Kerala HEALTH

Programmatic Management of Latent TB Infection among children & adolescents in Kerala

Implementation Plan

November 2020

Indian Academy of Paediatrics, Kerala Chapter & State TB Cell, Directorate of Health Services, National TB Elimination Program, Kerala

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Annexures

Definitions

Contact: is any individual who was exposed to a person with TB disease.

Contact investigation: is a systematic process for identifying previously undiagnosed people with TB disease and TB infection among the contacts of an index TB patient. Contact investigation consists of identification, clinical evaluation and/or testing and provision of appropriate anti-TB therapy (for people with confirmed TB) or TB preventive treatment (for those without TB disease).

Household contact: is a person who shared the same enclosed living space as the index patient for one or more nights or for frequent or extended daytime periods during the three months before the start of current treatment.

Index patient (index case) of TB: is the initially identified person of any age with new or recurrent TB in a specific household or other comparable setting in which others may have been exposed. An index patient is the person on whom a contact investigation is centred but is not necessarily the source.

Infant: is a child under one year (12 months) of age.

Latent tuberculosis infection (LTBI): is a state of persistent immune response to stimulation by M. tuberculosis antigens with no evidence of clinically manifest TB disease. There is no gold standard test for direct identification of M. tuberculosis infection in humans. Most infected people have no signs or symptoms of TB but are at risk for active TB disease.

TB preventive treatment: Treatment offered to individuals who are considered to be at risk of developing TB disease, in order to reduce that risk. Also referred to as treatment of LTBI.

Tuberculosis (TB): is the disease that occurs in someone infected with M. tuberculosis. It is characterized by signs or symptoms of TB disease, or both, and is distinct from TB infection, which occurs without signs or symptoms of TB. In this document, it is commonly referred to as “active” TB or TB “disease” to distinguish it from LTBI or TB infection.

Abbreviation

CLHIV	Children Living with Human Immunodeficiency Virus
CXR	Chest X-ray
EP TB	Extra Pulmonary Tuberculosis
FDC	Fixed Dose Combinations
HIV	Human Immuno Deficiency Virus
IGRA	Interferon-Gamma Release Assay
INH	Isoniazid
LTBI	Latent TB Infection
MDR-TB	Multidrug-resistant tuberculosis
PHC	Primary Health Centre
PHI	Peripheral Health Institution
STEPS	System for TB Elimination in Private Sector
TPT	TB Preventive Therapy
TST	Tuberculin Skin Test
TB	Tuberculosis

Background

With a good track record of social development indicators, especially in health and education sectors, Kerala is witnessing a demographic transition with a rise in the proportion of aged in the total population along with declining growth rate. The decadal growth rate (4.83%) is much slower than that of the country (17.64%). Pathanamthitta and Idukki districts in Kerala report negative growth rate. Except one district, all districts in Kerala have a declining child population. The Sex Ratio of the State is favorable for women. Many of its social and health indicators such as an Infant Mortality Rate of 7/1000 live births are at par with developed nations. Key contributing factors to these outcomes are often attributed to its effective health care system, which has ensured high accessibility at low cost, and non-health sector contributions addressing social determinants of health such as widespread education, high literacy rate (male 96.11% and female 92.07%), social and land reforms, public distribution of food, development of road and housing conditions. Primary Health care services have been systematically organised in rural areas of the state. All primary health centers are manned by modern medicine practitioners. This ample network that extends to the grass root level must have contributed to less urban-rural disparity. Kerala is one among the states with lowest HIV transmission and has nearly eliminated mother to child transmission of HIV.

Notification of TB patients from public sector in Kerala state is steadily decreasing since 2009 at a rate of 3.5% per year and TB drug sale in open market (as a proxy of private notification) is declining at a rate of 10% per year. Public sector notification was 27500 in 2009 which has declined to 20992 in 2019. Age specific notification of TB patients in Kerala has shifted to the right showing significant decrease of disease burden in younger age groups. Average annual decline in paediatric TB notification is 7.5% from 2009 to 2019. Age specific TB notification among children <14 years is around 1 per one lakh

population. Paediatric anti TB drug sale had a steeper decline. Pharmaceuticals reported sale of kid formulations declined by 90% from 2006 to 2019. Less than 1% of all presumptive paediatric TB samples tested in CB NAAT turned out to be positive in the state. This decline is in the background of increased case finding efforts with laboratory investigations and diagnostic practices conforming to standards. The state tested 1448 TB symptomatic/100,000 population in 2019 with the help of highly sensitive rapid molecular diagnostic tools like CBNAAT against 888/100,000 in 2009. A study done in 2006 showed that estimated Annual Risk of TB Infection (0.4) is only 1/5th of that of the national estimates (1.5). Proportion of TB patients with MDRTB is comparatively lower in Kerala. Among new TB patients Rifampicin resistance is less than 1% and among previously treated it is around 3.5%. Reported recurrence is less than 5% and long term follow up confirms low recurrence. Private sector follows a reasonable standards of TB care which is enhanced with System for TB Elimination in Private Sector (STEPS).

Government of Kerala has launched "Kerala TB elimination mission" aligning with the Sustainable Development Goals, with objectives to achieve TB Elimination by 2025, zero deaths due to tuberculosis in the state by the year 2020 and zero catastrophic expenditure for the families of tuberculosis patients. National Strategic Plan for TB Elimination in India was customised based on the local epidemiology of the state. The state aims to eliminate TB first among the children. The state has adopted the policy for offering upfront molecular tests for diagnosis of pulmonary TB and is moving to offer upfront molecular tests by December 1, 2020 onwards.

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest active TB. From the pool of infected but

asymptomatic persons, most cases of tuberculosis (TB) will arise. On average, 5–10% of those infected will develop active TB disease over the course of their lives, usually within the first 5 years after initial infection. The risk for active TB disease after infection depends on several factors, the most important being immunological status. The risk of developing TB disease after TB preventive therapy decreases 90% from 11.1% for those not taking LTBI treatment to 1.2% for those taken the same. Effective implementation of TB preventive therapy alone would result in a decline in annual TB incidence of 12%, independent of other background interventions.

There is no evidence of association between development of drug resistance and preventive therapy. Preventive therapy is administered to children without active disease, minimizing the risk of adverse reactions. Thus, risk for progression to active disease significantly exceeds the possible harm of preventive therapy in the contacts of TB.

Prevention of active TB disease by treatment of LTBI is a critical component of the WHO End TB Strategy. Rigorous, expansive and accountable “TB contact tracing investigation” for secondary TB case detection and treatment coupled with active screening for TB among the high-risk groups and “LTBI Management” is one of the key activities under the “Prevent” component of the National Strategic Plan 2017-25 for TB Elimination by 2025. Kerala state plans to launch programmatic management of Latent TB Infection & Management and plan to implement it first among children.

Principle

1. ‘Cascade of Care’ approach shall be followed while implementing programmatic management of LTBI among children and adolescents in Kerala.

   It is important that all children at-risk of developing TB are systematically reached out, screened, TB disease ruled out and provided continuum of care for LTBI Management.

2. Kerala with a lower incidence of paediatric TB & LTBI, it is suggested to have a ‘Test & Treat’ approach for management of LTBI.

Who all are Eligible?

- Children < 5 years who are household contacts of microbiologically confirmed pulmonary TB may continue to be given TB Preventive Therapy (TPT), after ruling out active TB, according to the current national guidelines.
- A child born to mother who was diagnosed to have TB in pregnancy should receive TPT, provided congenital TB has been ruled out.
- Children and adolescents (5-15 years) who are household contacts of microbiologically confirmed pulmonary TB, should be systematically tested for LTBI. If found to have LTBI, they shall be offered treatment for the same, after ruling out active TB.
- Children and adolescents (12 months -15 years) living with HIV should be given TPT after ruling out TB. (History of Contact Not necessary)
- CLHIV <12 months should also be given TPT if they are contact of a pulmonary TB, after ruling out active TB.
- Children & adolescents (< 15 years) planned to be initiated on anti-TNF treatment, receiving dialysis, preparing for an organ or haematological transplant, on immunosuppressive drugs for a longer duration (like >2mg/kg oral steroids for >2 weeks) (eg. nephrotic syndrome, acute leukemia, systemic inflammatory conditions) should be systematically tested for LTBI. If found to have LTBI, they shall be offered treatment for the same, after ruling out active TB. (History of contact Not Necessary)
- Apart from these categories, children and adolescents (< 15 years) on any chronic immunosuppressive conditions, as decided by the paediatrician, shall be tested & treated for LTBI.

Identification of Eligible Children

- For programmatic management and monitoring, children and adolescent (5-15 years) who are household contacts of all microbiologically confirmed pulmonary TB patients notified after 1st November 2020 shall be considered as eligible. Those children and adolescents shall be enumerated during household contact tracing of all microbiologically confirmed pulmonary TB cases by the primary health care team.

- Children presenting to peripheral health institutions/ clinics/ hospitals after November 1, 2020 shall be assessed for clinical eligibility to test for LTBI

Testing for LTBI

- LTBI testing is **not** a requirement for initiating TB preventive treatment for household contacts aged < 5 years and children and adolescents living with HIV. This decision will be reconsidered based on experiences with 'test and treat' among other eligible children.

- For all other eligible children and adolescents, Interferon-Gamma Release Assay (IGRA) shall be used for diagnosis of LTBI. IGRAs provide an *invitro* measure of Mtb hypersensitivity. Unlike Skin Test, this test can be done in the same sitting, does not cross react with BCG vaccination but is expensive. IGRA with commercial cut offs made available by the NTEP program, Kerala shall be used for testing children for the diagnosis of LTBI. Details of IGRA testing, SOP for sample collection, transportation and testing have been attached as annexure 1.

- Standardised Mantoux's tests or PPD in recommended strength of 2TU PPD RT23 is not available. Due to non-availability of any form of original RT23 PPD, un-standardized TST is often used in practice, which can cause problems in reading of test results as the cut-offs for these are not known. Currently available Mantoux's test shall be used with careful understanding of the test and ensuring correct technique (Annexure II) only in absence of free availability of IGRA tests or for children under 5 years when clinically indicated.

- Newer more specific C-Tb skin test from SSI, Copenhagen is not yet available commercially. Once such tests are available, the recommendations shall be reconsidered.

Ruling Out Active TB disease

Active TB to be ruled out in any children/adolescents before initiating LTBI treatment.

- Apart from history and clinical examination, Chest X-ray shall be taken for ruling out active TB. If CXR shows any abnormality, the child shall be further evaluated for TB according to the national guideline.

- Clinical examination for lymph nodes and through history for signs and symptoms of EP TB shall be done.

- A clinical committee shall be constituted at district level to take decisions regarding doubtful cases.

Treatment for LTBI

- All eligible children and adolescents (< 15 years) who were diagnosed to have LTBI, shall be provided treatment with a 3 months daily dose of Isoniazid plus Rifampicin, after ruling out active TB.

- Isoniazid plus Rifampicin was considered in view of comparatively lower risk of adverse effects compared to longer duration of INH alone regimen, chance of greater adherence due to shorter duration, familiarity of use for paediatricians, availability of child-friendly, fixed-dose combinations, safer to use in a setting with lower drug resistance to rifampicin and in place of adequate systems to rule out active TB.

- However, when INH plus Rifapentine regimen are available in the program, the current recommendations will be reconsidered. For PLHIV, INH for 6 months as per NACO-NTEP guidelines shall be continued for the time being.

- LTBI treatment regimens and dosages of drugs have been summarised in Table in page no.9

Treatment regimen for treatment for LTBI among eligible children and adolescents

Treatment Regimen	Dose
INH plus Rifampicin daily for 3 months	**Isoniazid** Age 10 years & older: 5 mg/kg/day Age <10 years: 10 mg/kg/day (range, 7–15 mg) **Rifampicin** Age 10 years & older: 10 mg/kg/day Age <10 years: 15 mg/kg/day (range, 10–20 mg)

Use of Rifampicin plus Isoniazid FDCs according to weight bands

Weight band	4–7 kg	8–11 kg	12–15 kg	16–24 kg	>25 kg
RH 75/50 mg (FDC)	1	2	3	4	Use adult formulations

Contacts of MDR TB

Close contacts of index cases with proven MDR-TB should be monitored closely for signs and symptoms of active TB. After a careful assessment of the intensity of exposure, certainty of the source case, reliable information on the drug resistance pattern of the source case and potential adverse events, an individualized preventive therapy shall be offered to high risk (e.g. children ≤ 5 years, people on immunosuppressive therapy and people living with HIV) household contacts of bacteriologically confirmed MDR cases, using drugs as per the drug sensitivity profile of index case. All such cases should be referred to district clinical committee and decision should be made by this committee. The regimen to be used shall be as per the recommendations of national TWG. Informed consent should be also taken from the parents before starting this.

Pyridoxine Supplementation

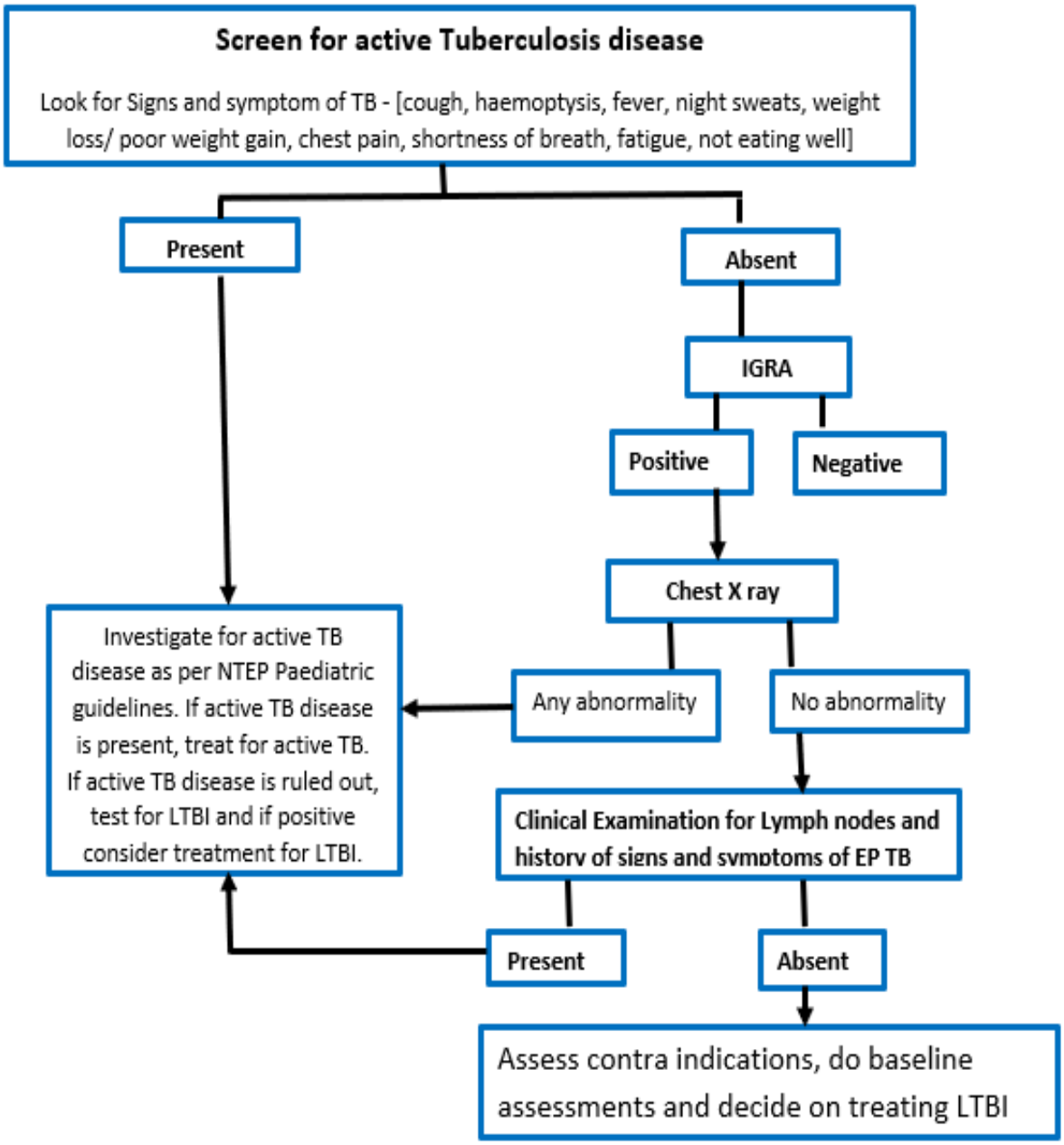
It is desirable to give pyridoxine supplementation to all children and adolescents on long duration INH therapy (> 3 months). Individuals at risk for peripheral neuropathy, such as those with malnutrition, HIV infection, renal failure or diabetes, should receive vitamin B6 supplements when taking isoniazid-containing regimen. Additionally, exclusively breastfed infants should receive vitamin B6 while taking isoniazid. The standard dose of pyridoxine when used prophylactically for prevention of neuropathy among patients taking isoniazid is 10–25 mg/day.

Contraindications for TPT

Contacts of Multi Drug Resistance TB may be given individualised preventive treatment as per the drug sensitivity profile of index case as decided by the district paediatric clinical committee with a regimen approved by National TWG on PMLTBI.

Active hepatitis (acute or chronic) and symptoms of peripheral neuropathy should prompt detailed investigations and application of clinical judgement to weigh harms versus the benefits of LTBI management.

Diagnostic Algorithm for diagnosis and treatment of LTBI among HIV negative eligible children and adolescents aged 5-15 years.



Baseline Assessment

At base line assess for the following to guide decision making

- History of drug allergy, other medications
- Contact with DRTB
- Potential contra indications to LTBI drugs
- Assessment of co-morbidity
- Assessment of social and financial situation of the family to arrange essential support in co-ordination with primary health care system
- Treatment supporter: Assess if a treatment supporter outside family is needed. If required it shall be arranged in coordination with primary health care team
- Testing of Liver Enzymes at baseline to be done.

Initial Counselling

Counsel the family regarding the following before initiation of LTBI management

- Rationale for LTBI management and benefits to the individual, the household and the community
- LTBI management is available free of charge through national programmes
- LTBI management regimen prescribed, including the duration, directions for intake of medicines and follow-up schedule
- Potential side effects and adverse events involved and what to do in the event of various side effects
- The importance of completing the full course of LTBI MANAGEMENT
- Reasons and schedule of regular clinical and laboratory follow-up for treatment monitoring
- Signs and symptoms of TB and advise on steps if they develop TB.

Adverse Events Monitoring, Adherence and completion of preventive treatment

Adherence to the LTBI therapy is of paramount importance and completion of the entire course leads to clinical benefit, both at individual and population levels. Irregular or inadequate treatment reduces the protective efficacy of LTBI regimen and further increase the risk of the individual developing active TB disease including drug-resistant TB. Efficacy of LTBI Management is greatest if at least 80% of the doses are taken within the duration of the regimen. Total number of doses taken is a key determinant of the extent of TB prevention

- Children on LTBI regimen shall be followed up through primary health care system in public sector or through STEPS model in the private sector.

- Treatment shall be under supervision. A treatment supporter from family is preferred. If family is identified to require external support on assessment, a treatment supporter form community shall be arranged.

- Treatment Supporter shall look for adverse events and monitor adherence daily.

- Primary Health Care team assesses the need for family. The family may be linked to the 'Treatment Support Groups' by the primary health care team if the family requires any assistance or support for completing the treatment.

- The Treatment Supporter needs to mark ✓ against each dose in the LTBI treatment card.

- The LTBI treatment card shall be reviewed every week by the primary health care team and update the information in LTBI application.

- Retrieval actions shall be taken by the primary health care team if a treatment interruption occurs.

- Child/adolescent on LTBI treatment shall be seen by a Medical Officer at least once in a month and look for the following
    - Signs and symptoms of TB disease
    - Adverse reactions especially symptoms and signs of hepatitis
    - Adherence to the prescribed regimen. Elicit reasons for any missed dose and extend necessary support to enable future adherence to LTBI management.

- Any adverse drug reactions shall be recorded in treatment card. Adverse events also need to be reported through pharmacovigilance program of India.

- Family where children on LTBI management need to contact health care worker/provider/ treatment supporter if they notice adverse events, such as anorexia, nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, dark-coloured urine, pale stools or jaundice. These are suggestive of liver injury and require urgent evaluation under the Medical Officer. Relevant investigations need to be done as clinically indicated.

Flow of events for HIV negative Children & Adolescents (5.15 years) for LTBI Management

Identification of all eligible children

- **Household Contacts**: Primary Health Care team enumerate all eligible children during Contact Tracing of all notified Pulmonary TB cases and refer those who are eligible to PHIs.
- **Children and adolescents fitting in to clinical criteria**: Clinicians identifies eligible children meeting the clinical criteria

Testing for LTBI

- Clinician at PHI decides on testing for LTBI if found eligible for testing based on diagnostic algorithm.
- Lab technician collects samples and do arrangemennts for transportation through specimen collection transportation systems in close co-ordination with Testing Lab
- Testing Laboratory performs tests as per SOP
- If found to have LTBI, child shall be referred to a pediatrician

Rule Out Active TB

- If a child /adolescent is diagnosed with LTBI, Pediatrician to rule out TB based on Chest Xray and clinical examination as per the guidelines.
- Pediatricians assess for any contra indications and decide on initiating treatment for LTBI.

Baseline Assessment & Counselling

- Pediatrician to do baseline assessment and initial counselling
- Refer the clhild to PHI/STEPS for initiation of LTBI treatment

Initiation of LTBI treatment

- Medical Officer of PHI initiates the child/adolescents on LTBI regimen
- Treatment Supportor shall be arranged in consultation with the family
- Initial counselling to be arranged by the Medical Officer of PHI

Adverse Events Monitoring and Ensuring treatment adherence

- Primary Health Care System to follow up the child to look for any adverse events and to ensure treatment adherence
- PHC team to co-ordinate with the Treatment Supportor to pick up any adverse events and treatment interruption timely for appropriate actions..

Monthly Clinical Follow up

- Children and adolescents on LTBI treatment shall be seen monthly by a clinician

Declaring Treatment Outcome

- Medical Officer of PHI declares treatment outcome

Long Term Follow Up

- All children and adolescents who completed LTBI treatment to be followed up every quarter by the primary health care team for five years to look for any active TB symptoms.

Treatment outcomes

● **Treatment completion**

– A child/adolescent initiated on LTBI management who completed at least

- 80% of recommended dose (68/84) consumed within 120% of planned LTBI MANAGEMENT duration (100 days) for 3HR

● **Died** – A person initiated on LTBI Management who died for any reason while on LTBI Management course.

● **Lost to follow-up** – LTBI Management interrupted by person for four consecutive weeks or more for 3HR.

● **LTBI Management discontinuation due to toxicity** – A person whose LTBI MANAGEMENT is discontinued by clinician due to adverse events or drug or drug interactions, without completing the treatment.

- **LTBI management discontinuation due to development of active TB** – A person initiated on LTBI Management who developed TB disease any time while on LTBI Management course.

● **Not evaluated** – such as records lost, transfer to another health facility without record of LTBI MANAGEMENT completion.

Long Term Follow Up

All children and adolescents who are household contacts of pulmonary TB shall be followed up every quarter by the primary health care team looking for development of active symptoms of TB.

The same vigil shall continue for all children and adolescents who were diagnosed with LTBI even after those who completed treatment.

If any child initiated on LTBI, later develops TB, tests for detecting resistance to INH and Rifampicin shall be offered at baseline if a biological specimen is available.

Monitoring Indicators

	Household Contacts	Eligible based on clinical criteria
A. Total Eligible children & adolescents (5-15 years) identified		
B. Out of (A), No. (%) tested for LTBI infection		
C. Out of (B), Proportion diagnosed to have LTBI		
D. Out of (C), Proportion eligible for TB preventive treatment		
E. Out of (D), proportion initiated on treatment		
F. Out of (E), proportion completed the course		

Monitoring Indicators for TPT among children < 5 years

a) Proportion of children < 5 years who are household contacts of pulmonary TB cases who have been initiated in TB preventive therapy

b) Proportion of children < 5 years who are household contacts of pulmonary TB cases who have completed a course of TB preventive treatment

Monitoring Indicators for TPT among CLHIV

c) Proportion of eligible children and adolescents living with HIV who were started on TB preventive Treatment

d) Proportion of eligible children and adolescents with HIV who completed a course of TPT.

Recording & Reporting

- Test Request shall be through IGRA test request form (Annexure 4.1). Laboratories need to maintain IGRA Lab register (Annexure 4.2)

- If the child/adolescent is diagnosed to have LTBI, clearly document it as LTBI in all the medical records for all eligible children.

- Information Management on LTBI shall be in a separate LTBI application linked to NIKSHAY, the current TB Management Information System.

- The provisions for enlisting all contacts and records of tracing and testing household contacts shall be maintained using a Contact Tracing Register (Annexure 4.3)

- There shall be a 2 physical LTBI record (Annexure 4.4) for every 'child & adolescent' tested positive for LTBI. One need to be kept with Treatment supporter and the second one at the treating facility. The card at treatment facility shall be updated monthly after following up the child/adolescents.

- On declaration of outcomes, the LTBI treatment card shall be collected and maintained at TU by STS.

- If any child/adolescent has interrupted the treatment, retrieval actions shall be taken and documented by the local primary health care team.

- LTBI treatment register (Annexure 4.5) & Contact Tracing Register to be maintained at TU level by STS.

- STS consolidate the quarterly report for TU.

- Consolidation happens through routine NTEP mechanisms.

District level Paediatric TB Clinical Expert Committee

A district level Pediatric TB Clinical Expert Committee shall be constituted with 5 members in each district. The committee shall consist of paediatricians form Medical Colleges, Health Services and Private Sector.

State IAP shall nominate members for the committee in every district. District Medical Officer (H) of the concerned district shall finalise the list and issue orders. Chair/ Vice Chair of the committees shall be nominated.

Consultant Pulmonologist at District TB Centre shall be the convenor for the committee.

Roles of the committee

1. To help clinicians to arrive at a final decision in any clinical dilemma related to pediatric TB or LTBI management.
2. To make decision on initiating individualised preventive treatment for contacts of resistant TB.
3. To oversee the practices regarding pediatric TB management in the district through a peer audit system and give recommendations for improving the standards of care
4. To oversee and suggest recommendations to the district authorities related to program implementation for ensuring that every child receive the TB services as envisioned.

Frequency of Meeting

Meeting could be in online platforms at a frequency of once in month or as and when required. At least 3 members are required for a quorum.

Process

- Any queries related to decision making shall be referred to the committee by any modern medicine doctors formally to Chair/ Convenor with detailed and sufficient clinical records. Committee shall give their clinical opinion in a documented manner.
- Apart from this, committee will do peer audit of at least 2 paediatric TB / LTBI on every sitting (based on Right Diagnosis/Right Drugs/ Right Dose/ Right Duration/ Right Frequency) in comparison to standards set by IAP/NTEP and give feedback to treating clinician. The entire exercise is purely a measure for quality and standards improvement.
- The committee shall give feedback to the district authorities periodically regarding measures to be taken to improve the program in the district.

Run in period for streamlining the process

The service delivery will be starting from Nov 1, 2020 onwards. However, since this is a new program, logistic challenges are expected. There might be delay in supply of FDC combination for children with weight >25kg. Public laboratories are performing IGRA for first time. Specimen collection and transportation systems need to be customised for blood sample collections. It may take a few days to streamline the services. As the COVID pandemic is at its peak, delays are expected. First two months shall be considered as a run-in period to streamline the entire process. TWG shall meet after one month of implementation and suggest mid-course corrections if any.

Evidence Generation & Documentation of Implementation

Evidences need to be generated and entire process of implementation shall be documented.

IAP Kerala chapter & STDC shall jointly prepare an Operations Research protocol focussing on the following

- Prevalence of LTBI among children and adolescents 1) who are household contacts of pulmonary TB & 2) clinically vulnerable group
- Adverse events among children receiving LTBI treatment
- Facilitators & challenges during the entire process
- Follow up of all these children for 5 years and study development of active TB.

Annexure 1: SOP – IGRA Testing

PURPOSE

This SOP describes the step by step procedure to perform IGRA (Interferon Gamma Release Assay). It is an in vitro diagnostic aid for detection of Latent Mycobacterium tuberculosis Infection (LTBI) (including disease).

SCOPE:

This SOP will enable the lab team members to process IGRA by automated/ manual procedure in an efficient and safe manner.

ORGANISING THE IGRA tests

- IGRA testing shall be setup at 48 public laboratories (2-3 per district) across the state. Apart from this, 16 Private Laboratories will also be performing IGRA tests.

- NTEP has established specimen collection and transportation systems from every PHI to transport samples in a Hub & Spoke Model. From peripheral hospitals where IGRA laboratory is not co-located, blood sample for IGRA have to be collected in Lithium heparin blood collection tubes and transported through the specimen collection and transportation system on prefixed days so as to reach the laboratory within 16 hours of collection if stored at room temperature or within 48 hours if stored at 2-8^0 C.

- Laboratories will be performing IGRA only on specific days. These date and time shall be disseminated.

RESPONSIBILITY

Trained lab technicians will perform the test. Senior Technical Assistant will monitor the activities.

PROCEDURES:

A) SAMPLE COLLECTION

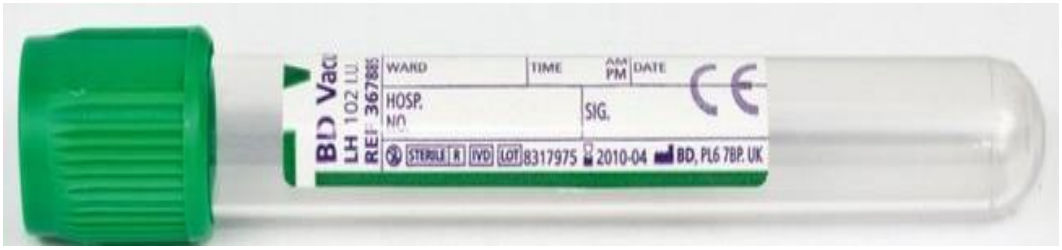
Procedure Requirements:

- Disposable gloves
- Alcohol swabs (isopropyl alcohol / spirit)
- Tourniquet
- Lithium Heparin Vacutainer specimen tubes
- Vacutainer holders
- Appropriate size sterile disposable needles
- Needle destroyer

- Cotton balls/swabs
- Container for sharps disposal
- 10% Hypochlorite Solution
- Marker

Procedure:

- Required amount of venous blood (5 ml) is collected using appropriate green cap lithium heparin Vacutainer as per predetermined patient schedule. Blood is mixed well to prevent clotting.



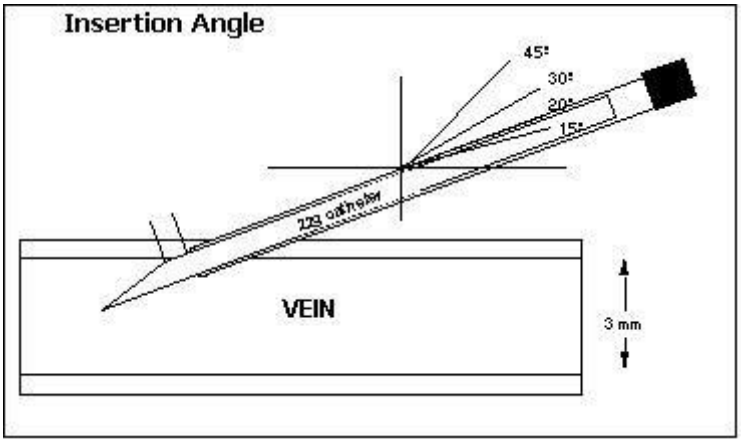
Pre procedural preparation:

- All the required materials for drawing blood are assembled before blood collection.
- Check whether the consent has been obtained prior to the blood draw from the participant.
- Be sure to verify the identity of the participant and registration number before labelling the tubes.
- Check the specific Lab requisition form to confirm the quantity of blood to be drawn and the kind of Vacutainer tubes to be used.
- Vacutainer tubes are labelled by patient identification number before sample collection.
- Do not prepare tubes for more than one subject at a time.
- Explain to the patient about the procedure and tell him/her to sit or lie down and feel comfortable. If it is a child, it is preferable to have the parent/guardian hold the child.
- The lab technician wears disposable gloves and uses aseptic technique during venepuncture.

- Seat ambulatory patients in a comfortable chair with the extremity from which blood will be drawn supported on a sturdy table or other support.

Steps of procedure:

- The preferred site for blood collection is the median ante-cubital vein. Veins on the dorsum of the hand and other forearm veins are possible alternative sites. A tourniquet may be used to transiently distend veins prior to drawing of blood. Do not leave the tourniquet for too long.



- Using the tip of the index finger, examine the blood collection site, feel the vein, and decide exactly where to place the puncture.
- Disinfect the blood collection site by cleansing the skin in small outward circles with an alcohol swab. Do not touch the prepared puncture site with your fingers after disinfecting the skin.
- New sterile, single use needles and Vacutainer tubes are to be used for each blood draw, and after completion, needles are properly disposed in a puncture resistant container.
- Insert the needle of the Vacutainer device into the vein. If possible, always allow the full amount of blood to be drawn into each tube when using the Vacutainer system tubes. After drawing the blood, invert the tubes several times to mix the blood with the additives.
- After drawing the required blood sample, release the tourniquet. Remove the needle from the vein, cover the puncture site with a cotton swab, and hold until adequate haemostasis is achieved.

B) PACKING AND SHIPPING OF BLOOD SAMPLE:

- Place a leak proof primary receptacle (Vacutainer® tube), in a leak proof secondary transport bag with a biohazard sign and seal. Ensure specimens are labelled in the same manner as sputum containers. Place a completed requisition in the unsealed pocket of the transport bag.
- Place blood tubes into the box in an upright position whenever possible. Always transport the specimen transport box (STB) in an upright position
- Draw into lithium-heparin tube and transport at 2–8°C with ice packs. Make sure that, the sample reaches designated laboratories within 16 hours of sample collection.

C) SAMPLE QUALIFICATION CRITERIA

1. Visually verify whether 5 ml blood is available
2. Sample should be free of clot
3. Sample tubes should be labelled properly
4. Sample should not be lipemic

D) TRANSFER BLOOD TO IGRA TUBES IN THE LABORATORY

1. Bring the tubes to room temperature prior to transfer into IGRA tubes.
2. Ensure that the blood is thoroughly mixed by gentle inversion.
3. Remove caps from the 4 IGRA tubes (4^{th} Generation kit) / 3 IGRA tubes (3^{rd} Generation kit) and dispense 1.0 ml aliquots into each tube.
4. Aliquot in order NIL– TUBE 1 – TUBE 2– MITOGEN (4^{Th} Generation kit) / NIL – TB ANTIGEN – MITOGEN (3^{rd} Generation kit)
5. Shake them ten (10) times just firmly enough to make sure the entire inner surface of the tube is coated with blood. This will dissolve antigens on tube walls or place the samples in the sample mixer for 10 minutes.

E) INCUBATION OF TUBES

Incubate IGRA tubes upright at 37°C ±1°C immediately after transfer of aliquots for 16-24 hours.

F) Post-incubation of blood collection tubes and harvesting of plasma

1. After incubation of the blood collection tubes at 37°C ± 1°C, tubes may be held between 4°C and 27°C for up to 3 days prior to centrifugation.

2. After incubation of the tubes at 37°C ± 1°C, harvesting of the plasma is facilitated by centrifuging tubes for 15 minutes at 2000 to 3000 RCF (g).

3. Plasma samples can be loaded directly from centrifuged blood collection tubes into the ELISA plate. Alternatively, plasma samples can be stored in centrifuged IGRA Blood Collection Tubes for up to 28 days at 2°C to 8°C. Or harvested plasma samples can be stored for up to 28 days at 2°C to 8°C. Harvested plasma samples can also be stored below –20°C (preferably less than –70°C) for extended periods. For adequate test samples, harvest at least 150 / 200 µl of plasma for 3rd Generation / 4Th Generation kit respectively.

G) PROCEDURE FOR ELISA

1. All plasma samples and reagents, except for Conjugate 100x Concentrate, must be brought to room temperature (22°C ± 5°C [71.6°F ± 9°F]) before use.
2. Allow at least 60 minutes for equilibration.
3. Remove ELISA plate strips that are not required from the frame, reseal in the foil pouch, and return to the refrigerator for storage until required.
4. Allow at least 1 strip for the IGRA standards and sufficient strips for the number of subjects being tested
5. After use, retain frame and lid for use with remaining strips.
6. Reconstitute the IFN-γ Standard with the volume of deionized or distilled water indicated on the label of the vial. Mix gently to minimize frothing and ensure that the entire content of the vial is completely dissolved.
7. Reconstitution of the IFN-γ standard to the correct volume will produce a solution with a concentration of 8.0 IU/ml.
8. Using the reconstituted standard, prepare a dilution series of 4 IFN-γ concentrations
9. Reconstitute lyophilized Conjugate 100x Concentrate with 0.3 ml of deionized or distilled water. Mix gently to minimize frothing and ensure that the entire content of the vial is completely dissolved. a) Working strength conjugate is prepared by diluting the required amount of reconstituted Conjugate 100x Concentrate in Green Diluent.

10. Working strength conjugate should be used within 6 hours of preparation.
11. Return any unused Conjugate 100x Concentrate to 2°C to 8°C immediately after use.
12. Dilute one part Wash Buffer 20X concentrate with 19 parts deionized water. This working strength wash buffer solution is stable for 2 weeks at room temperature.
13. For plasma samples harvested from blood collection tubes and subsequently stored (refrigerated or frozen), thoroughly mix the stored sample before addition to the ELISA well.
14. 50 µl of freshly prepared working strength conjugate is to be added to the required ELISA wells. This is followed by the addition of 50 µl of test plasma samples and 4 standards to their appropriate wells
15. Cover each plate with a lid and mix the conjugate and plasma samples/standards thoroughly using a microplate shaker for 1 minute.
16. Incubate the covered plate post mixing at room temperature away from direct sunlight for 120 ± 5 minutes.
17. Calculate the amount of working strength wash buffer required. Each well requires 400 µl * 6 cycles = 2.4 ml. Based on the number of wells dilute 1 part of wash buffer concentrate with 19 parts of deionized water to prepare the working strength was buffer. (Automated ELISA plate washer can also be used) Allow a soak period of atleast 5 seconds between each wash cycle.
18. Tap plates face down on absorbent, low-lint towel to remove residual wash buffer. Add 100 µl of Enzyme Substrate Solution to each well, cover each plate with a lid and mix thoroughly using a microplate shaker.
19. Cover the plate with a lid and incubate at room temperature (22°C ± 5°C) away from direct sunlight for 30 minutes.
20. Add 50 µl of stop solution to all wells. (Follow the same order and speed of addition as done for addition of substrate.)
21. Measure the Optical Density (OD) of each well within 5 minutes of stopping the reaction using a microplate reader fitted with a 450 nm filter and with a 620 nm to 650 nm reference filter. Document the OD values for calculation of results.

H) CALCULATIONS

QFT Analysis software can be used for analysis of raw data and calculation of results.

Alternatively, document the mean OD of the standard replicates on the plate. A standard curve is generated by plotting the mean OD on y axis and the corresponding IFN-γ

concentration of the standards in IU/ml (x-axis). Calculate the line of best fit for the standard curve by regression analysis.
Use this standard curve to determine the IFN-γ concentration (IU/ml) for each of the test plasma samples. Note: These calculations can be performed using software packages available with microplate readers, and standard spreadsheet or statistical software (such as Microsoft Excel®).

I) SAMPLE STORAGE

1. After incubation: Blood samples can be stored/transported for a max. of 3 days at 4°C – 27°C.
2. After incubation & centrifugation: Plasma samples can be stored up to 4 weeks at 4°C or, if harvested, below –20°C for extended periods IGRA kits are stored at 2-8 °C.

LIST OF IGRA TESTING LABORATORIES IN KERALA

SL NO	DISTRICTS	SITES
1	Alappuzha	DH Mavelikkara
2		THQH Chertala
3		TH Thuravur
4		TD Medical College
5		PH lab Alappuzha
6	Ernakulam	GH Muvathupuzha
7		GMC Kalamacherry
8		RPH Ernakulam
9	Idukki	THQH Adimali
10		DH Thodupuzha
11	Kannur	RPH lab Kannur
12		GMC Kannur
13		GH Thalassery
14	Kasaragod	GH Kasargod
15		DH Kanhangad
16		TH Panathady
17	Kollam	PH lab, Kollam
18		GMC kollam
19		THQH Punallur
20		Kottarakara
21		THQH Karunagapally
22	Kottayam	GH Kanjirapally
23		GH Kottayam
24		GH Pala
25		MCH Kottayam
26	Kozhikode	General Hospital Kozhikode

27		RPH lab Kozhikode
28		THQH Balussery
29		TH Perambra
30	Malappuram	PH Lab Malappuram
31		GMC Manjeri
32		DH Nilambur
33		DH Tirur
34		THQH Thirurangadi
35	Palakkad	DH Palakkad
36		GTSH Kottathara
37	Pathanamthitta	RPH lab, Pathanamthitta
38		THQH Thiruvalla
39		DH Kozhencherry
40	Thiruvananthapuram	CHC Vellanad
41		GH Neyyathinkara
42		THQH Chirayinkil
43	Thrissur	GMC Thrissur
44		THQH Chalakkudy
45	Wayanad	GH Kalpetta
46		PH Lab Bathery

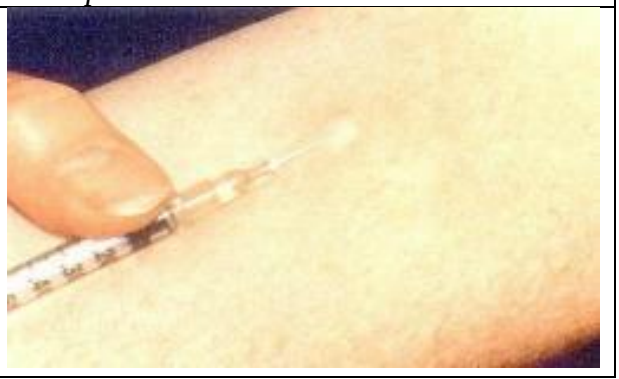
Annexure 2: Tuberculin Skin Test

What is the appropriate strength of PPD to be used?

Several studies were conducted in US and elsewhere in new recruits, using strengths 1, 5, 10, 250 units. Reaction to low doses was seen in persons with either history of contact, suspicion of disease or those with active tuberculosis. The increasing strength when used, started losing discrimination between infected (exposed) and non-infected (non-exposed). 5TU PPD-S had the best discriminatory power and is therefore the recommended dose for clinical testing. Later studies showed 1 TU PPD RT23 is equivalent to 2.5 TU of PPD-S, 2 TU RT 23 with Tween 80 is equivalent to 5 TU PPD-S. Lower dose were chosen due to fear of stronger reaction with environmental mycobacteria and BCG vaccination**. Current recommendation is to use 2TU PPD RT23 for all diagnostic purposes in our country. When 2 TU RT 23 PPD is not available 5 TU PPD–S with Tween 80 can be used (which ever preparation is used, the strength of PPD should not exceed 5 TU PPD-S).** Indigenous manufacturers available formulations are products standardised against PPD RT 23 made by SSI, Copenhagen. Commercially available tuberculins in the country are 1, 2 and 5 Tuberculin Unit (TU) PPD (RT23 equivalent). The RT23 lot originally prepared by SSI has since finished and not available anymore.

Best techniques for TST (Mantoux's test) administration, reading and interpretation

The technique of administration of tuberculin and reading of the test is described in box #.

Preparation of site • 5–10 cm (2–4 inches) below elbow joint, on ventral forearm • Forearm placed palm-up on a firm, well-lit surface • Skin should not have barriers e.g. scars, sores, veins • Clean with alcohol swab	***Record information*** • *Date and time of test* • *Site location* • *Lot number of tuberculin* • *Tuberculin strength*
Preparation of injection • Expiry date and Tuberculin strength (2 TU of PPD RT23) checked • A single-dose syringe with a short (1/4 to 1/2 inches) 27-gauge needle with a short bevel loaded with 0.1 ml tuberculin	***Instruction to the patient*** • *To avoid scratching the site,* • *Keep it clean and dry, and avoid putting creams/ lotions, adhesive bandages* • *Mention that getting the site wet with water is not harmful, but the site should not be wiped or scrubbed.*
Injection of test drug • Needle inserted slowly, bevel up, at angle of 5–15° • Needle bevel should be visible just below skin after penetration. • PPD injected gently raising an Intra-dermal wheal (orange peel appearance) of at least 6 mm diameter • If intradermal introduction is not confirmed (sub cutaneous	

administration suspected), repeated 2 inches away from the original site	

NOTE:
PPD must be kept refrigerated at 2-8*C (DO NOT FREEZE)
Check the expiry date and date that the vial was opened. The vial should be discarded if it has been opened for more than 30 days or expiry date has passed. The vaccine vial should be taken if the VVM (Vaccine Vial Monitor) on the box (of 10 vials) has changed its color.

NOTE: After the use, the tuberculin vial should be returned to the refrigerator

Test reading: Induration should be measured and not the erythema. Palpation with fingertips or using ball point method should be done to find margins of the induration across (horizontally). Induration may not always be visible, so palpation with fingertips should be relied upon to discover it. The area is lightly touched with pads of fingertips. Using a light, gentle motion, fingertips are swept over surface of forearm in a 2-inch diameter around injection site in all four directions to locate the margins or edges of induration. The margin is marked at the edges across the arm. The induration should only be measured using a transparent ruler/scale. "0" of ruler line should be placed on left edge of the induration and ruler line should be read on the right edge of the induration as identified (use lower measurement if between two gradations on mm scale). Measurement should be recorded in millimeters (mm) across the horizontal axis only. The test is not recorded as negative/positive. Instead, no induration is recorded as 0 mm. In case there is huge erythema but no induration, it may be due to an inadvertent subcutaneous leak. In such situations the test is repeated on the other arm.
Mantoux's test or PPD skin test is considered positive if the induration is 10 mm or more, In HIV coinfected and immunosuppressed children, 5mm may be taken as the cut off.
The cutoff at 10 mm reaction at 48 -72 hours was considered the best anti-mode cut off between the infected and uninfected populations using PPD-S 5TU (equivalent PPD RT23 2TU). This validates the current recommendations for using 10 mm cut off with 2 TU PPD RT23 in our country.

While the test is ideally read between 48 and 72 hours but in case a patient misses' appointment and reports beyond 72 hours but within 7 days, a test still positive should be interpreted as such while in case it is negative or if the patient comes >7 days after administration of test, it shall need to be repeated in other forearm.

Interpretation of fallacies
Degree of reaction, including local skin necrosis, vesiculation and ulceration does not differentiate infected from diseased. Reactivity in BCG vaccine recipients generally wane over time and about 10% may have reaction above 10mm; particularly in the first year after vaccination. In high burden countries a positive TST results is likely due to TB infection if risk factors are present even in a BCG vaccinated child.

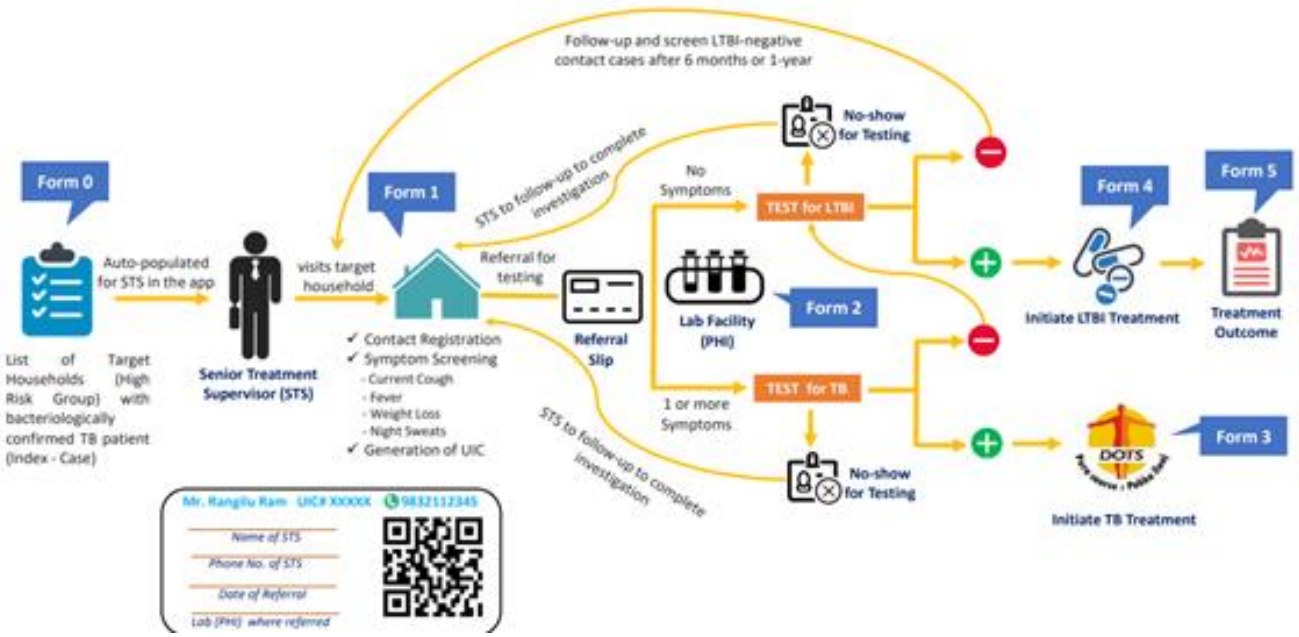
Causes of false negative	Causes of false positive
• Incorrect ***technique*** of administration or Interpretation • ***Improper storage*** of tuberculin • ***Immunodeficiency/suppression*** – Primary – Secondary like HIV infection, SAM, Immunosuppressive (e.g. steroids) • ***Infections*** – Viral (e.g. measles, varicella) – Bacterial (e.g. Typhoid, leprosy, pertussis) • ***Vaccinated*** with live viral vaccine (within 6 weeks) • ***Neonatal*** patients • ***Severe*** forms of TB	• Incorrect ***technique*** of Interpretation • ***BCG*** vaccination • Infection with ***mycobacterium other than TB***

Currently, the laboratories more often incorrectly use 5 TU PPD RT23 equivalent (which is as potent as about 12.5 TU of PPD-S), or sometimes even some other higher strengths or types of PPD are used. There is no linear relationship between the reaction obtained and strength of PPD used. Cut offs for higher strengths are not established. Higher strengths increase false positive reactions. The standard cut off of 10 mm can actually not be justified for any higher strength of PPD used. Degree of reaction, including necrosis and ulceration, may not necessarily differentiate infected from diseased. Prior BCG vaccine has minimal influence on PPD reaction.

Annexure 3. LTBI Prevent TB application

- Download LTBI application from Playstore
- STS level and District/State level login IDs are available for time being

- Workflow is as below



- It has Form 0-Form 5 now
- Form 0 – Index patient, Form 1- Contact Tracing details, Form 2- Lab Testing Results, Form 3- TB treatment details, Form 4- LTBI treatment details, Form-5- Treatment outcomes.
- STS to enter the details in LTBI application for the time being and update the information on a real time basis
- DTO to monitor the application regularly and ensure quality of data.

Annexure 4.1: IGRA Test Request Format

Name of Child: Gender:

Name of Parent/Guardian: Contact Number:

Age: [**IGRA testing is currently only for children 5-15 years old**]

Address:

Previous History of TB/LTBI treatment:

Indications for LTBI testing – Kindly Circle & Fill sub sections

(IGRA will be offered only to children who are eligible - without proper eligibility, the test will not be performed)

1. Children and adolescents (5-15 years) who are household contacts of microbiologically confirmed pulmonary TB
   a) Date of diagnosis of Index TB case:
   b) NIKSHAY ID of Index TB case:

2. Children & adolescents (< 15 years) planned to be initiated on anti-TNF treatment, receiving dialysis, preparing for an organ or haematological transplant, on immunosuppressive drugs for a longer duration

   Specify the clinical Indication:

Date: Name & Signature of Medical Officer:

Phone Number of Medical Officer:

Institution:

Email ID:

Time of Sample Collection: -------- AM / PM Date of Sample Collection:

Name of LT/Nurse/Doctor Collected sample, Packed & Transported:

Results of IGRA Testing

Name: **Age:** **Gender:** **Referred by:**

Time of Receipt of Sample at Lab: ……. AM/PM Date of receipt of sample at lab:

Cut off Titre: **Titre Recorded (IU/ml):**

Interpretation Note:

Date of Reporting:

Name of Laboratory: Signature of Lab Technician

Annexure 4.2: IGRA Lab Register

Programmatic Management of Latent TB Infection – IGRA Lab Register

Name	Age	Gender	Address	Phone Number	Indications for LTBI Testing (1. Contact/ 2. Clinically Vulnerable)	If Contact, Date of Diagnosis of Index Case and NIKSHAY ID of Index Case	If Clinically Vulnerable, specify Indication	Name of Doctor who requested test & Institution	Date & Time of sample Collection	Date & Time Sample is received in Laboratory	Date & Time of Reporting of Results	Date & Time of Issuing Results	Cut of Titre	Titre Recorder in IU/ml	Interpretation of Result	Signature of Lab Technician

Annexure 4.3. Contact Tracing Register

Contact Tracing Register

Name of Index TB case	Date of Diagnosis	NIKSHAY ID	Name of Household Contacts	Age of Contacts	Gender of Contacts	Tested for LTBI (Y/N)	Result of testing for LTBI (Positive/Negative/ Indeterminate)	Details of any co-morbidity	Contact Tracing for active TB diagnosis 1				Contact Tracing 2				Contact Tracing 3				Contact Tracing 4				Contact Tracing 5			
									Date	Symptom (Y/N)	Tested (Y/N)	Results	Date	Symptom (Y/N)	Tested (Y/N)	Results	Date	Symptom (Y/N)	Tested (Y/N)	Results	Date	Symptom (Y/N)	Tested (Y/N)	Results	Date	Symptom (Y/N)	Tested (Y/N)	Results

Annexure 4.4 LTBI Treatment Card

TB Preventive Therapy- Treatment Card

Name: Age: Gender: Parent/Guardian:

Address with Landmark:

Phone Number: ..... /..... PHI: TU: District:

Treatment Supporter: Phone Number:

LTBI ID..... NIKSHAY ID of Index Case .....

Indication for testing for LTBI: Household Contact of TB / Clinically Vulnerable

Details of clinical vulnerability (If any):

Result of LTBI tests

Type of Test Done:

Date of Test:

Place of Tests:

Results of Test:

Ruling out Active TB

Chest X ray Findings: Date:

Details of other Investigations:

Baseline Assessment

Weight: Date: .....

LFT Results (Date.....)

S. Bil..... SGOT.....SGPT.....

Any other Co-morbidity:

H/o Drug Allergy:

Contact with DRTB:

LTBI Treatment

Prescribed by:

Date of Initiation:

Initial Counselling Provided by: ..... On.....

Dose of Formulation: INH Rifampicin

Number of tablets per day.....

Pyridoxine:

TB Preventive Therapy- Treatment Card

Date of Treatment Initiation:

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

A tick mark '(√)' to recorded in the appropriate box (according to the dates of the month 1 – 31 as the case may be) to indicate the day the drugs were consumed under direct observation. Missed dose, is denoted by a circle (0) in the appropriate box. The entry for unsupervised doses should be recorded by encircling the tick mark on the TB Treatment Card √

Details of Adverse Events

Actions Taken

Treatment Support

Retrieval Actions

Treatment Outcome (Circle)

Treatment Completed / Died / Lost to Follow Up / Stopped due to toxicity/ Stopped due to active TB/ Not Evaluated

Date of declaring Outcome:

Monthly Clinical Follow Up

	Date	Date	Date	Date
Weight				
Adherence				
Adverse Events				
Jaundice				
LFT results (only if indicated)				
Peripheral Neuropathy				
Gastro Intestinal				
Any other Adverse events				
Any symptoms of active TB				
Co-morbidity				
Signature of MO				

ADDITIONAL NOTES:

Annexure 4.5 LTBI Treatment Register

Programmatic Management of LTBI- Treatment Register

LTBI ID	Name	Age	Gender	Address	Phone Number	Indications for LTBI Testing (1. Contact/ 2. Clinically Vulnerable)	If Contact, Date of Diagnosis of Index Case and NIKSHAY ID of Index Case	If Clinically Vulnerable, specify Indication	Date of IGRA test	Result of IGRA	Name of laboratory which has done IGRA	Name of Doctor who prescribed LTBI regimen	PHI	Date of initiation of Treatment	Details of Treatment Supporter	Dates of Monthly clinical Follow Ups	Treatment Outcome	Date of Treatment Outcome	Dates of Follow Up after Treatment Completion	Remarks

Annexure 5: List of Paediatric LTBI Sub Committee Members, Kerala

Dr Sanjeev Nair	Chair, TWG, Kerala
Dr Sunilkumar M	State TB Officer, Kerala & Member National TWG
Dr Narayanan M	State President, IAP, Kerala
Dr Lalitha Kailas	Professor & HOD, Sree Gokulam Medical College, TVM
Dr Ashraf T P	Addl Prof IMCH, Kozhikode
Dr Shameem	Asst Prof, MCH Kozhikode
Dr Narayana Naik	Sr Con Peds, GH Kasaragod
Dr Mridula Shankar	Health Services, Kannur
Dr Krishnapriya	Health Services, Wayanad
Dr Fysal	HOD, MES Medical College, Perinthalmana, Malappuram
Dr S. ChandraMohan Reddy	HOD of Pediatrics, Karuna Medical College, Palakkad
Dr Rehna .T	Al Azhar Medical College, Thodupuzha
Dr Ananda Kesavan T.M	Addl Prof, GMC Thrissur
Dr Nisha Narendran	Asso Prof, GMC Thrissur
Dr Manjusha K	Asst Prof, SNIMS Cochin
Dr Jijo Joseph John	Believer's Medical College, Pathanamthitta
Dr Sreeprasad T G	Jr Cons Pediatrics, THQ Kayamkulam, Alappuzha
Dr Suresh Vadakedom	Asso Prof, ICH Kottayam
Dr Binu Abraham	Asst Prof, GMC Paripally,Kollam
Dr Geetha.S	Addl Prof, SATH TVM
Dr Bindusha	Asso Prof, SATH TVM
Dr Rekha	Asso Prof, SATH TVM
Dr Balachandar. D	Sr Con Paediatrics, GH Pathanamthitta & Secretary IAP Kerala
Dr Neetha Murthy	Microbiologist, IRL, Kerala
Dr Arshad Kalliath	STDC Consultant, Kerala
Dr Manu MS	Junior Consultant, STDC Kerala
Dr Deepu Surendran	Medical Officer, State TB Cell, Kerala
Dr Shibu Balakrishnan	National TWG Member, RTL South, WHO
Dr Rakesh PS	WHO Consultant

We acknowledge the technical inputs and guidance from Central TB Division, MOHFW, WHO India Office and National Technical Working Group.

Annexure 6: Frequently Asked Questions

Q 1. If a child who received a course of TPT was again exposed to active pulmonary TB at household, do we need to offer LTBI treatment/TPT again?

Ans: TPT can halt progression to TB very effectively for many years, but re-infection with TB bacilli after completing treatment may reverse this protection. Studies of the benefit of repeated TPT are ongoing. In such rare instances, refer the child to District Paediatric TB Expert Committee for further decision on TPT.

Q2: Is there chance of developing drug resistance by giving TPT to any?

Ans: TPT are being offered after ruling out active TB. In such situations, chance of developing drug resistant TB is not there.

Q3: Is pyridoxine mandatory while administering TPT?

Ans: Vitamin B6 (pyridoxine) supplementation is not a routine requirement in individuals who are otherwise healthy and who receive isoniazid at the dose recommended for TPT. However, even low doses of isoniazid can lead to nerve injury among malnourished people or those who metabolise isoniazid slowly.

Other conditions that can predispose to isoniazid-related nerve damage are chronic alcohol dependence, HIV infection, kidney failure or diabetes, or in women who are pregnant or breastfeeding. Concurrent administration of vitamin B6 with isoniazid protects against the development of nerve damage in these individuals. During monthly clinical review, look for signs and symptoms of peripheral neuropathy. If signs of nerve toxicity develop - often starting with “needles and pins” or burning sensation in the feet or hands – then think whether treatment with vitamin B6 at a higher dose is necessary or to stop INH and change the regimen. Refer to District Paediatric TB Expert Committee for appropriate decisions.

Q4: Why are we not testing children less than 5 years who are household contacts of pulmonary TB, for LTBI?

Ans: Infants and young children who are infected with TB are known to have a significantly higher risk of progressing to active TB. Furthermore, TB can develop rapidly in young children who are also at greatest risk for disseminated disease, which is associated with high morbidity and mortality. Sensitivity of IGRA is not well established in children under 5 years. Lack of standardised reagents and poor sensitivity in younger children are also limitations of Mantoux. In this context, state will be adhering to current national policy.

Q5: When to stop TPT in case of hepatitis? Is it advisable to continue TPT once a child develops adverse events?

Ans: It is generally recommended that TPT to be withheld if a patient's transaminase level exceeds three times the upper limit of normal if associated with symptoms or five times the upper limit of normal if the patient is asymptomatic. If hepatitis occurs it is also important to rule out other possible causes of injury (such as recrudescence of viral hepatitis). Parents should be instructed, at the start of treatment and at each monthly visit, to stop taking treatment and seek medical attention immediately if symptoms suggestive of hepatitis develop. Completion of TPT is always preferred. However, it depends on weighing the individual's benefits Vs risk. Clinician will always have the privilege of referring the child to District Paediatric TB Expert committee whenever in doubt.

Q6: In a child less than 5 years with Immunosuppressive condition, how to proceed with TPT? Which test is advisable to diagnose LTBI?

Ans: For children less than 5 years who are household contacts of a microbiologically confirmed pulmonary TB, no testing for LTBI is required to start TPT. Child less than 5 years who is HIV negative and who is clinically eligible (eg initiating on steroids), a judicious assessment for initiating TPT need to be done. Sensitivity of IGRA has not been well established among children less than 5 years. For younger children, IGRA and TST perform with similarly low sensitivity. Standardised TSTs are not available. All precautions need to be taken while performing and interpreting TST in children under 5 years. False positive results are possible due to BCG vaccine or due to NTMs. As such, a negative or indeterminate TST in an immunocompromised child does not rule out LTBI. History of close contact with a case of microbiologically confirmed pulmonary TB shall be elicited carefully. Such a definite history will be of more value in a setting like Kerala for deciding about offering TPT.

Q7: Is there any recommendations for restarting the regimen once it is interrupted?

Scenario	Action
If child discontinued TPT for less than 4 continuous weeks	Conduct adherence counselling, Address reasons for discontinuation. Rule out active TB Continue TPT and give all missed doses Ensure they complete the course
If the child has taken TPT for less than 4 weeks in total and discontinued for any reason for more than 4 weeks	Conduct adherence counselling, Address reasons for discontinuation. Rule out active TB Reinitiate TPT course afresh and give complete course Ensure they complete the course.
After taking TPT for more than 4 weeks If child discontinued TPT for more than 4 weeks, or has discontinued (>1 week) more than once	Re-initiate TPT only after consultation with District Paediatric TB Clinical Committee. Closely follow up the child.

Q 8: What is the child develops symptoms of active TB while on TPT?

Ans: Investigate for active TB disease as per the diagnostic algorithm. If found to have TB disease, in addition to NAAT, offer FL-LPA at baseline itself to detect resistance to INH if any. Stop LTBI regimen and Treat TB disease as per the NTEP guidelines.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