





#### Kerala HEALTH

# PROGRAMMATIC MANAGEMENT OF LATENT TB INFECTION AMONG CHILDREN & ADOLESCENTS IN KERALA

Implementation Plan

#### Kerala

- Declining Growth Rate
- Infant Mortality Rate 7/1000
- High literacy rate (male 96.11% and female 92.07%)
- Systematically Organized Primary Health Care System
- Low HIV Transmission

#### Paediatric TB in Kerala

- 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.
- 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)

#### **Kerala TB Elimination Mission**

 To achieve Sustainable Development Goals related to TB

 The mission is envisaged as a peoples' movement against TB.

 Strategy Document which is the customised version of National Strategic Plan India has enumerated 48 activities for
the peoples' movement
against
Tuberculosis in Kerala

Kerala TB
Elimination
Mission

### Theme is "My TB Free Panchayat"

•561 Panchayats had ZERO Under 5TB in 2019

•688 Panchayats had ZERO Lost to Follow Up in 2019

709 Panchayats had ZERO DR TB in 2019

### Kerala – Standards of TB Care is good

 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%. 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).

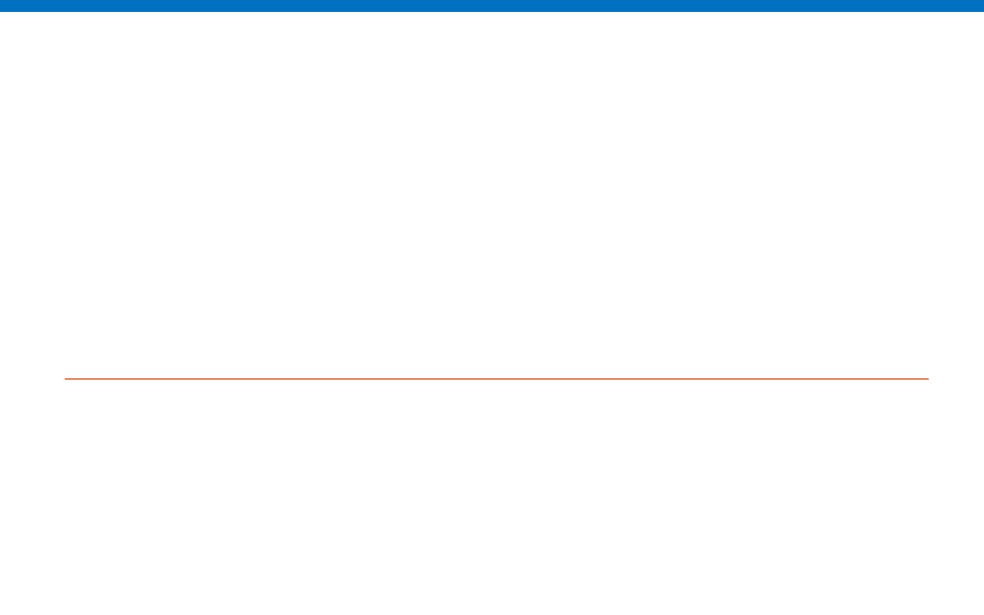
### "AKSHAYA KERALAM"

TB Preventive Therapy to all children less than 15 years	Starting from November, 2020	Detecting and treating Latent TB Infection among children will help to achieve the goal of "Childhood TB Free Kerala". It will prevent 1000 children getting TB every year in the state.
TB Services at Door steps	Efforts for reorienting field services shall start from 1 November 2020	TB services become more 'people centric' with minimal inconveniences to the people.
Upfront Molecular tests for TB diagnosis	From December 1 2020 onwards	Early & accurate detection of all TB cases including detection of drug resistance at baseline.

#### TB Free Air for Every Child in Kerala-IAP Kerala

- Protecting Child Rights is the theme of IAP Kerala Chapter.
- 'TB Free Air' is the right of every child.
- IAP is raising the voice for children





### **TB Preventive Therapy**

•Prevention of active TB disease by treatment of LTBI is a critical component of the WHO End TB Strategy.

•Draft National Plan for PMLTBI, developed by NTWG is ready. Kerala State has locally customised the national plan.

#### Pre requisites to roll out PMLTBI services

- Training of all paediatricians, program management staff, treatment supporters
- Laboratory Assessment, Training for IGRA, Specimen Collection & Transportation System and Mapping of laboratories
- Logistics- Drugs, Test Kits, Recording & Reporting
- Setting up of District Paediatric TB Committees

### SESSION 2

LTBI Basics & Eligibility Criteria

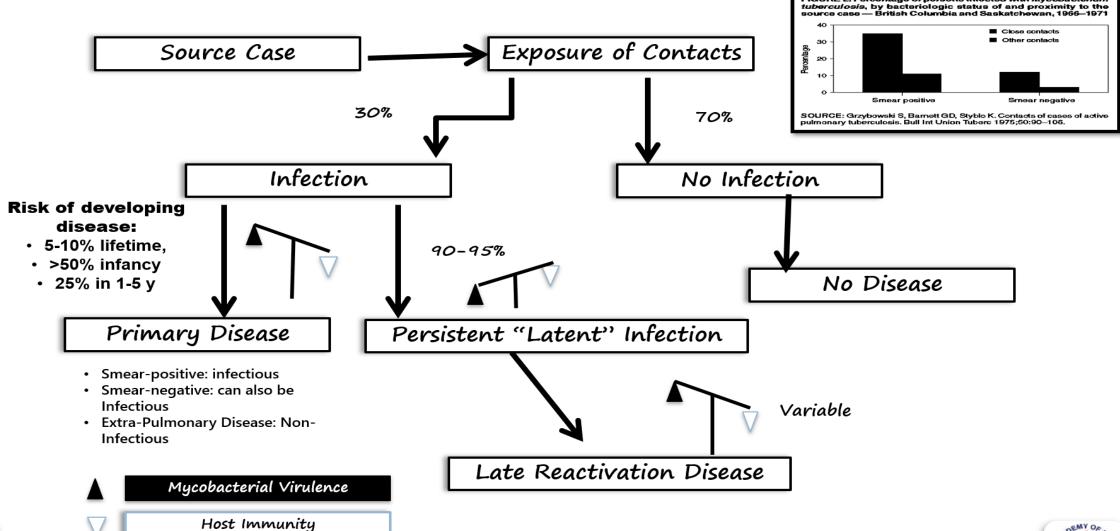






FIGURE 2. Percentage of persons infected with Mycobacterium

### Latent TB Infection- Why we need to Treat?

- 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.

#### Principle of PMLTBI in Kerala

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

#### **Household contact**

• A 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.

### Who all are Eligible?

(1/3)

- 1. 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.
- 2. A child born to mother who was diagnosed to have TB in pregnancy should receive TPT, provided congenital TB has been ruled out.

### Who all are Eligible?

(2/3)

- 3. 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.
- 4. Children and adolescents (12 months -15 years) living with HIV should be given TPT after ruling out TB (No contact is needed)
- 5. CLHIV <12 months should also be given TPT if they are contact of a pulmonary TB, after ruling out active TB.

### Who all are Eligible?

(3/3)

- 6. 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.(No contact is needed)
- 7. 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 (< 15 years) who are household contacts of all microbiologically confirmed pulmonary TB patients notified after 1<sup>st</sup> 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.

### **Testing for LTBI**

•LTBI testing is currently **not** a requirement for initiating TB preventive treatment for household contacts aged < 5 years and children and adolescents living with HIV.

• For all other eligible children and adolescents, Interferon-Gamma Release Assay (IGRA) shall be used for diagnosis of LTBI

# SESSION 3

**IGRA** 

#### **IGRA & Tuberculin Skin Test**

IGRA	Tuberculin Skin Test
• In vitro	• In vivo
Well identified antigens	<ul> <li>Multiple uncharacterized/ unquantified antigens</li> </ul>
<ul> <li>No boosting</li> </ul>	Boosting
<ul> <li>Not affected by BCG</li> </ul>	May be affected
<ul> <li>One patient visit</li> </ul>	Two patient visits
<ul> <li>Minimal inter-reader variability</li> </ul>	<ul> <li>Significant inter-reader variability</li> </ul>
<ul> <li>Results in one day</li> </ul>	• Results in 2-3 days
	Standardised TST Not available

### Test for LTBI



**IGRA** 

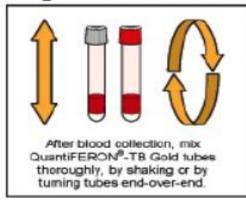
#### Organising the IGRA test

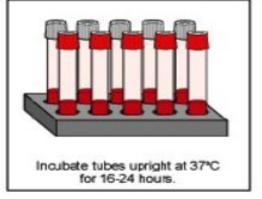
- IGRA testing shall be setup at 46 public laboratories (2-4 per district) across the state. Apart from this, 16 Private Laboratories will also be performing IGRA tests.
- NTEP has established specimen collection and transportation systems from every PHI to transport samples in a Hub & Spoke Model. From 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°C.

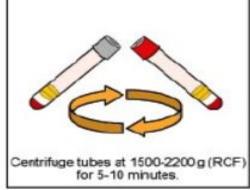
• Laboratories will be performing IGRA only on specific days. These date and time shall be disseminated.

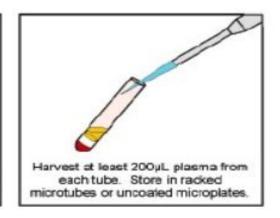
### Steps in SOP

#### Stage One - Blood Incubation and Harvesting

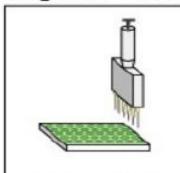




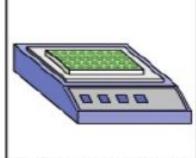




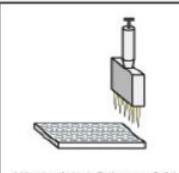
#### Stage Two - Human IFN-y ELISA



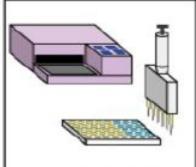
Add 50 µL of conjugate solution to each well. Add 50µL of plasma or standard.



Shake covered plate for 1 min. Incubate for 120 minutes at Room Temperature.



Wash plate ≥6 times. Add 100µL substrate. Incubate 30 min at Room Temperature.



Add 50 µL of stop solution. Read absorbance within 5 min at 450nm (620-650nm ref).



Calculate Results using QuantiFERON®-TB Gold In-Tube Analysis Software.

## SESSION 4

**Ruling Out Active TB** 

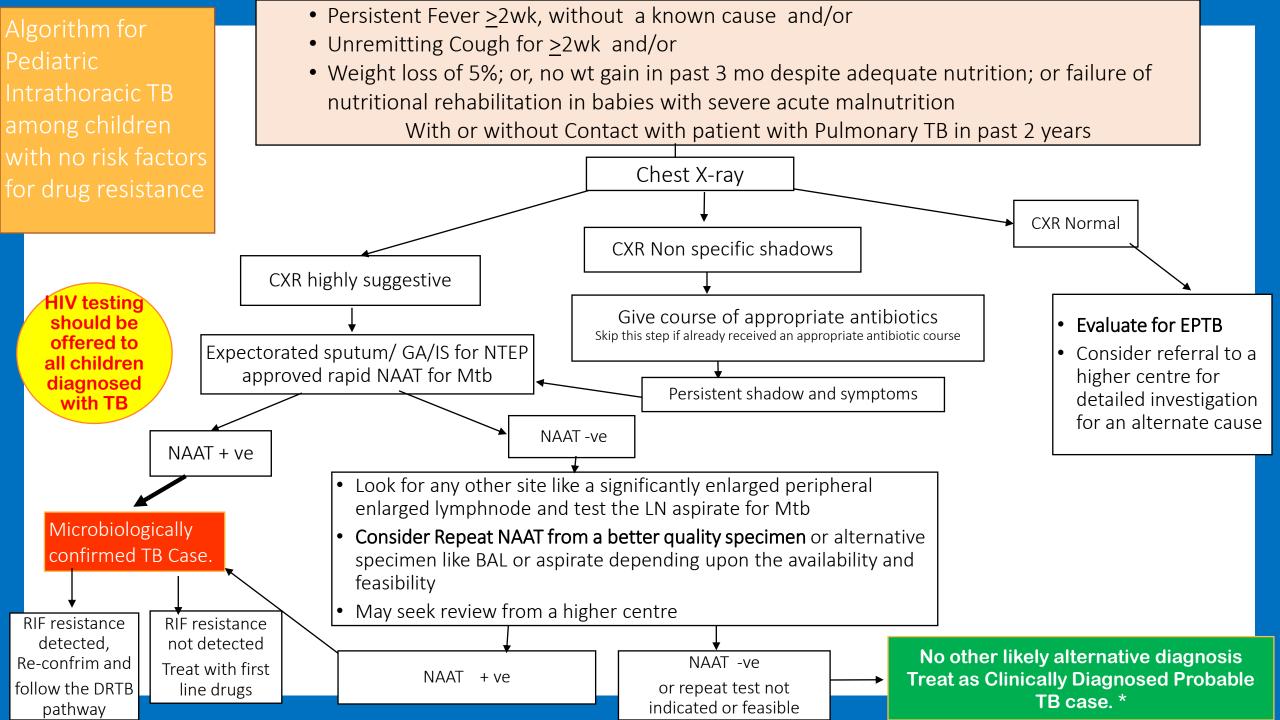
### Ruling out Active TB

- 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.

## Clinical presentation of the common forms of TB in a child

#### Common Symptoms

- Fever for 2 weeks or more\*
- Unremitting cough for 2 weeks or more
- No weight gain despite adequate nutrition or loss of >5% of body weight in past 3 mo.
- Peripheral Painless swellings (lymphnodes)
- Meningitis of insidious onset
- Spine gibbus
- Any non specific symptoms in a contact of an infectious TB case



#### Lymphadenopathy: Frontal radiographs

- Direct signs:
  - Sharply demarcated and lobulated density or ill-defined with vague borders, occupying the hilum & obliterating hilar point.
- Indirect signs:
  - Contour & caliber of trachea obliterated
  - Splaying of carina can be seen



#### **Lateral Chest films**

- Good to visualise retro-cardiac disease and hila
- Dough nut sign
  - Lobulated densities posterior to the bronchus intermedius
  - Upper half is seen in normal individuals as an up-side-down 'horse-shoe' made up of the RPA and LPA and the aortic arch
- Can view of the 'hidden areas' like left lower lobes which are hidden behind the heart

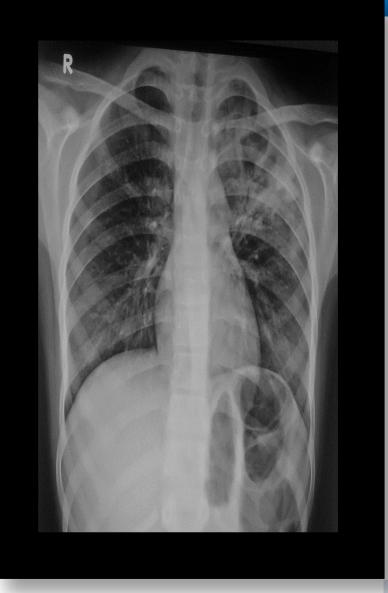


# **Primary diagnostic test** Suggestive of TB X ray chest ¥3>90 Fibrocavitary Miliary LN SIOL

Primary TB Primary Complex

Progressive Primary TB







Fibro cavitory lesions on the Rt & Lt Lung

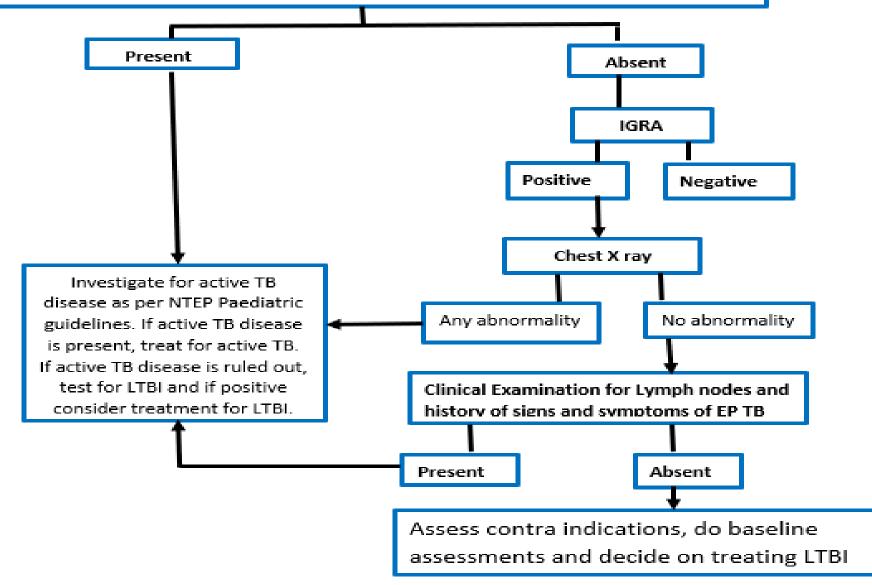
#### EPTB –aim to get microbiological diagnosis

Lymph node TB – cervical / Mx 70%*	FNAC, CBNAAT , AFB smear , MGIT→ excision biopsy & test if all others neg
Pleural	CBNAAT sputum, GA, Pleural fluid → pleural tissue biopsy → DEFINITIVE Clinical + lymphocytic fluid (>50%), Protein >3g%(E), straw color, Mx +ve, not sick, long history → probable. NO ADA
Abdominal (intestinal, nodal, peritoneal ,visceral)**	Plain Xray, USG, Ba studies, CECT /CT enterography
CNS TB - TBM (infarcts (BG) , hydrocephalus / tuberculoma	CSF – clear,10-100L, Low G, High P, CBNAAT(5ml),TST(50%+), CXR, LNE NO ADA, CECT, contrast MRI
Bone & joint TB (Potts*, dactylitis*, OM, arthritis, reactive arthritis, bursitis)	Xray spine(30-50% loss), MRI(100% sensitive)

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



Look for Signs and symptom of TB - [cough, haemoptysis, fever, night sweats, weight loss/ poor weight gain, chest pain, shortness of breath, fatigue, not eating well]



## SESSION 5

**Treatment of LTBI** 

#### Regimes for Latent TB treatment- Options available

6 months of INH (H)

3months of INH and Rifampicin (HR)

4 months of Rifampicin (R)

Weekly Rifapentine with INH for > 2 yrs old

# Treatment of LTBI- preferred regimen in Kerala

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.</li>

### Why 3 HR?

- 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
- In place of adequate systems to rule out active TB.

### Treating Regimen- Available Evidences

- The efficacy and the safety profile of 3–4 months' daily rifampicin plus isoniazid were similar to those of 6 months' isoniazid in treatment of LTBI
- RCT reported no clinical disease in either group and used new radiographic findings suggestive of active TB as a proxy for clinical disease. Fewer participants given daily rifampicin plus isoniazid than those given 9 months of isoniazid developed radiographic changes (RR 0.49, 95% Cl 0.32;0.76).
- The authors also reported a lower risk for adverse events (RR 0.33, 95% CI 0.20;0.56) and a higher adherence rate (RR 1.07 95% CI 1.01;1.14) among children given daily rifampicin plus isoniazid.
- Similar findings were reported in the two observational studies

#### 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

### Pyridoxine supplementation

Pyridoxine – 10 -25 mg daily for > 3 months of INH Why?

Risk of peripheral neuropathy more &

Often undetected in young children

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.

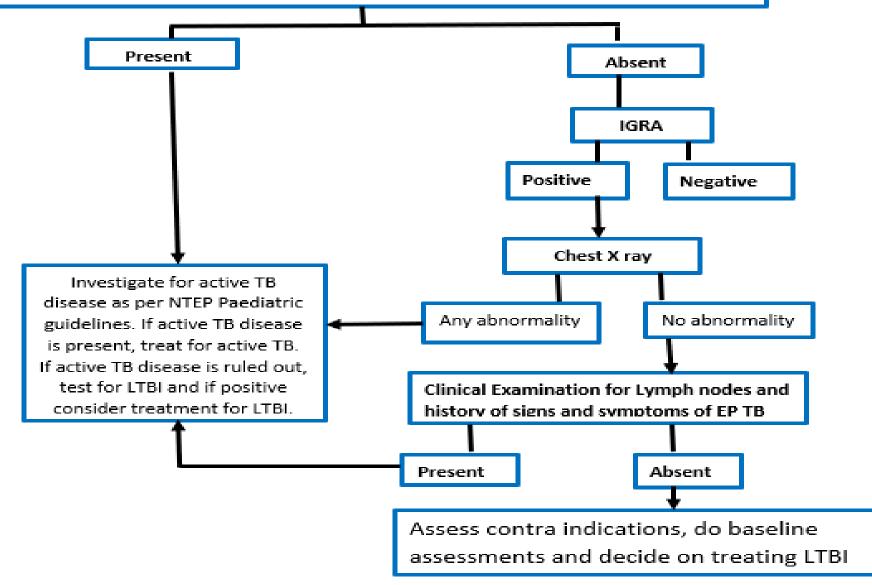
#### Contraindications for TB Preventive Therapy

- Contacts of any 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)
- Symptoms of peripheral neuropathy

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



Look for Signs and symptom of TB - [cough, haemoptysis, fever, night sweats, weight loss/ poor weight gain, chest pain, shortness of breath, fatigue, not eating well]



## SESSION 6

**Baseline Assessment, Initial Counselling** 

#### Baseline Assessment

- 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 coordination 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

- 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 symptoms of TB.

## SESSION 7

Adverse Event Monitoring, Ensuring Treatment Adherence

## Adverse Events Monitoring, Adherence and completion of preventive treatment (1/5)

- 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

## Adverse Events Monitoring, Adherence and completion of preventive treatment (2/5)

- 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.

## Adverse Events Monitoring, Adherence and completion of preventive treatment (3/5)

• The Treatment Supporter needs to mark ✓ gainst 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.

### Monthly Clinical Follow Up

- 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.

## Adverse Events Monitoring, Adherence and completion of preventive treatment (5/5)

 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.

## SESSION 8

Monitoring Indicators, Treatment Outcome, Long Term Follow Up, Flow of Events

### 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		

#### **Treatment Outcome**

- 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)
- Treatment Failed A person initiated on LTBI Management who developed TB disease any time while on LTBI Management course.
- 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 for 3HR.
- LTBI Management discontinuation due to toxicity A person whose LTBI MANAGEMENT is discontinued by clinician due to adverse events or drug—drug interactions, without treatment completion.
- 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.

#### **Evidence Generation**

- 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 & drug resistance.

# Flow of Events

Identification of Eligible Children – Contact Tracing Testing for LTBI Rule Out Active TB Baseline Assessment Initiation of LTBI treatment Adverse event Monitoring & Ensuring Treatment Adherence Monthly Clinical Follow Up **Declaring Treatment Outcome** Long Term Follow Up

## SESSION 9

**Recording & Reporting** 

### **Recording & Reporting**

(1/2)

- 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 recording of tracing and testing household contacts shall be there at treatment card of every TB patient.
- There shall be a 2 physical LTBI record 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.

### **Recording & Reporting**

(2/2)

- 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/STS
- PHC Medical Officer where the child resides compiles the quarterly report with the help of STS
- Consolidation happens through routine NTEP mechanisms

#### Run-In-Period

- The service delivery will be starting from Nov 15, 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.

## SESSION 10

**District Paediatric TB Committee** 

#### 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.

#### **Role 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.

