children is not known, the pre-study sample size could be calculated based on an estimate, then recalculated after outcomes have been assigned to all children included during the first month of the study.

Table 1 includes a range of study sample sizes based on assumptions about the sensitivity of the algorithm and the prevalence of TB amongst included children. A larger number of permutations are presented in Annex 9.

| Sensitivity | Prevalence | Precision | alpha | Subjects |
| --- | --- | --- | --- | --- |
| 0.7 | 0.05 | 0.1 | 0.05 | 1,699 |
| 0.8 | 0.05 | 0.1 | 0.05 | 1,294 |
| 0.9 | 0.05 | 0.1 | 0.05 | 728 |
| 0.7 | 0.06 | 0.1 | 0.05 | 1,416 |
| 0.8 | 0.06 | 0.1 | 0.05 | 1,079 |
| 0.9 | 0.06 | 0.1 | 0.05 | 607 |
| 0.7 | 0.07 | 0.1 | 0.05 | 1,214 |
| 0.8 | 0.07 | 0.1 | 0.05 | 925 |
| 0.9 | 0.07 | 0.1 | 0.05 | 520 |
| 0.7 | 0.08 | 0.1 | 0.05 | 1,062 |
| 0.8 | 0.08 | 0.1 | 0.05 | 809 |
| 0.9 | 0.08 | 0.1 | 0.05 | 455 |
| 0.7 | 0.09 | 0.1 | 0.05 | 944 |
| 0.8 | 0.09 | 0.1 | 0.05 | 719 |
| 0.9 | 0.09 | 0.1 | 0.05 | 405 |

Table 1 Sample size estimates based on assumed 5% loss to follow up, and presented algorithm sensitivity, TB prevalence amongst include participants, accuracy of sensitivity estimate and alpha.

## Statistical analysis

If investigators propose to compare study TDAs with those already implemented at study sites, additional information about the proposed analysis should be included. More advanced techniques to adjust for confounding may be added by investigators.

### Per protocol (PP) study population

For the performance evaluation of the algorithm, children with any of the following reference standard outcomes AND any of the TDA outcomes will be included:

**Reference standard outcomes**

“*Confirmed tuberculosis”,*

*“Unconfirmed tuberculosis”,*

*“Unlikely tuberculosis”*

**TDA outcomes**

“*Initiate TB treatment*”,

“*Do not initiate TB treatment*”,

“*Treated successfully for non-TB condition(s)*”

See 11.2 and 11.3 for Endpoint Definitions. The TDA outcome groups “*Do not initiate TB treatment*” and “*Treated* *successfully for non-TB condition(s)*” will be combined to represent the TDA recommendation to not start TB treatment.

### Modified intention to treat (MITT) study population

A modified intention-to-treat analysis will include the PP cohort and any child with a reference standard outcome of “*Unclassifiable*”. For the MITT analysis children with “*Unclassifiable*” reference standard outcomes will be categorized as “*Unconfirmed tuberculosis*” to yield conservative estimates of TDA diagnostic performance.

For both study populations, sensitivity, specificity, negative predictive value, and positive predictive value will be calculated by defining true or false positive and true or false negative against reference definition for pulmonary TB in children (Annex 1) (7). Definitions for true positives and true negatives are provided in 11.3.

The proportion and reason for unreportable outcomes will be described.

Data from the healthcare worker semi-structured questionnaire (Annex 6) will be stratified by participant role, site health care level and the number of children assessed with the algorithm.

Algorithm feasibility will be reported from data collected through semi-structured questionnaires completed by healthcare workers and process variables recording the number of children appropriately assessed at relevant steps in each algorithm. Appropriateness and acceptability will be described from questionnaire data. Focus group discussions may be arranged by site investigators where open questions within the questionnaire reveal additional topics that require further exploration.

Distribution of continuous variables will be assessed for normality, and where this is present, will be described using means and standard deviation. Medians and interquartile ranges will be used if not normally distributed. Categorical variables will be summarised as counts and percentages. Comparisons of categorical variables across groups will use Chi-squared or Fisher’s exact test. Comparisons of continuous variables across groups will use the t-test or Wilcoxon rank sum test depending on data distribution. All estimates will be presented with respective 95% confidence intervals. Concordance between diagnostic methods will be evaluated with McNemar’s test and Receiver Operating Characteristic (ROC) curve analysis.

The TB notification rate by month or trimester at each study site and aggregated across the study will be stratified by age-group (0-4, 5-9, 10-14 and over 15 years), sex, HIV status, SAM status and healthcare level. A TB rate trend analysis before and during the intervention will be performed. The association between monthly pre-study notification rates and corresponding monthly notification rates after study initiation will be reported as a rate ratio with 95% confidence intervals.

Statistical analyses will be performed using standard statistical software such as Stata 14 (Stata Corporation, College Station, Texas, USA) or R (R Foundation for Statistical Computing, Vienna, Austria).

## Missing outcome data

Assessments which are given the outcome “*Transferred out due to presence of danger signs*” (see Endpoint Definitions 11.2) will be excluded from the performance evaluation of the algorithm.

The number of children with missing algorithm and/or the reference standard outcome “*Unclassifiable*” will be described using numbers and proportions. Investigators may minimise missing data by using telephone consultations to establish outcome information for children.

In the MITT analysis, “*Unclassifiable*” reference standard outcomes will be replaced with “*Unconfirmed tuberculosis*” for all children with valid TDA outcomes except “*Transferred out due to presence of danger signs*”.

# Ethical considerations

## Ethical approval

In this section, investigators should describe the ethical approval process for their context. This may include a summary of local, national and international ethical approval committees. Efforts to gather input from civil society, members of affected communities and, where present, community advisory boards should be described. Reference can be made to approval of the master protocol template by the research Ethics Review Committee of the WHO. Confidentiality

The protection of patient confidentiality is essential. The study will follow the principles of the 2018 Declaration of Helsinki. No child may be enrolled into this study until written informed consent has been provided.

The patient file that will be used to input data into the Case Report Form (CRF) will be kept in a secure place at the study site. The CRF does not include a name and other data from which an individual can be identified. Instead, a patient number will be generated based on e.g. the TB register number and the study site identification code, year of diagnosis etc. This will be used to facilitate linkage back to the register and medical records in case that is needed for quality control, validation of data or a collection of treatment outcome data for study participants. Only authorised study staff will have access to the patient file. All study staff will be trained in principles of Good Clinical Practice before the study commences.

## Informed consent

Caregivers of children who are eligible for inclusion in the study will be given information about TB and how it is diagnosed. Information will be provided in a language they can read or read to them by a study team member if requested.

Caregivers should have the opportunity to seek additional information about the study from the medical officer or treatment supporter. The decision to participate in the study will not affect the quality of care they receive.

Written consent from the caregiver will be sought (see Annex 3 for ICF). Where the caregiver cannot sign, a thumb print in the presence of a witness will be accepted. Consent will be sought by a dedicated study team member who has been trained to be able to explain the study and document the outcome of the consent process in the informed consent form. This person will not be involved in the child’s diagnostic process.

Children who are ineligible for participation or who subsequently withdraw, will be managed according to national guidelines with no negative consequences for their ongoing care.

## Assent

The process of gaining assent from children involved in research can be vary in different settings. Investigators should review this section and adjust to ensure that local norms, recommendations and guidelines are followed.

Assent should be sought from children over 7 years old or younger children who are expected to understand the implications of participating in this study. It represents the child’s affirmative agreement to participate and involves the sharing of information from the study team through a scripted discussion (Annex 8) and an assent form which may be signed by the child (Annex 7). The assent process will be facilitated by a sufficiently trained study team member.

Children should not be included in the study where a caregiver provides informed consent but the child refuses to participate.

# Data ownership and results dissemination

In this section, investigators should describe who owns data created by the study and how findings from the study will be disseminated (e.g. through technical reports, scientific publications, presentations), fed back to the participating communities, and shared with national health authorities, the larger scientific community and the larger affected community with the aim to influence and improve TB case finding in children at the country level and globally.

# Study budget

In this section, investigators should provide an overall budget for the study and indicate the funding source. An indicative budget will be provided.

Provision should be made for the following activities:

* + Ethical submission,
  + Salary for a study coordinator who will be responsible for day-to-day activities,
  + Salary for a study focal person for each site who will supervise study conduct,
  + Salary for
    1. Data entry - depending on the data flow, entry could be performed in each study site or data collected on paper with centralised electronic data entry,
    2. Data management (e.g., storage, backup, cleaning, reporting)
  + Salary for study supervision/internal monitoring,
  + Training of study sites,

This list is just indicative and not exhaustive. It needs to be adapted to the organisation of the study in each country.

# References

1. WHO Consolidated Guidelines on Tuberculosis: Module 5 Management of tuberculosis and children and adolescents. Geneva, Switzerland: World Health Organization; 2022.

2. Gunasekera KS, Marcy O, Muñoz J, Lopez-Varela E, Sekadde MP, Franke MF, et al. Development of treatment-decision algorithms for children evaluated for pulmonary tuberculosis: an individual participant data meta-analysis. The Lancet Child & Adolescent Health. 2023.

3. WHO Operational Handbook on Tuberculosis: Module 5 Management of tuberculosis in children and adolescents. Geneva, Switzerland: World Health Organization; 2022.

4. Global Tuberculosis Report 2022. Geneva, Switzerland: World Health Organisation; 2022.

5. Ranasinghe L, Achar J, Groschel MI, Whittaker E, Dodd PJ, Seddon JA. Global impact of COVID-19 on childhood tuberculosis: an analysis of notification data. Lancet Glob Health. 2022;10(12):e1774-e81.

6. The Union’s Desk Guide for the diagnosis and management of TB in children. Paris, France: International Union Against Tuberculosis and Lung Disease; 2016.

7. Graham SM, Cuevas LE, Jean-Philippe P, Browning R, Casenghi M, Detjen AK, et al. Clinical Case Definitions for Classification of Intrathoracic Tuberculosis in Children: An Update. Clin Infect Dis. 2015;61Suppl 3:S179-87.

8. WHO Operational Handbook on Tuberculosis: Module 2 Screening. Geneva, Switzerland: World Health Organization; 2021.