Ministry of Health & Family Welfare
Government of India

Paediatric TB Management
Guideline 2022

DEVELOPED BY THE NATIONAL TUBERCULOSIS ELIMINATION PROGRAMME

CENTRAL TB DIVISION, MINISTRY OF HEALTH AND FAMILY WELFARE, NEW DELHI

Draft

National Tuberculosis Elimination Programme
Central TB Division, Ministry of Health and Family Welfare, New Delhi

Acknowledgement

The Paediatric TB Management Guidelines, 2022, under the stewardship of the Central TB Division (CTD), has been a culmination of a host of conferring and consultations with national experts from the Government of India (GoI), the Indian Academy of Paediatrics (IAP), the World Health Organization (WHO) Country Office for India, key technical and development partners.

These deliberations were organised by the Central TB Division (CTD), Ministry of Health and Family Welfare (MoHFW), and the GoI with technical support from the IAP, and encompassed consultations with several stakeholders, an extensive review of the literature and existing national and international recommendations. A compendium of the clinical updates, diagnostic tools, programmatic management, and care for children with TB, The Guidelines for Management of Paediatric TB, 2022 are aligned with other NTEP guidelines such as Programmatic Management of Drug Resistant TB 2021, Programmatic Management of TB Preventive Therapy 2021, as well as other programme policy documents.

We express our gratitude to Shri Rajesh Bhushan, Union Secretary, MoHFW, GoI; Dr Rajiv Garg, Director General Health Services (DGHS), GoI; Ms Roli Singh, Additional Secretary & Mission Director, National Health Mission (NHM), MoHFW, GoI; Dr P Ashok Babu, JS (RCH & TB), MoHFW, GoI; Ex-DDG (TB): Dr Sunil D Khaparde, Dr Kuldeep Singh Sachdeva, and Dr Sudarsan Mandal; Ex-ADDG (TB): Dr Devesh Gupta, Dr V S Salhotra; and Dr Chaman Prakash, MoHFW, GoI.

Our sincere thanks to Dr R. P. Joshi - DDG (TB), GoI for his leadership and spearheading this collaborative initiative; Dr Sanjay Kumar Mattoo - ADDG (TB), for his constant support and encouragement, and Dr Alok Mathur – ADDG (TB), Dr Raghuram Rao– ADDG (TB); Dr Nishant Kumar – Joint Director (TB), and Dr Ravinder Kumar, TB Specialist- for their valuable guidance.

We want to offer our deepest gratitude to Dr Varinder Singh - Professor of Paediatrics, LHMC, New Delhi, for his infallible support and valuable insights throughout the entire spectrum of development of these guidelines. We thank the Indian Academy of Paediatrics (IAP) for their collaborative support. We appreciate the technical experts involved at different stages of the development of this guideline: Dr Remesh Kumar R – President, IAP; Dr Santosh Soans – Ex-President IAP; Dr Sushil K. Kabra - Professor of Paediatrics. AIIMS; Dr Uday Govindrao Bodhankar - Honorary Professor of Paediatrics, IGMC; Dr Ira Shah - Head of Pediatric Infectious Diseases, BJ Wadia Hospital for Children; Dr Yogesh Jain - Jan Swasthya Sahyog, Bilaspur; Dr Sangeeta Yadav - Professor & HOD of Pediatrics, MAMC & Joint Secretary IAP; Dr Sangeeta Sharma - Professor & HOD of Pediatrics, NITRD; Dr Gowri Shankar - Paediatric Pulmonologist, Mehta Hospital, Chennai; Dr Janani Shankar - Paediatrician, Child trust hospital; Dr Nilofer Mujawar - Professor and Head, Paediatrics, NKP Salve Institute of Medical Sciences and Research Center, Nagpur; Dr Tanu Singhal - ID expert, Kokilaben Ambani Hospital, Mumbai; Dr Winsley Rose - Professor, Department of Child Health III, CMC Vellore; Dr Rupak Singla - Prof and Head Pulmonary Medicine-NITRD, New Delhi; Dr Vineet Bhatia - Medical Officer Drug Resistant and Latent TB- Office of WHO SEARO; Dr Rohit Sarin - Chairman NTEG-Treatment and Technical Advisor NTEP; Dr Anuj K Bhatnagar - Prof and Head Pulmonary Medicine RBIPMT New Delhi; Dr Urvashi B Singh – In-charge TB Division, Dept of Microbiology, AIIMS, New Delhi; Dr Rajesh Solanki - Professor and Head, Pulmonary Medicine, Nootan Medical College, Mehsana; Dr Amita Joshi - Professor and Head, Dept. of Microbiology, JJ Hospital, Mumbai; Dr Sridhar Rathinam - Chest Physician, GHTM Tambram, Chennai; Dr. Malik Parmar, National Professional Officer – Drug Resistant and Latent TB, WHO Country Office for India; Dr Kiran Rade – NPO (TB Epidemiology), WHO Country Office for India; Dr. R Ramachandran - National Professional Officer TB & Labs, WHO Country Office for India; Dr Debadutta Parija – RTL, WHO; Dr Neerja Arora – – Project Director, Public Health, IQVIA.

We appreciate the contributions of all individuals who helped with the development of the Guidelines, including present and former CTD consultants: Dr Deepak Balasubramanian – VP Public Health, Everwell Health Solutions; Dr (Maj) Priyanka Agarwal - Team Lead, Technical Support Unit, Wadhwani AI; Dr Pooja Tripathi – National Consultant Paediatric TB & Gender; Dr S Anand – National Consultant TB Laboratories; Dr Almas Shamim - National Consultant PPM; Dr Sandeep Chahuhan – National Consultant DR-TB; Dr Hardik Solanki – National Consultant TPT; Ms Kavita Nair – National Consultant Procurement and Donor Coordination; Dr Aniket Chouhdhary – National Consultant M&E; Dr Vaibhav Shah– Nikshay & Digital Surveillance; Dr Yogesh Patel – Ex National Consultant DR – TB; Dr Amit Karad – Ex National Consultant Partnership; Dr Sunita Paliwal – Ex National Consultant; Dr Bhavin Vadera – Ex National Consultant PPM.
We appreciate the contributions of all individuals who helped with the development of the Guidelines, including present and former CTD colleagues and colleagues from the Child Health, RBSK and DGHS divisions.

We are deeply thankful to all those who reviewed the draft guidelines and shared inputs for improvisation, including IAP representatives, academicians from medical colleges, paediatricians from private hospitals, national professional officers from the WHO country office for India and colleagues from non-government organisations, including Jan Swasthya Sahyog, IQVIA and The Union South East Asia.

We express our sincere gratitude to SAATHII for its facilitation and support.

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Abbreviations

ADDG	Additional Deputy-Director General
ADA	Adenosine Deaminase
ADR	Adverse Drug Reaction
aDSM	Active Drug Safety Monitoring And Management
AE	Adverse Event
AFB	Acid Fast Bacilli
AIC	Airborne Infection Control
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
Am	Amikacin
Amx/Clv	Amoxicillin/Clavulanate
ART	Anti-Retroviral Treatment
ARV	Anti-Retroviral
ATT	Anti-Tubercular Treatment
AST	Aspartate Aminotransferase
BAL	Bronchoalveolar Lavage
BCG	Bacillus Calmette–Guérin
Bdq	Bedaquiline
BPaL	Bedaquiline, Pretomanid, Linezolid
CBNAAT	Cartridge Based Nucleic Acid Amplification Test
C&DST	Culture And Drug Susceptibility Test
CECT	Contrast-enhanced Computed Tomography
Cfz	Clofazimine
CI	Confidence Interval
CLHIV	Children Living With HIV
Clr	Clarithromycin
Cm	Capreomycin
CP	Continuation Phase
Cs	Cycloserine
CPT	Co-Trimoxazole Preventive Treatment
CSF	Cerebrospinal Fluid
CTD	Central TB Division
CT	Computed Tomography

DBT	Direct Beneficiary Transfer
DDG	Deputy-Director General
DDR-TBC	District Dr-Tb Centre
DDS	District Drug Store
DG	Director General
Dlm	Delamanid
DM	Diabetes Mellitus
DOT	Directly Observed Treatment
DR-TB	Drug-Resistant Tuberculosis
DR-TBC	Drug-Resistant Tuberculosis Centre
DST	Drug Susceptibility Testing
DT	Dispersible Tablets
DTO	District TB Officer
E	Ethambutol
ECG	Electrocardiogram
EGPAF	Elizabeth Glaser Pediatric AIDS Foundation
EPTB	Extrapulmonary Tuberculosis
Eto	Ethionamide
FDC	Fixed Drug Combinations
FLD	First Line Drugs
FL LPA	First Line-Line Probe Assay
FNAC	Fine Needle Aspiration Cytology
FQ	Fluoroquinolone
GA	Gastric Aspirate
Gfx	Gatifloxacin
GoI	Government Of India
H; INH	Isoniazid
HHC	Household Contact
HF	Health Facility
Hh	High Dose Isoniazid
HPE	Histopathological Examination
HRCT	High Resolution CT Scan
Hr-TB	Isoniazid-Resistant TB
HWC	Health & Wellness Centres
IAP	Indian Academy of Paediatrics
ICSOL	Intracranial Space-Occupying Lesion

ICT	Information Communication Technology
IGRA	Interferon-Gamma Release Assays
IS	Induced Sputum
IP	Intensive Phase
Ipm	Imipenem
IRIS	Immune Reconstitution Inflammatory Syndrome
IRL	Intermediate Reference Laboratory
JRA	Juvenile Rheumatoid Arthritis
Km	Kanamycin
LAC	Link ART Centre
LC	Liquid Culture
LFT	Liver Function Test
Lfx	Levofloxacin
LPA	Line Probe Assay
LTBI	Latent TB Infection
LTFU	Lost-To-Follow Up
Lzd	Linezolid
LN	Lymph Node
MAC	Mycobacterium Avium Complex
MDR-TB	Multi-Drug Resistant TB
MERM	Medication Event Reminder Monitor Device
Mfx	Moxifloxacin
Mfxh	High Dose Moxifloxacin
MGIT	Mycobacteria Growth Indicator Tube
MIC	Minimum Inhibitory Concentration
MoHFW	Ministry of Health And Family Welfare
MOTT	Mycobacterium Other Than Tubercle Bacilli
MO-TU	Officer Of TB Unit (Block Medical Officer)
MoU	Memorandum Of Understanding
Mpm	Meropenem
MRI	Magnetic Resonance Imaging
MR	Mono Resistance
NAAT	Nucleic Acid Amplification Test
NACO	National AIDS Control Organisation
NACP	National AIDS Control Programme
NDRS	National Drug Resistance Survey

NDR-TBC	Nodal DR-TB Centre
NGO	Non-Government Organization
NNRTI	Non-Nucleoside Reverse-Transcriptase Inhibitors
NPY	Nikshay Poshan Yojana
NRC	Nutrition Rehabilitation Centres
NTEG	National Technical Expert Group
NTEP	National Tuberculosis Elimination Programme
Ofx	Ofloxacin
PAS	P-Aminosalicylic Acid
pCoE TB	Paediatric Centre of Excellence for TB
PCR	Polymerase Chain Reaction
Pdx	Pyridoxine
PDR	Poly Drug Resistance
PE	Pleural Effusion
PHA	Public Health Action
PI	Protease Inhibitor
PK/PD	Pharmacokinetic/ Pharmacodynamics
PLHIV	People Living With HIV
PMDT	Programmatic Management Of Drug-Resistant Tuberculosis
PP	Private Provider
PPSA	Patient Provider Support Agency
PPD	Purified Protein Derivative
PPM	Public-Private Mix
PTE	Pre-Treatment Evaluation
Pto	Protionamide
PUR	Paradoxical Upgrading Reactions
QTcF	QT Prolongation (Fredericia's Correction)
R; RMP	Rifampicin
RBSK	Rashtriya Bal Swasthya Karyakram
RBS	Random Blood Sugar
RKSK	Rashtriya Kishor Swasthya Karyakram
RR	Rifampicin Resistance
RR-TB	Rifampicin-Resistant Tuberculosis
RS-TB	Rifampicin-Sensitive Tuberculosis
R&R	Recording & Reporting
S	Streptomycin

SAATHII	Solidarity and Action Against The HIV Infection in India
SAE	Serious Adverse Event
SAM	Severe Acute Malnutrition
SLD	Second-Line Anti-TB Drugs
SLI	Second-Line Injectable
SL-LPA	Second-Line-Line Probe Assay
SoP	Standard Operating Procedures
STLS	Senior Tb Laboratory Supervisor
STR	Standardized Treatment Regimen
STS	Senior Treatment Supervisor
TB	Tuberculosis
TDC	TB Detection Centre
TBHV	TB Health Visitor
TBI	Tuberculosis Infection
TBM	Tuberculosis Meningitis
TLD	Tenofovir disoproxil, Lamivudine, Dolutegravir
TPT	Tuberculosis Preventive Treatment
Trd	Terizidone
TU	TB Unit
TST	Tuberculin Skin Test
UDST	Universal Drug Susceptibility Testing
ULN	Upper Limit Of Normal
UPT	Urine Pregnancy Test
USG	Ultrasonography
WHO	World Health Organization
XDR-TB	Extensively-Drug Resistant TB
Z	Pyrazinamide
ZN	Ziehl-Neelsen stain

Glossary:

A second-line TB drug: This is an agent reserved for the treatment of drug-resistant TB. First-line TB drugs used to treat drug-susceptible TB – ethambutol, isoniazid and pyrazinamide – may also be used in MDR-TB regimens (streptomycin is now considered a second-line TB drug and used only as a substitute for amikacin when amikacin is not available or there is confirmed resistance to it).

Active case finding (ACF): It is defined programmatically as systematic screening for TB disease through outreach activities outside health facility settings.

At-risk Group: Is any group of people in whom the prevalence or incidence of TB is significantly higher than in the general population.

Bacteriologically confirmed TB: TB diagnosed in a biological specimen by smear microscopy, culture or a World Health Organization-endorsed (WHO) rapid molecular test and adopted by NTEP such as Xpert MTB /RIF®/Truenat®.

Child: For the programmatic purpose in India, a child is a person up to and including 18 years of age. (This includes adolescents aged 10–18 years).

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

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

Close contact: This is a person who is not in the household but shares an enclosed space, such as at a social gathering, workplace or facility, for extended periods during the day with the index TB patient during the three months before the commencement of the current TB treatment episode. This Group will be included for all interventions as applicable for household contacts in these guidelines.

Drug susceptibility testing: DST refers to in-vitro testing using either of the phenotypic methods to determine susceptibility.

Drug resistance testing: DRT refers to in-vitro testing using genotypic methods (molecular techniques) to determine resistance.

Extensively drug-resistant TB (XDR-TB): TB caused by Mycobacterium tuberculosis strains that fulfil the definition of MDR/RR-TB and are also resistant to any fluoroquinolone (levofloxacin or moxifloxacin) and at least one additional Group A drug (presently to either Bedaquiline or linezolid [or both]).

Extent or severity of the disease: In patients older than 18 years, this is usually defined by the presence of cavities or bilateral disease on chest radiography or smear positivity. In children under 18 years, severe disease is usually defined by the presence of cavities or bilateral disease on chest radiography or extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression). In children, the occurrence of advanced malnutrition (defined by syndrome or by metrics) or advanced immunosuppression or positive tuberculosis (TB) bacteriology (smear, NAAT, culture) may also be considered when determining disease severity.

High TB transmission setting: This is a setting with a high frequency of individuals with undetected or undiagnosed TB disease, or where infectious TB patients are present, and there is an increased risk of TB transmission. (TB patients are most infectious when they are untreated or inadequately treated. The transmission will be increased by aerosol-generating procedures and by the presence of susceptible individuals. These settings with healthcare workers, prisoners, miners, slum dwellers, tribal, migrant labourers etc., could be mapped out as part of the vulnerability mapping exercise done for and prioritized by states for specific TPT interventions guided by differential TB epidemiology in the respective state).

Index patient of TB: This is the initially identified person of any age with new or recurrent TB in a specific household or other comparable settings in which others may have been exposed. (An index TB patient is a 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.

Isoniazid-resistant TB (Hr-TB): A TB patient whose biological specimen is resistant to isoniazid and susceptibility to rifampicin has been confirmed.

Mono-resistant TB (MR TB): A TB patient whose biological specimen is resistant to one first-line anti-TB drug only.

Multidrug-resistant TB (MDR-TB): A TB patient whose biological specimen is resistant to both H and R with or without resistance to other first-line anti-TB drugs. MDR-TB patients may have additional resistance to any/all FQ or any other anti-TB drug.

Presumptive TB: This refers to a person with any of the symptoms or signs suggestive of TB. (Diagnosis of TB is difficult in certain key groups of the presumptive TB patients like extra- pulmonary, PLHIV, children, smear negative /NA with x-ray suggestive of TB, other vulnerable groups as defined in TOG-2016 and DR-TB contacts, hence, NAAT is offered upfront for diagnosis of TB among these presumptive TB patients).

Presumptive DR-TB: It refers to the patient eligible for rifampicin-resistant screening at the time of diagnosis OR/and during the course of treatment for DS-TB or H mono/poly DR-TB. [This includes all notified TB patients (Public and private), follow-up positive on microscopy including treatment failures on standard first-line treatment and H mono/poly DR-TB regimen and any clinical non-responder including paediatric].

Pre-extensively drug-resistant TB (Pre-XDR-TB): TB caused by Mycobacterium tuberculosis strains that fulfil the definition of MDR/RR-TB and are also resistant to any fluoroquinolone.

Poly-drug resistant TB (PDR-TB): A TB patient whose biological specimen is resistant to more than one first-line anti-TB drug, other than both H and R.

Programmatic management of TB preventive treatment: PMTPT includes all coordinated activities by public and private health caregivers and the community to scale up TB preventive treatment to people who need it.

Rifampicin resistant TB (RR-TB): A TB patient whose biological specimen is resistant to R was detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to R in the form of mono-resistance, poly-resistance, MDR or XDR.

Serious adverse events: SAEs are those adverse events (AEs) classified as Grade 3 (severe), Grade 4 (life-threatening or disabling) or Grade 5 (death related to AE), or which led to the drug being stopped permanently. SAEs are otherwise often defined as AEs that lead to death or a life-threatening experience, initial or prolonged hospitalization, persistent or significant disability, or congenital anomaly. The management of SAEs may require termination of the drug suspected of having caused the event.

Systematic screening for TB disease is a systematic identification of people with presumed TB disease in a predetermined target population, using tests, examinations, or other procedures that can be applied rapidly. (Among those screened positive, the diagnosis needs to be established by one or several diagnostic tests and additional clinical assessments, which together have high accuracy).

Tuberculosis (TB) is a 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 TB infection).

Tuberculosis infection (TBI) 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 developing TB disease. TB infection is also known as “latent TB infection” (LTBI), although this term is being discarded given that infection cannot always be considered latent).

Tuberculosis preventive treatment (TPT) is offered to individuals who are at risk of developing TB disease to reduce that risk. (Also referred to as the treatment of TB infection).

Universal DST refers to universal access to rapid DST for at least Rifampicin (and where possible INH). It also includes DST for fluoroquinolones among all TB patients with Rifampicin resistance (preferably before initiation of treatment or as soon as possible).

Underweight: In adults and adolescents, underweight usually refers to a body mass index <18.5 kg/m2 and in children < 10 years to a weight-for-age < −2 z-scores.

CHAPTER 1 BACKGROUND

Childhood Tuberculosis (TB) is a staggering problem. In India, approximately 3.42 lakh children (0-14 years of age) are estimated to get TB every year, and account for about 6% of total TB cases reported to NTEP in 2020[1]. In 2020, approximately one lakh children with TB (0 to 14 years of age) were reported to the NTEP, while an additional 1.4 lakh children were reported to the NTEP in the age group of 15-18 years[2]. Consistently, children constitute 6-7% of all the patients treated under NTEP annually. Nevertheless, there are some variations in the case reporting across the states, attributed to differences in the burden of disease, health-seeking behaviour, and availability of services.

Nearly a third of the children with TB globally are from India, despite an estimated detection gap of about 56%. Children up to the age of 14 years constitute 35% of the population in our country and are estimated to contribute approximately 10% of the caseload. However, reported numbers may be low as many children are treated outside the National TB programme. Pulmonary TB is the most common form of TB in children; however, extra-pulmonary TB (EPTB) in children forms a more significant proportion of cases than adults. Adults comprise the largest proportion of TB cases as the adulthood span is far longer than paediatric. In addition, TB control does not figure prominently as one of the child survival strategies. The child survival strategies are expectedly focused on the diseases with the highest mortality among the under-five, including premature birth, perinatal asphyxia and injuries, pneumonia and diarrhoea. Among the other causes of childhood, mortality is TB, albeit unrecognised yet important. However, the exact contribution of TB to 'Under-5 Mortality' is unknown. Many TB related deaths are possibly reported as pneumonia due to similar respiratory symptoms, and autopsy studies from few African nations support this contention. As a singular organism, *Mycobacterium tuberculosis (M.tb)* contributes to most death of under-five among the world's middle and lower-income countries.

Although the principles of diagnosis and treatment remain similar in children and adults, the differences in the type of disease and specific host characteristics bring up some challenging variations. Adults and older children more often have the infectious form of TB, which may be confirmed by testing sputum, while in general, younger children have forms of TB that show up poorly on sputum smears. Moreover, difficulties in accessing the specimen from children who swallow rather than bring out sputum add further challenge. Whereas alternative methods to collect respiratory samples are more invasive and require professional skills. Confirmation of TB and its drug sensitivity does require microbiological testing but the sophistication of diagnosis among children often makes it challenging to decentralise it to the community level.

[1] Central TB Division, 2020. India TB Report - 2020. National Tuberculosis Elimination Program - Annual Report. New Delhi: Central TB Division, Ministry of Health and Family Welfare, Government of India.

[2] Central TB Division, 2021, Nikshay Data from National Tuberculosis Elimination Program, Ministry of Health and Family Welfare, Government of India.

Rapid molecular diagnostic methods like newer generation cartridge-based nucleic acid amplification tests (Xpert-RifTM /TruenatTM) and Line Probe Assays (LPA) have been approved and employed by the National TB elimination Program (NTEP). These tests can rapidly identify Mycobacterium tuberculosis with much-improved sensitivity compared to conventional smear testing, even among specimens from children but are far more expensive when pursued in the private sector. Nevertheless, the final yield of TB testing is better if the microbiological confirmation is done on good quality specimens from cases with high suspicion of TB based on clinical and radiological abnormalities. As the symptoms suggestive of pulmonary TB are non-specific and overlapping, initial screening with chest imaging helps prioritise cases for testing by NAAT.

Furthermore, newer molecular tests can simultaneously detect much critical rifampicin resistance as they are nested or two-step automated Polymerase Chain Reaction (PCR), leading to a significant shift in diagnostic strategy. Such diagnostic modalities have paved ways for Universal drug sensitivity testing (U-DST), the core programmatic strategy and refers to upfront testing of all TB cases for Rifampicin resistance and further for Fluoroquinolones and Isoniazid (INH). Therefore, all TB cases (new or retreatment) must now be tested for drug resistance upfront and instituted specific treatment as per the resistance pattern detected.

In addition, several changes have come up in the treatment of TB. Firstly, for children, dosages of anti TB drugs have been revised upwardly to achieve optimal drug levels, and now the Fixed Drug Combinations (FDCs) are used to decrease the risk of missing a particular drug from the prescribed regimen. Secondly, awareness about high initial Isoniazid resistance and its contribution to the failure of the retreatment regimen has led to the use of a third companion drug (Ethambutol) in the continuation phase of the first-line therapy. Lastly, the standard retreatment regimen, commonly known as category II therapy, has been withdrawn.

The current decade has witnessed a revitalisation in new activities led by recent innovations in TB with a renewed commitment to eliminate the disease from the world. Understanding the disease, drug therapy and its pharmacokinetics, resistance amplification, and newer diagnostics and drugs have created an opportunity to use this knowledge to improve child TB care in specific and child health care in particular. The present updated guidelines capture the use of newer diagnostics and therapy modifications for managing TB in children to achieve the goal of early diagnosis, prompt and effective therapy guided by the sensitivity pattern to key drugs.

CHAPTER 2 DIAGNOSIS OF TB IN CHILDREN

2.1 Presumptive Paediatric TB

Presumptive Paediatric TB refers to children suspected to be suffering from TB based on any of the following symptoms: persistent fever, cough for more than two weeks, loss of weight. A definite weight loss (≥5% loss in the past three months) or failure to gain weight in the past three months despite adequate nutrition with no other apparent cause should prompt detailed history, examination and investigation, including investigations for TB.

Moreover, presumptive TB cases (Pulmonary or Extrapulmonary) would often have known contact with an infectious TB patient. In a symptomatic child, contact with a person with any form of active TB within the last two year**s** may be deemed significant.

The diagnostic algorithm below gives the recommended pathway for the diagnosis of intrathoracic tuberculosis in children. Experts believe that while the symptoms suggestive of TB can be mimicked by several other diseases; however, if they are properly characterised, the probability of finding those with TB improves. Persistent cough and fever for two weeks or more without a known cause is an excellent clinical marker, particularly if associated with weight loss or a history of exposure to a case of active TB. Weight loss or not gaining weight should always be documented with appropriate and proper weighing. The patient should always be weighed with minimal clothing and without shoes using a tared scale.

All these presumed cases are subjected to further investigation for TB. The initial specific investigation recommended is a frontal Chest skiagram. If a recent good quality chest x-ray film is available, repeat testing is not routinely recommended. This is a significant shift from the earlier guidelines where a sputum smear examination was the initial recommended test.

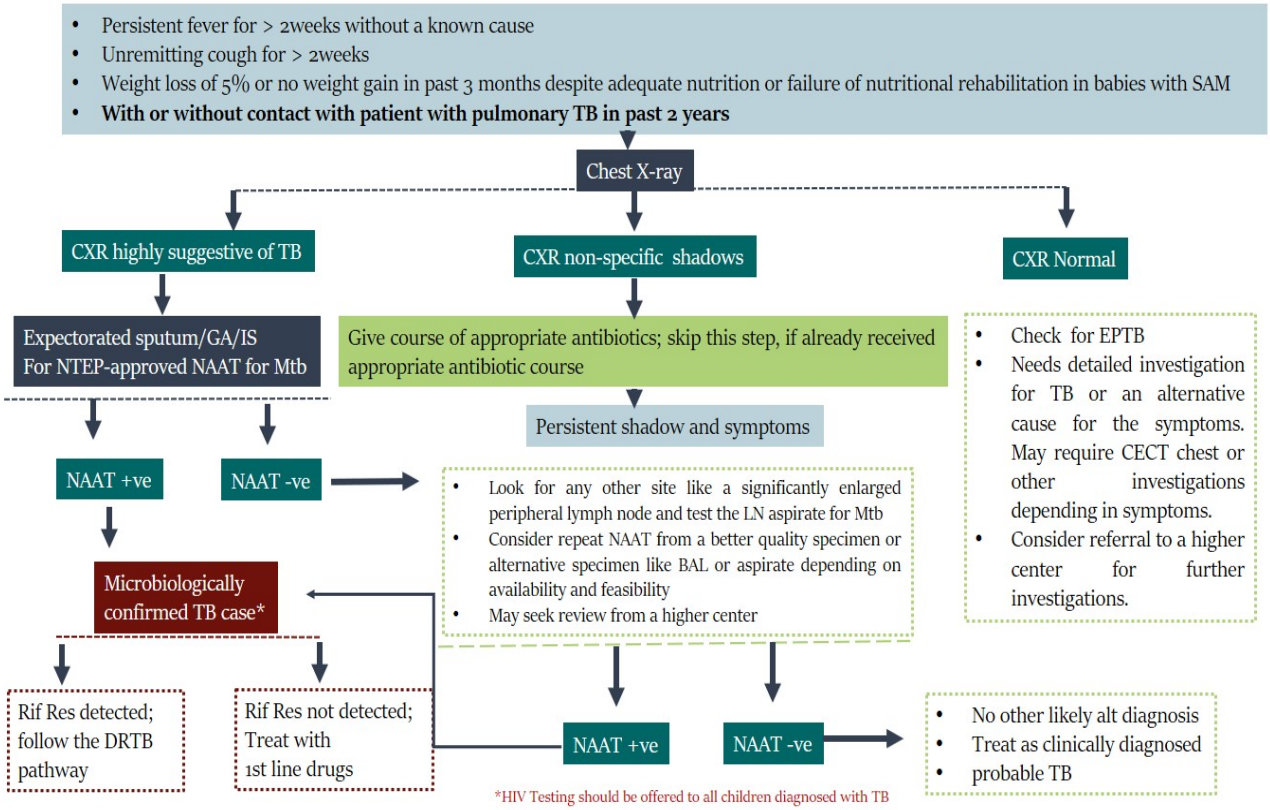
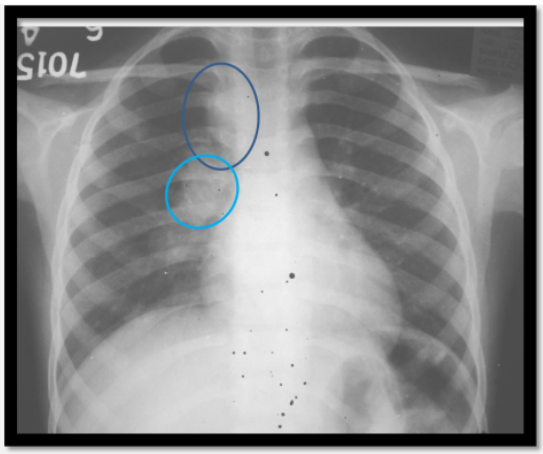


Figure. 1 Diagnostic Algorithm for Pulmonary TB in Children

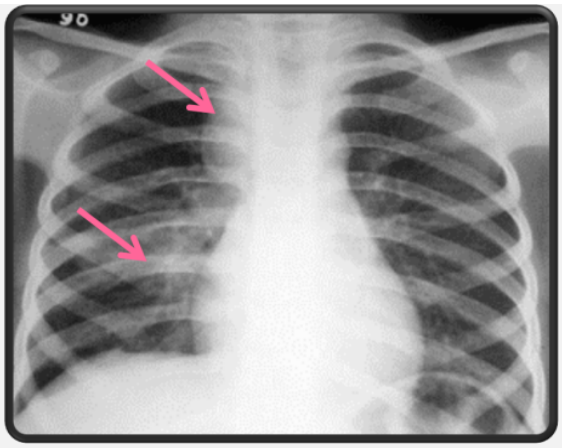
2.2. Chest Imaging for Tuberculosis in Children

A plain radiograph with a frontal view of the chest is the initial investigation advised. Radiological findings considered highly suggestive of tuberculosis in the suggested clinical setting include a) miliary shadows – diffuse micronodular shadows affecting both the lungs like a snowstorm. b) intrathoracic lymphadenopathy (usually seen as a dense well-circumscribed ellipsoid or rounded shadows in the hilar or mediastinal regions), c) Chronic fibro-cavitary shadows (usually, but not exclusively, seen in the apical regions).

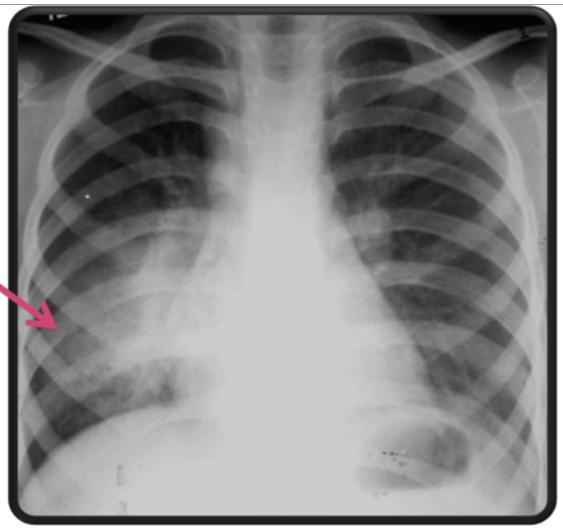
Findings like consolidations, in-homogenous shadows or bronchopneumonia, etc. are considered non-specific as they may also be seen in other bacterial diseases. The following set of chest skiagrams show the various highly suggestive lesions seen on chest imaging in TB.



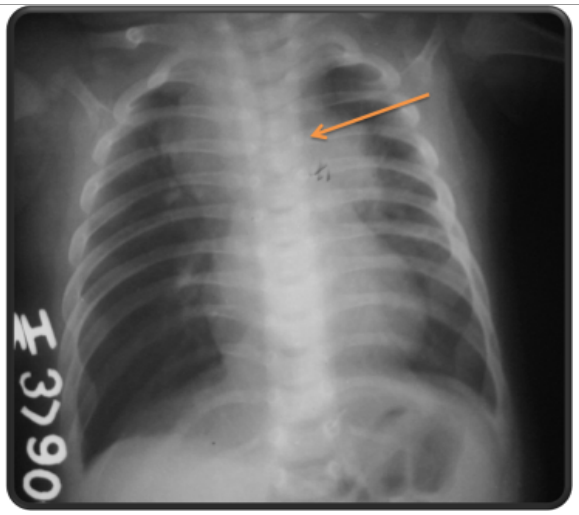
Right paratracheal and hilar node enlargement.



A parenchymal lesion is seen on the Right lower zone with the associated right paratracheal node enlargement.

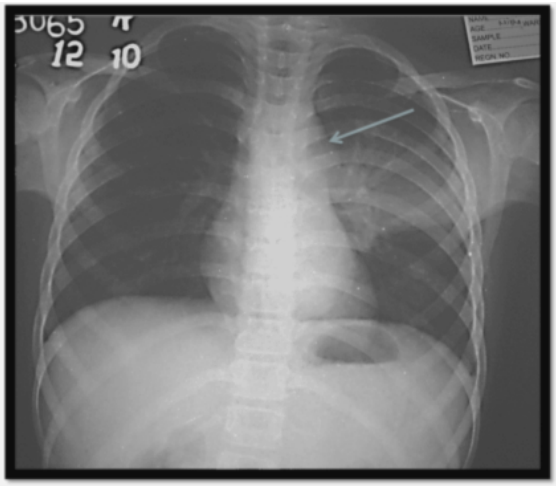


In some cases, there might be a consolidation with a contralateral nodal enlargement (as shown) but it can sometimes be without any discernible node on frontal view.

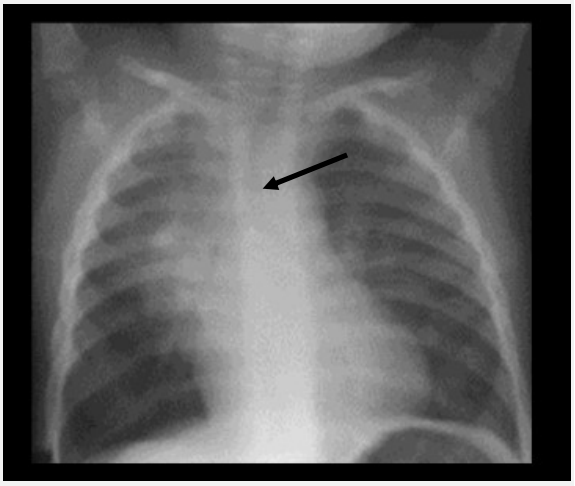


A Lymph Node mass with airway compression (arrow) with radiological suggestion of partial obstruction with Right sided hyperinflation.

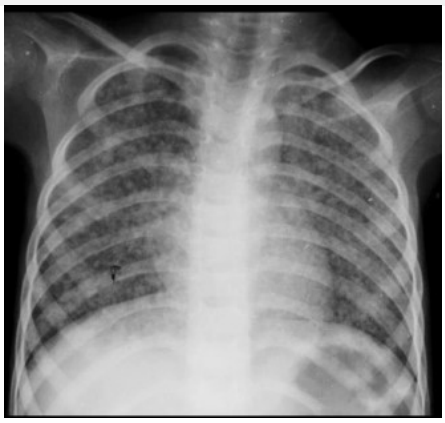
Figure 2a. Chest Imaging in TB



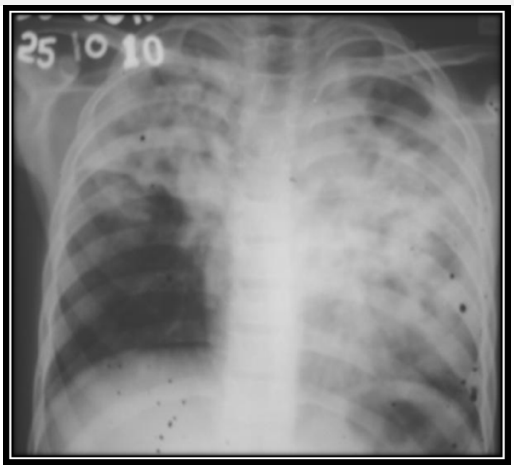
The x-ray shows a lymph node shadow in the aorto-pulmonary window with an accompanying area of consolidation



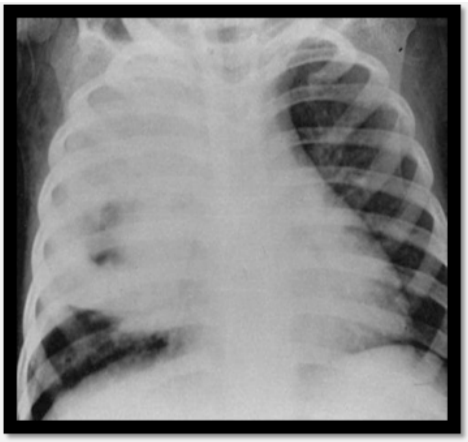
Pulmonary Primary Complex with the compression of lower third of trachea (arrow) and right airway



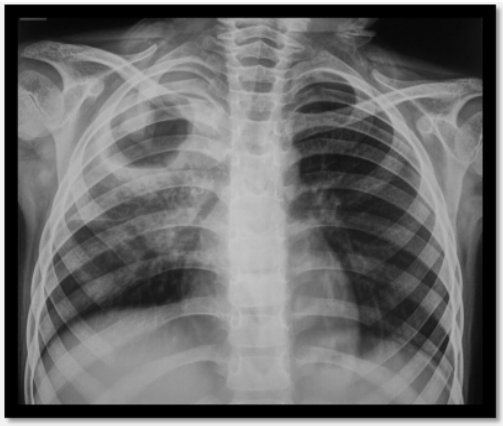
Miliary shadows in both lung fields are highly suggestive of TB in our s.et up



Extensive disease with multiple areas of breakdown, more on the left side (Fibro-cavitary pneumonia)



Cavitary Pneumonia



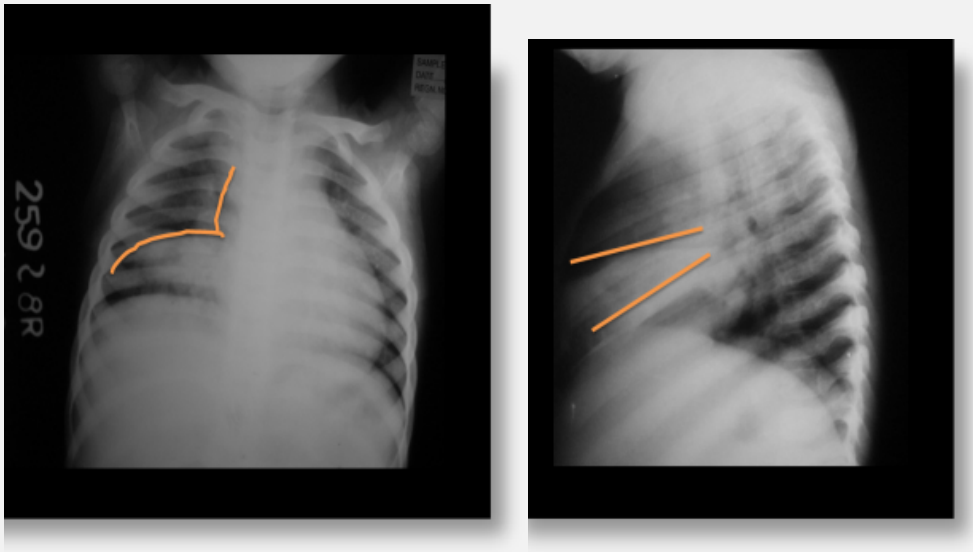
Cavitary Pneumonia

Figure 2b. Chest Imaging in TB

Chest radiography is also an important tool to support the diagnosis of pulmonary TB in children. In the relevant clinical setting, a diagnosis of TB may need to be made on a clinical basis based on highly suggestive imaging findings of tuberculosis (miliary pattern, hilar or paratracheal lymphadenopathy with or without parenchymal involvement and fibro-cavitary lesions). It is worth remembering that all these imaging patterns also have other differential diagnoses. All presumptive TB cases with these radiological patterns are considered to be probable cases and should be subjected to microbiology to confirm the diagnosis. If microbiological investigations are negative, these children can be deemed to be cases of ***clinically diagnosed tuberculosis*** (TB), provided alternative causes are ruled out. Specificity of diagnosis in such situations increases in the presence of pointers like positive TST or history of contact.

Non-specific findings on chest X-ray refer to patterns other than highly suggestive patterns described above and includes: consolidations, in-homogenous shadows or bronchopneumonia, etc. As these abnormalities can often be seen with other aetiologies like bacterial disease, such patients should be given a course of appropriate antibiotics (Amoxycillin or co-amoxiclav), mainly if the blood counts show neutrophilia.

Antibiotics like Linezolid or any quinolone should not be used as they have anti-TB action. Clinical clues may prompt earlier investigation for TB in some cases, e.g. widespread bacterial pneumonia is unlikely to be clinically silent (absence of significant distress or fever). In contrast, mycobacterial pneumonia may have disproportionately lesser clinical findings than the extent of radiological changes.



The PA chest x-ray shows an area of consolidation on the right side lower zone with silhouetting of the right cardiac border. Right lateral film of the same case is showing the shadow in the middle lobe area overlying the cardiac shadow

Figure 2c. Chest Imaging in TB

Suppose the non-specific radiological patterns do not resolve despite adequate antibiotic therapy in a symptomatic child. In that case, they need to be evaluated with Induced Sputum (IS)/ Gastric Aspirate (GA) for *M.tb* . If negative by NAAT or culture, a further evaluation like CT chest and flexible bronchoscopy for persistent pneumonia are required. The differential diagnosis in such situations is significant, of which TB might be one of the possibilities. These children need to be referred for further evaluation, and a trial of Anti-Tubercular Treatment (ATT) is not justified without ruling out other diseases.

Chest radiographs in a patient who has been treated in the past can have post-TB changes like opacities secondary to pleural thickening, fibro-atelectatic changes or areas of bronchiectasis. These children are usually asymptomatic except in children with post-TB bronchiectasis, where they may show symptoms of suppurative lung disease. Such cases also need expert evaluation to differentiate and confirm disease recurrence if new symptoms come up after successful treatment.

It is crucial to remember that several factors can lead to both under and overdiagnosis of TB on chest radiology. Leading issues associated with possible errors include technical quality of films like exposure, rotation, motion blur, etc.; inter and intra-individual variations in reading; errors in interpretation due to artefacts; confounders like a thymic shadow, etc.

CT Scan is sometimes necessary but is costly and gives significant radiation. Therefore, it should be used judicially; however, CT is an essential tool for evaluating children with persistent pneumonia or persistent fever without apparent focus. Certain CT patterns that can be highly suggestive of TB, although not diagnostic, are necrotic mediastinal lymphadenopathy, centrilobular nodules with tree-in-bud pattern and cavities with surrounding consolidations. Chest CT scan also may offer an opportunity for CT guided biopsy for tissue diagnosis.

Ultrasonography (USG) of the chest is helpful to assess the pleural fluid collection. It is useful for differentiating thymus and anterior lymph nodes and identifying the best spot for aspiration/ Fine Needle Aspiration Cytology / biopsy in a peripheral lesion.

2.3. Microbiological Tests

The new strategy is to test all TB patients upfront for resistance, particularly rifampicin using NTEP-approved rapid NAAT on relevant body specimens. For pulmonary TB, respiratory secretions like self-expectorated sputum or induced sputum or gastric aspirate or lavage, etc., can be used. As the access to samples among children is not easy, there is merit in targeting collection among children after a positive screening on chest radiography. While the patient is immediately subjected to relevant specimen collection and testing if the screening chest imaging shows highly suggestive radiological features, but in case the screening radiograph shows non-specific findings (described before), the respiratory specimen collection for M. tb is advised if the symptom persists even after a full seven days' course of a potent suitable antibiotic (like Amoxycillin or Co-amoxiclav). Exceptions may need to be made if there is a clinical urgency and the child has a high probability of having tuberculosis.

As most young children cannot expectorate sputum, alternatively, the swallowed sputum is collected from the stomach after a period of fasting (usually 4-6 hrs, preferably overnight) as gastric aspirate. Early morning gastric aspirate is a preferred specimen for most young children with presumptive TB. It needs to be done on an empty stomach and requires skilled staff. While it should ideally be done early in the morning, after overnight fasting (usually feasible in an inpatient), but as an alternative, it can also be collected in ambulatory settings after 4-6 hours of fasting with some compromise on the yield. (See Annexure 2 for Method to collect gastric aspirate; video available at: https://tbcindia.gov.in/index1.php?lang=1&level=2&sublinkid=5305&lid=3415)

Induced sputum is another sample that can be obtained in children who are unable to produce sputum. Induction of sputum can be easily performed in young children, including infants with an acceptable yield of the sample. It does not require prolonged fasting and should be done with adequate infection control practices as the procedure provokes cough, increasing the risk of transmission. (See Annexure 3 for Method to collect induced sputum; Video available at: https://tbcindia.gov.in/index1.php?lang=1&level=2&sublinkid=5305&lid=3415).

A good sputum sample consists of recently discharged material from deep inside the chest (the inner airways) with a minimum amount of oral or nasopharyngeal material, has mucoid or mucopurulent character and should be 2-5 ml in volume. It should be collected in a sterile container after rinsing the oral cavity with clean water. Under the programmatic conditions, a conical tube, like Falcon's tube, is the preferred container. The collected specimens should be labelled appropriately, safely packaged and transported to the laboratory as soon as possible after collection. If a delay is unavoidable, the samples can be refrigerated to inhibit the growth of unwanted microorganisms and tested no later than seven days after collection. If the patient does not produce any sputum, even after induction, any other available respiratory specimen like bronchoalveolar lavage (BAL), lung aspirate, etc., can be collected by a skilled health care provider depending upon available facilities.

Bronchoscopy and bronchoalveolar lavage are required in select cases of persistent pneumonia for final diagnosis. They may be performed when routine investigations for TB are inconclusive or for children who are drug-resistant TB suspects. Precious or challenging to get specimens like BAL or lung aspirate should also be subjected to culture and drug sensitivity, particularly if the rapid test is negative.

Many children with TB may have a concomitant extra-pulmonary (EP) disease. Specimens from the EP site can also be used to establish a diagnosis. However, no preservative should be used for any extra-pulmonary sample for culture. Moreover, necessary instructions are to be given to the concerned staff for sending the biopsy specimen in normal saline for culture and not in preservatives like formaldehyde as it kills bacilli.

The available initial diagnostic tests are NTEP approved rapid NAAT (Xpert Rif™ - a cartridge-based nested NAAT for detecting *M.tb* and its resistance to Rifampicin; Truenat™ M.tb Plus – a chip-based NAAT to detect *M.tb* and then sequentially test for Rifampicin resistance using *M.tb* Rif Dx™). These rapid NAATs can test several different types of clinical specimens like sputum, induced sputum, gastric aspirate or lavage, and

various other body fluids. In addition, line probe assays (LPA) are also available under the programme (Hain test/ MTB DRplus™, MTB DRsl™). These tests take up to 72 hours and can be used only on smear-positive sputum specimens or culture isolates for Genotypic DST. This is currently the only WHO, and NTEP recommended rapid test to detect additional drug resistance in MDR-TB and XDR-TB patients. The First Line-LPA thus detects *M.tb* and the presence of resistance to R and H (MTB DRplus™). A second Line-LPA (MTB DRsl™) is available for testing for resistance to class Fluoroquinolones (FQ) and class second-line injectables (SLI).

A single good quality specimen with the newer rapid molecular tests is usually adequate (unlike two samples needed for the Acid Fast Bacilli smear test). Despite the more recent rapid tests having a much higher sensitivity and specificity than the smear for Acid Fast Bacilli (AFB), the newer tests perform poorly in culture-negative cases. Their sensitivity is less than the culture, which detects between a third to nearly half the cases. Thus, more recent molecular tests are good "Rule–in tests" due to their high specificity. Still, a negative test does not rule out TB disease as approximately half of the paediatric TB cases are culture negative due to the very nature of the disease.

Moreover, studies have shown that newer rapid NAAT tests perform very poorly with pleural or ascitic fluid compared to respiratory specimens, Lymph Node (LN) aspirates, pus and CSF. It is suggested that children with persistent symptoms, non-specific shadows, and negative results of smears and other NAAT samples (GA/IS) should undergo further workup to diagnose persistent pneumonia at appropriate facilities. Many such cases are diagnosed as TB based on the clinical and radiological features after excluding other diagnoses.

As discussed previously, NAAT being a nested PCR, provides additional information about Rifampicin resistance. Furthermore, when Rifampicin resistance (RR) is seen, the patient is offered First Line (FL) and Second Line (SL) Line Probe Assay (LPA). RR detected in a new case with no risk factors for Drug-Resistant Tuberculosis (DR-TB) needs to be retested, only if *M.tb* detected was very low as that could be a false positive. If there is a discordance in Rifampicin resistance between NAAT and LPA, a second NAAT is performed at the Culture and Drug Susceptibility Test (C & DST) laboratory using the decontaminated deposit, and the microbiologist will provide the final decision. Additionally, direct LPA can be performed only on smear-positive specimens. In instances where the smear is negative, culture is set up, and if the culture is positive, an indirect LPA is performed on the isolate.

Xpert Ultra is increasingly being used in the Private sector. Machine printouts of results from Xpert Ultra may be considered for guiding treatment; however, uncertainty in trace calls warrants clinical correlation / additional tests to be ordered by the treating physician.

2.4. Skin Test and Interferon-Gamma release assays (IGRAs) and Other Tests for TB

Tuberculin Skin Test (TST) is an intradermal injection of Purified Protein Derivative (PPD). (See Annexure 6 for TST technique) The current recommendation is to use 2TU PPD RT23 for all diagnostic purposes. Mantoux's test or PPD skin test is considered positive if the induration is 10 mm or more. In HIV co-infected

cases, 5 mm may be taken as the cut-off. It is an immunological test that elicits delayed-type hypersensitivity. TST is used as an adjunct to other tests, and in the diagnosis of TB, it has the same connotation as a history of contact. A positive test indicates present or past infection with *M.tb.* but cannot distinguish infection from disease. Currently, this test is not possible due to the non-availability of any form of the original lot of RT23 PPD. Most commercially available products are not from the standard mother lot and thus can cause problems in interpretation as the cut-offs derived for the standard product may not be applicable (Annexure 6). The utility of skin tests to assist the diagnosis of TB has decreased as the availability and sensitivity of microbiological tests has improved.

Interferon-Gamma Release Assays (IGRAs), which provide an *in vitro* measure of *M.tb* hypersensitivity, offer the same information as TST and the tests currently approved by the WHO are TB Quantiferon Gold™ and TB Spot™ are available. Unlike Tuberculin Skin Test, they do not require a repeat visit for test reading and do not cross-react with BCG vaccination but need to be rapidly transferred to the lab and are expensive. A positive test marks the presence of TB infection in an individual but cannot confirm the presence of disease.

Diagnostics like serology (IgM, IgG, IgA antibodies against M. *tb* antigens), various in-house or non-validated commercial PCR tests and Bacillus Calmette–Guérin (BCG) tests are not recommended as TB diagnostic tools as they are often inaccurate. ESR is another test often used as a supportive investigation. Still, it is of no value in ruling in or ruling out the diagnosis of TB due to its non-specificity and the possibility to be affected by many variables other than the disease. A positive test result by either of the two available methods is not a reliable indicator that the person will progress to TB disease as the possibility of false-positive results cannot be ruled out. Conversely, a negative test result does not rule out TBI, given the case of a false-negative test result among at-risk groups, such as young children or among those recently infected.

C-Tb (Statens Serum Institut, Copenhagen, Denmark) is the next-generation skin test for the detection of TBI, which SSI Copenhagen has developed. It is an easy-to-use point-of-care test. It can deliver IGRA-like performance in a skin test format and uses a universal 5 mm cut off to differentiate the infected from the uninfected. The test is based on ESAT-6 and CFP-10 antigens (same as those used in IGRA) specific for *M. tb* and is unaffected by BCG vaccination. However, it is currently unavailable commercially and will be adopted in the programme once available and approved.

CHAPTER 3 DIAGNOSIS OF EXTRAPULMONARY TB

Extrapulmonary TB (EPTB) refers to any microbiologically confirmed or clinically diagnosed case of TB involving organs other than lungs, e.g. lymph nodes, pleura, bones, joints, intestine, genitourinary tract, meninges of the brain etc.

Presumptive Extrapulmonary TB refers to the presence of organ-specific symptoms and signs like swelling of lymph nodes, pain & swelling in joints, neck stiffness, disorientation etc. They may also have constitutional symptoms like significant weight loss, persistent fever for more than two weeks, night sweats. An effort should be made to establish microbiological confirmation in case of presumptive EPTB. Appropriate specimens from the likely sites of involvement must be obtained from every presumptive EPTB patient for NAAT/smear microscopy/ culture and DST for *M.tb* / histopathological examination etc., based on feasibility. Chest X-ray, USG, etc., are other investigations that can be used as supportive tools for diagnosing EPTB.

Sensitivity of NAAT for *M.tb* detection in pus, aspirate/biopsy specimen from lymph nodes, other tissue samples, and CSF is low to moderately high but poor in pericardial, ascitic and synovial fluid samples and still poorer in pleural fluid. A positive result by culture or NAAT provides useful confirmation. However, a negative culture or NAAT cannot rule out TB due to the inadequate sensitivity of these tests in extrapulmonary specimens. Therefore, if investigations like NAAT/smear microscopy/culture, etc., turn out to be negative or if an appropriate specimen is not available for these investigations, consultation with a specialist followed by other tests, e.g. histopathology, radiology, cytology etc. may be undertaken to reach a diagnosis. Often, the diagnosis in these situations is clinically based on suggestive history, presentation and other supportive investigations. Possible alternative diagnoses must be diligently ruled out in a patient who is clinically diagnosed to have TB.

3.1. TB Lymphadenitis

Lymph node TB is one of the most common forms of EPTB, and cervical lymph nodes are the most common site with or without associated disease of other lymphoid tissue. It usually occurs in the age group of 5-9 years. The presenting features are enlarging masses over weeks to months. Cervical lymph nodes, particularly jugular, posterior triangle and supraclavicular, are affected; axillary and inguinal are sometimes involved. Systemic symptoms may be seen in some patients. A clinical correlate of diagnosis includes progressive enlargement of lymph node for more than two weeks, firm, minimally tender or non-tender, with or without fluctuation. Affected nodes may get matted, turn into a cold abscess and may rupture and develop chronic sinus. Moreover, large lymph nodes may be present due to various infections or malignancy. Histopathology is the usual gold standard test for establishing the aetiology of enlarged nodes. Fine Needle Aspiration Cytology (FNAC) is an alternative test usually considered adequate for accurate diagnosis as it correlates well with biopsy in more than 90% of cases. However, both these tests require a skilled pathologist to report on the specimen and therefore, these tests are may not always be feasible in the peripheries. Besides, needle

aspirate from the node can be easily tested for the presence of AFB or NAAT to diagnose TB in such cases in a more decentralised fashion without needing the services of a skilled pathologist. However, since there are better alternatives available and the yield of smear for AFB / NAAT is moderate at best, all cases negative for these tests should be subjected to a detailed FNAC/ histopathology. In the case of tuberculosis, histopathology typically shows epithelioid granuloma with or without central acellular necrosis (Annexure 4 for Needle aspiration of LN and similar swellings video available at: https://tbcindia.gov.in/index1.php?lang=1&level=3&sublinkid=5320&lid=3419)

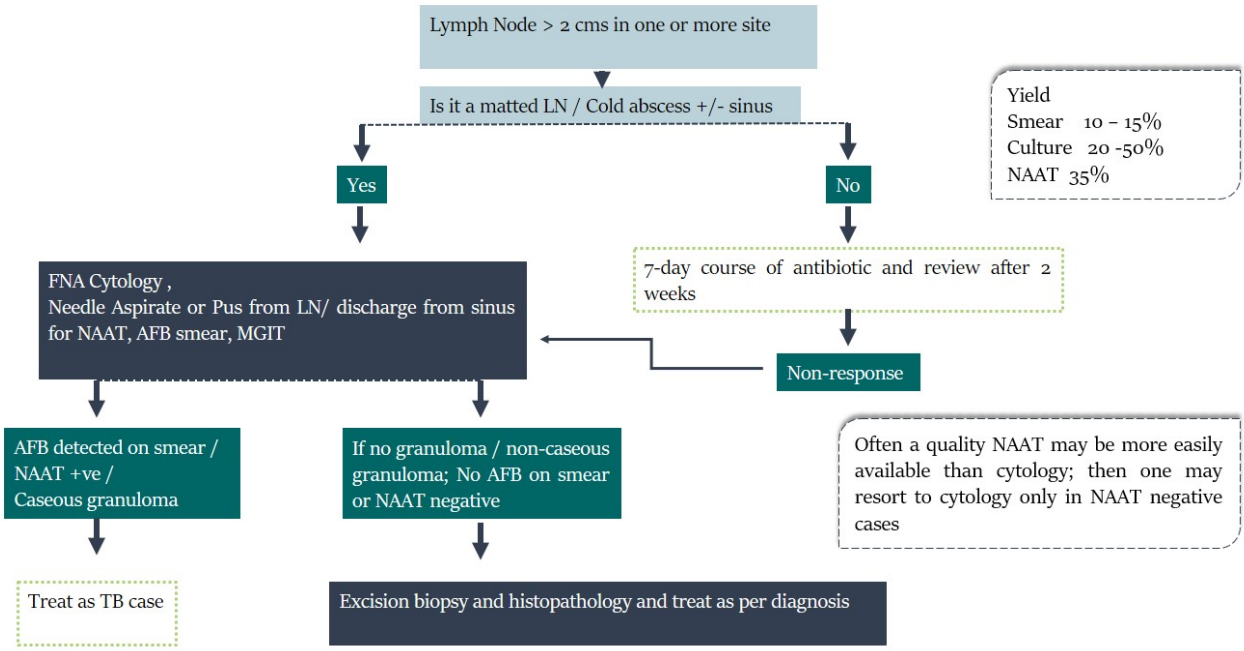


Figure. 3 Diagnostic Algorithm for Tubercular Lymphadenitis

Ultrasonography may be helpful to identify affected non-palpable or deep-seated nodes for needle aspiration and testing. Central hypoechogenicity in a node on USG is considered suggestive of TB and may improve testing yield by targeting such nodes for aspiration.

Furthermore, on chest X-Ray, 5-40% of patients identified to have peripheral TB lymphadenitis may have pulmonary/ pleural abnormalities, hilar/ mediastinal lymph nodes, parenchymal lesions or pleural effusion. Skin test for TB test is positive in a significant proportion (>70%) of patients but does not contribute to establishing the diagnosis. Reactive adenitis in a child with positive TST does not mean TB adenitis.

In children, lymphadenopathy is expected due to recurrent tonsillitis and upper respiratory tract infections. Reactive lymphadenitis may clinically mimic tuberculosis but do not warrant anti-TB drugs. Hence, anti-TB drugs should not be given unless the diagnosis of TB is confirmed by microbiological tests (smear for AFB or

NAAT / Mycobacteria Growth Indicator Tube (MGIT) for *M.tb*) or by suggestive FNAC or histopathology. **Figure 3,** depicts the diagnostic algorithm for tubercular lymphadenitis.

3.2. Pleural Effusion

Children with tuberculous Pleural Effusion (PE) usually present with fever, chest pain, anorexia and weight loss. While more prolonged duration symptoms may make TB aetiology more likely, TB PE can often present acutely. TB effusion can present with high-grade fever. The clinical examination would reveal signs of effusion (decreased air entry with dull percussion).

The presence of effusion can be confirmed by chest imaging (USG or chest radiograph). Pleural diseases are best imaged with a USG, and its benefit relates to establishing the presence and extent of PE and not for establishing an etiological diagnosis. Nevertheless, CT Chest makes little contribution to suggest aetiology. Pleural fluid aspiration should always be performed, and the aspirate should be sent for biochemical, cytological and smear examination by Ziehl-Neelsen (ZN) stain to confirm the diagnosis. In the absence of a pleural fluid examination, it is usually not possible to infer any aetiology based on radiology alone. Typically, a tubercular effusion fluid is straw-coloured (pus, if aspirated, is very rarely due to TB aetiology) has large numbers of cells (in hundreds; predominantly mononuclear), with high proteins (>3g/dL). Moreover, the high protein content of the exudative effusion in tuberculosis causes it to form a cobweb on standing. However, the yield of NAAT in tubercular pleural effusion is low. Induced sputum/GA should always be tested for *M.tb* as about a quarter of the children with PE, GA or IS were positive on culture. On the other hand, the *M.tb* detection in Pleural fluid, by culture or NAAT, is about 5%. Similarly, positive skin test for TB is supportive and not diagnostic. Blood count within the normal range makes empyema or a complicated para-pneumonic effusion less likely. ESR has no role in establishing the aetiological diagnosis.

Although Adenosine Deaminase (ADA) has been used extensively to diagnose TB effusion in adults, its utility in children appears limited. Studies among adults have compared TB effusions with malignant effusions and have found it to be a good marker. However, very few studies compare TB effusion with parapneumonic effusions, which is the commonest other cause in children. Limited data suggest a significant overlap between the ADA values in TB effusion and pyogenic effusions, and therefore, it is not recommended to be used for children.

A pleural biopsy may be performed in unclear situations using Cope's or Abraham's pleural biopsy needle. The pleural tissue can be subjected to histopathology, ZN staining and MGIT cultures. The findings of granulomas with caseous necrotic tissue in the pleural biopsy makes the diagnosis of tuberculosis highly probable. The yield of pleural biopsy is more than 80%. In most circumstances, the diagnosis can be made by a combination of a long history, a non-sick child, an exudative (not pus) lymphocytic effusion. A skin test for TB may be another supportive clue.

3.3. Abdominal TB

Abdominal TB is a broad term as the disease can be present in intestinal, nodal, peritoneal, visceral and disseminated forms, with almost one-third of patients having the involvement of more than one of these sites. Symptoms and signs vary as per the site. However, common symptoms are abdominal pain, fever, distension, weight loss and anorexia. On examination, doughy abdomen, ascites, omental mass, organomegaly may be seen. Isolated recurrent or chronic pain without any other symptom is usually not due to TB.

Multimodality evaluation, including clinical, laboratory, radiology, endoscopy, microbiology, histopathology, is needed to reach a definitive diagnosis of abdominal TB. Tissue diagnosis remains most reliable though it is often not feasible. Plain X-Rays are not helpful for the diagnosis of abdominal TB. It may sometimes show non-specific features like enteroliths, perforation and features of intestinal obstruction.

Abdominal TB imaging

- CT enteropathy
- Ileocecal area is the commonest involved region
- Uniform and concentric bowel thickening
- Contracted and pulled up caecum
- Ileocecal angle is distorted and often obtuse
- Short strictures of less than 3 cm

USG / Contrast-enhanced Computed Tomography (CECT)

- Abdominal lymph node with central necrosis, conglomerate, peripheral enhancement
- Mesentric thickening of more than 15 mm
- Caked omentum, multiple SOL liver / spleen, loculated ascites

Box 1. Characteristic Image Findings of Abdominal TB

Ultrasonography is recommended as an initial modality of choice and may pick up lymphadenopathy, peritoneal thickening, omental thickening, bowel wall thickening, and ascites. Non-specific bowel wall thickening, a small amount of fluid in the mesentery or dependent areas of the abdomen, or the presence of non-matted intra-abdominal lymphadenopathy can be misleading. Contrast-enhanced CT and CT enterography provide adequate cross-sectional imaging in depicting various forms of abdominal TB. Barium studies are gold standards in diagnosing strictures, fistulae, erosions etc. Typical imaging findings are detailed in the box.

For peritoneal TB diagnosis, peritoneoscopy has a very high sensitivity (93%) and specificity (98%). There are usually one of these three types of findings on peritoneoscopy, *viz.* Hyperemic peritoneum with ascites and whitish miliary nodules, hyperemic peritoneum with ascites and adhesions and markedly thickened parietal peritoneum with yellowish nodules multiple thickened adhesions.

Diagnosis of abdominal TB is a challenge because of non-specific variable symptoms, low microbiological yield, need for multimodality investigations, complications of the wrong diagnosis. Many times, there is insufficient evidence to start ATT. Children with fever or failure to gain weight or functional abdominal pain often get diagnosed with abdominal TB as lymph nodes (usually around a centimetre in size) are detected on the USG abdomen. Chronic diarrhoea without proper evaluation is also often wrongly treated as TB abdomen.

3.4. Neurological TB

3.4.1. TB Meningitis (TBM)

TBM most commonly presents between six months to four years of age but can occur at any age. It is the most severe form of TB in children and uniformly leads to mortality if not treated timely and effectively. The clinical presentation is divided into three stages. The disease usually progresses over several weeks from stage one to three and may progress rapidly over days in infants and young children. The stage at which treatment begins predicts the prognosis.

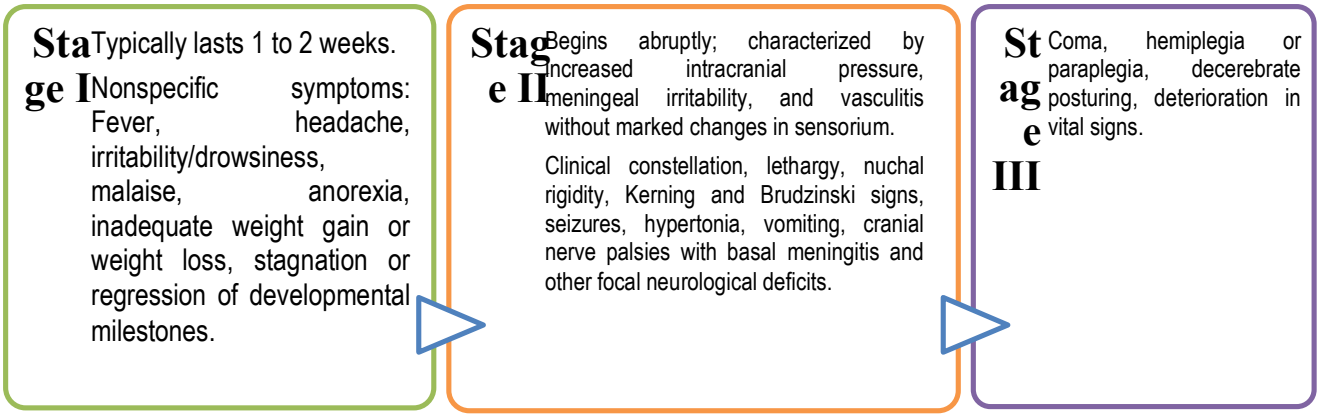
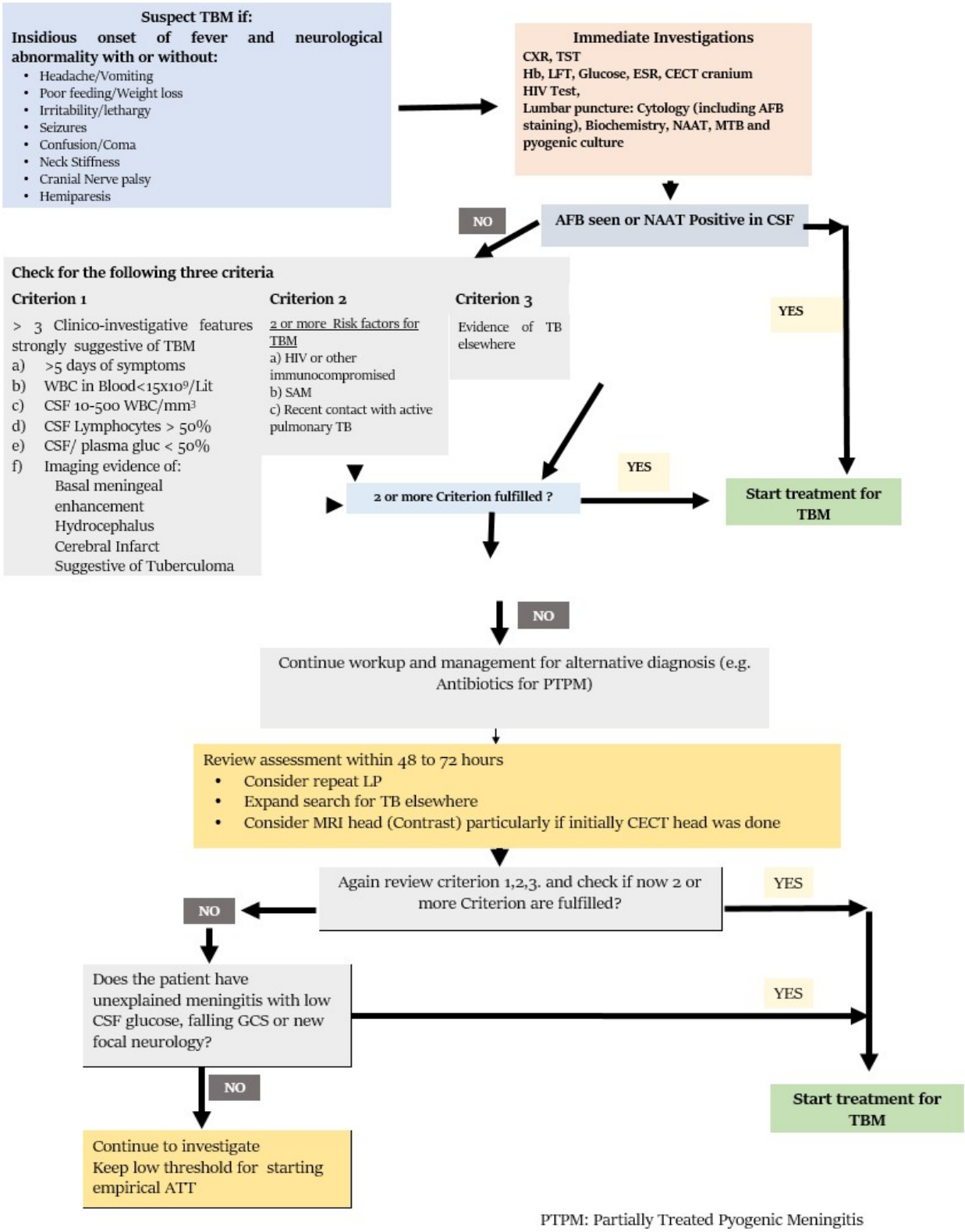


Table 1. Stages of TB Meningitis

Cerebrospinal fluid (CSF) tap is mostly clear, and CSF leukocyte count usually ranges from 10 to 500 cells /mm3 (occasionally higher), and the majority are usually lymphocytes. CSF glucose usually remains below 40mg/dl (CSF glucose / blood glucose below 0.5, protein is elevated (often more than 100 mg/dl). Rapid NAAT may be positive in about 30-40% of cases. Tuberculin Skin Test may not be reactive in 50% of cases. Chest X-ray may show abnormality in 20-50% of cases. Not uncommonly, the aetiological diagnosis may come from concomitant extra-neural disease.

The CECT head is the initial modality of diagnosis. It may have one or more of the following: basal meningeal enhancement, hydrocephalus, tuberculoma, infarcts in different areas, especially the basal ganglia and pre-contrast basal hyperdensity. It sometimes is even found normal. Contrast MRI has higher sensitivity than CECT for abnormalities such as meningeal enhancements, infarcts, and tuberculoma, especially of brain stem lesions.

Usually, Magnetic Resonance Imaging (MRI) is preferred when CT is inconclusive, and suspicion is high. Cryptococcal meningitis, Cytomegalovirus encephalitis, toxoplasmosis, sarcoidosis, meningeal metastases, and lymphoma can result in similar radiological findings.



PTPM: Partially Treated Pyogenic Meningitis

Figure 4. Algorithm for diagnosis of TBM

3.4.2. CNS tuberculosis other than TBM - Tuberculoma

Tuberculoma in the brain presents an intracranial space-occupying lesion (ICSOL). Its location, size and peri-lesional oedema predisposes the manifestations like seizures, headache and focal neurological deficits. Neurocysticercosis (NCC) is an important differential diagnosis.

The table below describes the differentiating features of these two entities on neuroimaging.

IMAGING	PARAMETERS	TUBERCULOMA	NEUROCYSTICERCOSIS (NCC)
CECT	Appearance	>2 cm, irregular thick outline, marked perilesional edema	≤ 2cm, regular, thin, rounded outline with variable edema
	Location	Infratentorial or supratentorial	Predominantly supratentorial
	Midline shift	More likely	Less likely
CONTRAST MRI	Appearance	T2 - usually hypointense core	usually T2 hyperintense core, eccentric dot. Scolex best seen on FLAIR or Differential Weighted images
	MRS	Lipid peak present	Lipid peak absent
	T2 relaxation time	Shorter (83-290 ms)	Longer (305-1365 ms)

Table 2. Differences Between Tuberculoma and Neurocysticercosis

3.5. Bone and Joint TB

Bone and Joint TB roughly accounts for 5-15% of all EPTB and 2-5% of all TB in children and adults. It occurs due to the reactivation of bacilli which had seeded the bones during the initial mycobacteremia. The symptomatic disease usually develops within 1-3years of infection, but TB dactylitis can have an early manifestation (usually one month). Typical presentations of Bone and Joint TB are Potts spine (50% of osteoarticular TB), Dactylitis, Arthritis (as an extension from the metaphysitis), Osteomyelitis. A few uncommon ones are reactive arthritis (Poncet's arthritis), tenosynovitis and bursitis.

3.5.1. Dactylitis (Spina ventosa)

Tuberculous osteitis, the dactylitis form, often affects children. It may involve multiple or consecutive bones. In children, short tubular bones of the hands and feet are usually affected, typically involving the proximal phalanx of the index/middle fingers and middle/ring finger metacarpals. It often follows a benign course without pyrexia and acute inflammatory signs. On X-Ray, the involved bones show a diaphyseal expansile lesion, a periosteal reaction is uncommon, and healing is by sclerosis.

3.5.2. Spinal TB or Pott's Spine

The most common site of Pott's Spine is thoracic, followed by lumbar/ cervical areas. Pain may be localized over the involved vertebra or could be referred to due to root pains. There can be local tenderness or deformity. Fever and constitutional symptoms are present in one among three cases. Neurological complications include paraparesis (20-50% cases), and cauda equina syndrome. Moreover, about 15% of patients can have a paradoxical response with increased neurologic deficit following therapy. However, this entity is diagnosed only after ruling out other causes of non-response like DRTB, pus collection, etc. There is a risk of kyphosis later in life, especially in children below 7-10 years.

Plain X-Ray of the spine is less sensitive in early disease as it does not reveal any abnormality till about 30-50% of bone loss has occurred. The typical findings are one more of the following: endplate erosion decreased vertebra height, collapse and narrowing of discal space and paravertebral soft tissue shadow. MRI is the most sensitive for picking up abnormalities (nearly 100%). Features in MRI are marrow oedema, destruction of adjacent vertebral bodies and opposing endplates, destruction of the intervening disc, occurrence of prevertebral, paravertebral, and epidural abscesses.

Microbiology should always be attempted for definitive diagnosis and to pick up MDR-TB. One should look for the coexistence of pulmonary TB. If surgery is not planned, a CT-guided biopsy of the paravertebral soft tissue/ vertebral body should be carried out and subjected to histopathological examination (HPE), culture, or NAAT. Diagnostic yield varies with various methods from 50-70%.

3.5.3. TB Arthritis

TB arthritis occurs from intra-articular spread from osteomyelitis. Usually, it involves the weight-bearing joints such as the hip and knee (90%). There is single joint involvement commonly. Pain is the first symptom (usually at night) later followed by local tenderness and restriction of joint movement. Fever and constitutional symptoms may be absent. Often, TB arthritis may be confused sometimes with oligoarticular J*uvenile Rheumatoid Arthritis (*JRA). Plain X-ray shows soft tissue swelling, osteopenia, periarticular bone destruction and periosteal reactions. Moreover, MRI is very sensitive. However, joint fluid aspiration or synovial biopsy should be carried out for a definitive diagnosis and subjected to HPE or culture or CBNAAT.

Chapter 4 TREATMENT OF TUBERCULOSIS

4A. Rifampicin Sensitive Tuberculosis

4A.1. Basis of Pharmacotherapy

The choice of anti-TB drugs is based on several determinants such as bacillary and metabolic subpopulation, bacillary load, drug-resistant strains, pharmacokinetic profile, pathological factors, etc. There are different types of bacillary metabolic populations in every case of tuberculosis. Hence, drugs are selected in a combination to attack the entire (extracellular and intracellular, slow and rapidly growing) bacillary population for successful chemotherapy. Isoniazid (INH) and rifampicin (RMP) kill the fast-growing bacilli, pyrazinamide (Z) acts against intracellular organisms in an acidic medium, while RMP best kills extracellular slow-growing bacilli. Thus, every case of tuberculosis must be treated at least with these four drugs. Ethambutol (E) is recommended as the fourth drug in the intensive phase and as a third drug in the continuation phase due to high INH resistance (around 13% in new cases) in our country.

TB treatment is biphasic. The chances of naturally occurring mutations are higher if the bacillary load is more, and therefore, such cases need more drugs like in the initial stage of the disease. The Intensive Phase (IP) results in early and rapid killing of M. *tb*, prevent deterioration and death, reduces infectivity. Sputum conversion is achieved in 80-90%. In addition to PZA to RMP, INH minimises the duration of therapy to 6 months due to its sterilising effect. The addition of E is valuable if initial drug resistance to INH is high. The Continuation Phase (CP) eliminates most residual bacilli and thus reduces failures and relapses. As fewer bacilli are left after eight weeks of therapy, the continuation phase needs fewer drugs (usually RMP and INH). However, if there is a high prevalence of background resistance to INH, another medication may be necessary to prevent amplification of drug resistance during CP. In our country, the continuation phase has thus ethambutol added as the third drug for all new cases.

Standardised therapy with presumed drug sensitivity had been the way TB was treated until recent times, as testing for drug resistance was challenging and not pragmatic due to the long lead time. We currently understand that treating rifampicin-resistant strain with a standardised first-line regimen can lead to therapy failure and increase the risk of amplifying resistance to other drugs. Therefore, now first-line standardised regimen is preferably used after ruling out resistance to rifampicin upfront in all cases (U-DST). Molecular testing for rifampicin using a rapid test (e,g, Xpert Rif, Truenat, LPA) is now possible and available throughout the country. Molecular tests and liquid culture (MGIT™) are used to detect resistance to other drugs. The standard retreatment regimen (erstwhile category II) has been withdrawn due to the risk of poor outcomes and amplification of drug resistance. Furthermore, no routine extension of IP is done at the end of 2 months for a patient with slower or non-response; instead, investigations for DR-TB are carried out again.

As the dividing time of TB bacilli is about 21 hours, all the drugs are administered to achieve peak concentration at once to inundate the bacilli. Intermittent therapy has been replaced by daily treatment with continued treatment support.

Fixed Drug Combination tablets have replaced erstwhile combipacks and patient-wise boxes. Furthermore, studies have also shown that most non-rifampicin resistance has poor outcomes due to INH mono/poly resistance. A new regimen for INH mono-poly resistance is advised (detailed in DR-TB section). Tests for INH resistance are carried out using first-line drug line probe assay (FL LPA) either directly on a clinical sample if it is smear-positive or on the isolate obtained through liquid culture. All Rifampicin-Sensitive TB (RS-TB) cases are given the standard therapy even if they have been treated in the past. Adjunctive surgical therapy may be needed in certain situations like spinal compression. As the anti-TB drug concentration achieved in a caseum and sequestrated tissue is poor, surgical removal should be done wherever feasible.

To summarise, now the patients are no more classified as New and Previously treated (see Box 2. for definitions) to allocate them standard four-drug (erstwhile category I) and five drug regimens (former category II). The primary aim is to segregate the patients upfront as rifampicin resistance detected (RR-TB) or rifampicin resistance not detected (RS-TB). All RS-TB cases are given the standard therapy even if they have been treated in the past. All patients undergo testing for other drugs for INH (mono or poly) and are treated with a different regimen if INH resistance is identified (discussed under DR-TB section).

Case Definitions

New Cases

- A TB patient who has never had treatment for TB or has taken anti-TB drugs for less than one month is considered a new case.

Previously Treated Cases:

- **Recurrent TB case**-A TB patient previously declared as successfully treated (cured/treatment completed) and is subsequently found to be microbiologically confirmed TB case.
- **Treatment After Failure Case**- patients are those who have previously been treated for TB and whose treatment failed at the end of their most recent course of treatment.
- **Treatment After Lost to Follow UP Case**- A TB patient was previously treated for TB for one month or more and was declared lost to follow up in their most recent course of treatment and subsequently found a microbiologically confirmed TB case.
- **Other Previously Treated Case**- are those who have previously been treated for TB but without outcome after their most recent course of treatment is unknown or undocumented.

Box 2. Case Definitions

Type of Patient[a]	*Regimens*
New microbiologically confirmed RS Pulmonary TB New Clinically diagnosed Pulmonary TB (Probable RS-TB) New microbiologically confirmed RS extra-pulmonary TB New Clinically Diagnosed extra-pulmonary TB (Probable RS-TB) Drug sensitive Previously Treated TB[c] (Recurrent, Treatment after loss to follow up, Treatment after Failure)	2HRZE+ 4HRE[b]

4A. 2. Treatment Regimen

Table 3. Treatment Regimen for Rifampicin-Sensitive TB

a. Molecular testing shall be done in all new cases in children with suspected TB at diagnosis and RSTB (Rifampicin resistance not detected) cases included in this regimen.

b. In the case of Neuro and spinal TB, the continuation phase is extended to 10 months.

c. All these categories of children shall be evaluated as DR-TB suspects and assessed as per the DR-TB Algorithm. DST based treatment shall be followed. If they are found to be Rifampin (and INH) sensitive, they shall be re-started on the regimen as for a new case. This group was earlier treated with CAT II regimen, which is now withdrawn from NTEP.

The drug dosages have been rationalised based on recent data on pharmacokinetics of ATT drugs and are as shown in the table below (Table 4):

		Range mg/kg/day	**Average mg/kg/day**	**Maximum dose (mg) for up to 60kg body weight)**
Rifampicin	**R**	10-20	15	600
Isoniazid	**H**	7-15	10	300
Pyrazinamide	**Z**	30-40	35	2000
Ethambutol	**E**	15-25	20	1500
Streptomycin	**S**	15-20	20	1000

Table 4. Drug Dosages for Rifampicin-Sensitive TB Treatment

NTEP has introduced Fixed Drug Combinations (FDCs) incorporating multi-drug therapy for TB. FDCs are preferred due to safety, simplified treatment, and avoiding errors in missing one or more of the combination drugs, thus reducing the risk of emergence of drug-resistant strains. From a programmatic viewpoint, it has simplified drug supply management, shipping and distribution. FDC tablets of good quality and proven bioavailability of rifampicin are being used in combination in treating TB.

There are two types of Paediatric FDCs available under NTEP-Formulation: Dispersible and Flavoured.

- For Intensive Phase (IP): 3 Drugs FDC Dispersible Tablets (DT) (H 50, R 75, Z150) (10:15:30)

- For Continuation Phase (CP): 2 Drug FDC DT (H 50, R 75) (10:15)

As Ethambutol is not available in the DT form, a non-DT 100 mg Ethambutol tablet is given for each Paediatric FDC during IP and CP.

There are two types of Adult FDCs available under NTEP, which are used in older children:

- For Intensive Phase: 4 FDC (H 75, R 150, Z 400, E 275)
- For Continuation Phase: 3FDC (H 75, R 150, E 275)

The therapy recommended as per body weight is detailed below (Table 5):

RECOMMENDED DRUG DOSAGES AND FDC PILL COMBINATION FROM 0-18 YEARS OF AGE	
Weight band (kg)	**Dose**
4-7	1 P +1 E
8- 11	2 P+ 2E
12-15	3 P+ 3E
16-24	4 P+ 4E
25-29	3 P + 3E+ 1 A
30- 39	2 P + 2E+2 A
For older children weighing > 39Kgs, the formulations are used as for adults.	

Table 5. Recommended Drug dosages and FDC Pill combination from 0-18 years of age

4A.3. Adjunct Therapy along with anti-Tuberculosis Drugs

I. Steroids in Tuberculosis

Definite indications for concomitant steroid therapy in TB include TB Meningitis, pericarditis, Addison's disease, miliary TB with alveolo-capillary block and TB uveitis. The evidence in other forms of intracranial TB like tuberculomas is unclear. In addition, steroids may be used in endobronchial tuberculosis, bronchial compression, mediastinal compression syndrome, pleurisy with severe distress, laryngeal TB, TB Immune Reconstitution Inflammatory Syndrome (IRIS) and miliary disease with alveolo-capillary block.

Steroids decrease inflammation-related injury. They are shown to reduce the mortality in pericardial disease and improve outcomes in intracranial TB by reducing the development of hydrocephalus and vasculitis. Moreover, the interaction between the microbial factors and host immunological factors in the lung, lymph nodes, intracranial tuberculosis lesions may cause paradoxical worsening of symptoms due to the release of pro-inflammatory markers like IL 2 and Interferon-gamma. Most such cases recover with the continuation of therapy. However, few circumstances can have severe life-threatening manifestations and sequelae. In such cases, steroids may bring relief by suppressing inflammation.

Steroids like prednisolone 1-2 mg/kg/day or dexamethasone 0.6 mg/kg/day or its equivalent are used for 2-4 weeks and then are tapered over the next four weeks. Any steroid in equipotent doses can be used.

II. Adjunctive Pyridoxine Therapy

Usually, no adjunctive therapy in the form of multivitamin or multi-mineral is advised as there is no evidence of these improving outcomes of TB patients. However, Isoniazid interferes competitively with pyridoxine (Pdx) metabolism by inhibiting the formation of the active form of the vitamin and can result in peripheral neuropathy. Furthermore, earlier, the adjunctive vitamin B6 (Pyridoxine) was not recommended routinely for all children on TB treatment. Previously it was recommended only for high-risk groups like HIV, alcohol abuse, malnutrition, Diabetes Mellitus (DM), Renal failure, Liver failure, and Multi-Drug Resistant TB (M-DR TB) treatment and. Nonetheless, it is worth mentioning that earlier, every child in the continuation phase of the Intermittent Directly Observed Treatment (DOT) regimen was getting Pyridoxine on drug holidays.

However, now there has been a rethink on the need for Vitamin B6 (Pyridoxine) supplementation due to:
(a) increased dose of INH (10-15 mg/kg/d) has potential for an increase in dose-related adverse effects,
(b) The high prevalence of malnutrition in children with TB makes them prone to peripheral neuropathy. Moreover, peripheral neuropathy in young children can go unrecognised and untreated with severe and prolonged morbidity.

Lastly, low cost, safety and lack of interference with INH action by the small prophylactic dose favour its use for likely benefit. Therefore, Pyridoxine (Vitamin B6) supplementation (10mg per day) is recommended to all patients receiving therapy with INH containing regimens.

4B. Monitoring and Follow-Up of Rifampicin-Sensitive Paediatric TB Cases

Children should be closely monitored for treatment progress and disease response. There are two components of follow up:

1. Clinical follow up
2. Laboratory follow up

Clinical follow up should be done every month during treatment. After completion of treatment, it may be done every six months for two years. Furthermore, an additional initial visit within two weeks of starting the therapy is desirable, where possible, to reassess that patient is on the correct dose and combination and is tolerating all drugs,

I. Clinical Follow Up:

On each follow-up child should be assessed for the following:

a. Improvement in clinical symptoms, including cough, fever, appetite or other clinical signs. These will be assessed as no improvement, partial improvement or improved after asking parents or attendants. Most patients will show amelioration of symptoms by the end of four weeks of therapy.

b. Physical examination: This will include individualised relevant examination including respiratory rate, heart rate, temperature (if fever), blood pressure if indicated, chest examination for breath sound, crackles, evidence of pleural effusion, chest indrawing, recording of lymph node size, anaemia, abdomen for organomegaly or distension. Furthermore, examination of the relevant system, e.g. cardiovascular system in pericardial TB, the central nervous system in TBM or intracranial TB, etc., should be done. The physician will record their assessment as either no improvement, partial improvement or improvement.

Lastly, the treating physician should also record the child's weight (as precise to 0.1 Kg) by using an appropriate weighing scale (Bassinette type electronic weighing scale for infants and lever type scale for children who can stand) and check for weight gain in comparison to weight on the last visit. Causes of poor weight gain may be insufficient intake, vomiting, a side effect of medications, wrong diagnosis, comorbid conditions, concurrent infections such as diarrhoea, pneumonia or poor response to treatment. These causes will be assessed by asking history and performing the examination. If the assessment suggests no clinical deterioration, the family will be counselled for increasing food intake. Suppose a child is losing weight or is assessed to be unresponsive to treatment. In that case, they should be re-evaluated for TB, drug-resistant TB or alternative diagnosis by seeking expert advice. In a co-infected case, this may also signify Anti-Retroviral Treatment (ART) failure. With appropriate therapy, catch-up growth and the expected growth of a child as per age could remain unimpeded. This may necessitate an upward revision of drug dosage whenever a patient crosses his pre-treatment weight band.

c. Side effects of medications: Common side effects of ATT are given in table V. Most of these are minor and consist of vomiting, rashes, pain abdomen etc. Significant side effects of ATT include hepatotoxicity manifesting as nausea, vomiting, pain abdomen, poor appetite or clinically evident jaundice. The treating physician will also assess for rashes, visual acuity, colour vision for older children. The adverse effects of anti-TB drugs as well their management are outlined in subsequent chapters.

d. Treatment of Comorbid conditions like HIV, Severe Acute Malnutrition (SAM), DM etc., should be monitored during each visit. Decongestive measures and anti-convulsants are often prescribed in neurological TB and should be observed at follow-up. Refer for paediatric consultation in the case of pneumothorax or lungs collapse (manifested as respiratory difficulty on assessment). Similarly, in instances of a subacute intestinal obstruction, refer for gastroenterology and surgical opinion.

e. Adherence to therapy should be revisited and ensured at each follow-up visit or unscheduled visit. Use Pill count, social support, family-based DOT and Treatment supervisor as needed.

In case the patient has interrupted treatment:
Interruption of TB treatment up to four weeks is managed by resuming the therapy. However, if the drugs are interrupted for over four weeks, the patient is investigated for DR-TB. If Rif resistance is not detected on testing, re-treat with first-line four drugs, check for INH resistance, then treat appropriately as DS or INH mono-poly resistance case. If Rifampicin resistance is detected – then treat the child as an MDR-TB case.

Box 3. Interrupted TB Treatment

II. Monitoring by Laboratory Investigations will include sputum or gastric aspirate examination, imaging X-ray film of chest, Ultrasound abdomen, Echocardiography, CT scan of organ involved (Head, Chest, Abdomen) or MRI (spine). Lab investigation for side effects of medications comprises monitoring drug levels for antiepileptic drugs, Liver function test (LFT) if hepatotoxicity is considered or developed.

a. Microbiological: The respiratory secretions, if available, are tested at the end of IP and completion of treatment (Bacterial negativity- sputum, GA etc. with smear and culture; repeat NAAT for any acquisition of Rif Resistance, if follow up smear is positive)

Mycobacteria Growth Indicator Tube (MGIT) culture: should be performed if the child is not responding even after four weeks of therapy. However, as most of the children in their young years are unable to produce sputum or may have complete resolution of their cough and sputum. In such situations, response to treatment may need to be assessed clinically with help of radiological testing. Other relevant investigations may also be taken.

b. **Liver function test:** No routine or baseline LFT testing is required for patients on first-line drugs without evidence of any hepatopathy. These tests are done if any child shows symptoms or signs suggesting hepatic dysfunction.

c. **Follow up Chest radiographs** should be performed only at the end of therapy or earlier if assessed to be: clinically non-improvement, emerging complications or deterioration.

d. **Other imaging, including Ultrasound of abdomen, echocardiography, CT/MRI scan** of the affected organ system, is advised at the completion of treatment or when the patient is unresponsive to treatment or shows deterioration while on treatment.

III. Clinical or Radiological non-response or Deterioration during follow up:

The causes for a clinical non-response could be:

1. Incorrect diagnosis (particularly if a clinically diagnosed case of TB)
2. Lack of adherence to therapy
3. Incorrect drugs or dosages
4. Inability to retain drugs- children often may vomit out medications due to the bad taste or upon forceful consumption of the medicine.
5. Secondary infection or a comorbidity
6. Drug resistance
7. Paradoxical upgrading reactions

Further pertinent investigations are decided based on clinical clues for any of the above conditions. Detailed analyses for drug resistance should be sent for MGIT DST or LPA, or CBNAAT. Moreover, drug resistance should not be labelled without microbiological confirmation in most circumstances. Diagnosis of drug-resistant TB through bacteriological diagnosis is often untenable, with few notable exceptions where lack of access to appropriate specimen may not allow microbiological confirmation of drug resistance. History of contact with a proven case of M-DR or history of prolonged or irregular therapy in a source case within household or peer groups of the child is a good clue for suspecting DR-TB. Often such history is not available upfront but is provided later on follow-up by the family as they become more aware of the disease and may check around for such a case to whom the child may have been exposed.

Lastly, radiological deterioration alone without clinical symptoms should be reviewed with a skilled radiologist. The difference in respiration phase, rotation, and radiological factors can seriously affect the assessment of improvement (or lack of it) on follow-up images.

IV. Paradoxical Upgrading Reactions (PURs)

It refers to enlargement of existing lesions or unexpected appearance of new lesions during apparently adequate ATT. It usually occurs 3–12 weeks after the beginning of therapy, most frequently after treatment for 6- 7 weeks, & lasts for approximately two months. PURs are generally self-limiting and resolve without

serious sequelae. It usually regresses without a change of initial drug regimen. It may occur post-treatment (as late as two years) in cases of lymph node TB as the retained caseum may track up and result in sinus formation.

Active TB can result in depression of immunity. Nevertheless, after successful ATT, the focal immune response improves. Accumulation of inflammatory exudates at previously invisible microscopic tuberculous foci elsewhere may appear as new lesions. Reversible roentgenographic progression in the initial treatment of TB may be more common than previously expected if there is frequent monitoring by chest radiograph. It is for this very reason, routine monitoring by radiographs is not recommended.

Types of reported Paradoxical Upgrading Reactions (PRUs)

- Increase in size of mediastinal lymph nodes or areas of pulmonary infiltration in paediatric patients with primary TB
- Appearance of new lung infiltrates in patients with extrapulmonary TB
- Development of TB pleural effusion
- Increase in size of effusion/appearance of effusion on the contra lateral side
- Appearance of new lymph nodes/ enlargement of original nodes
- Increase in size or number of tuberculoma/ infarctions / hydrocephalus on treatment of intracranial TB

Box 4. Types of reported Paradoxical Upgrading Reactions (PRUs)

The absence of any systemic symptoms is a helpful indicator of PUR. Moreover, a lack of systemic symptoms is usually seen in paradoxical reactions (non-HIV settings). It might be difficult to distinguish a paradoxical response from an actual drug resistance TB- and thus, PUR is never diagnosed without excluding DR-TB.

V. Long-term follow up: After completion of treatment, the patients should be followed up every six months for two years to assess for early detection of any relapse of illness. Monitoring on each visit will include the same as described above.

Chapter 5 MANAGEMENT OF PAEDIATRIC DRUG RESISTANT TB INCLUDING MDR TB

DR-TB refers to the presence of drug resistance to any of the first-line or second-line drugs. The definitions below explain the terminology used for various types of drug resistance. Resistance to some key drugs has more severe consequences than others, e.g. resistance to INH or Rifampicin clearly compromises the initial four-drug therapy. Likewise, additional resistance to Group A second line drugs like Fluoroquinolones (FQ) or newer drugs like Bedaquiline or Linezolid in a patient with MDR-TB seriously impacts therapy with second-line drugs.
Prevalence of MDR-TB, i.e. *M. tuberculosis* resistant to isoniazid and Rifampicin with or without resistance to other drugs, is estimated to be about 2.8% (2.3–3.5) among new cases and 14% (12–17) among the previously treated patients[3].

Minimal data is available regarding MDR-TB in children. In children, it primarily results from the transmission of drug-resistant bugs from the source case (usually adolescents and adults). Less commonly, it does also result from previous inadequate TB treatment. The prevalence of MDR-TB in children mirrors MDR-TB in adults. Thus, it is common in settings where the MDR-TB pool exists in adults and is associated with higher morbidity and mortality than the drug-sensitive disease.

Based on the pattern of drug resistance, the cases may be further classified for treatment purposes as**:**

a. **Mono-resistant TB (MR-TB).** A TB patient whose biological specimen is resistant to one first-line anti-TB drug only.
b. **Isoniazid-resistant TB (Hr-TB).** A TB patient whose biological specimen is resistant to isoniazid and susceptibility to Rifampicin has been confirmed.
c. **Poly-drug resistant TB (PDR-TB**). A TB patient whose biological specimen is resistant to more than one first-line anti-TB drug, other than both H and R.
d. **Rifampicin resistant TB (RR-TB**). A TB patient whose biological specimen is resistant to R detected via phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to R in the form of mono-resistance, poly-resistance, MDR or XDR.

[3] Central TB Division, MoHFW G of I. Report of the First National Anti-Tuberculosis Drug Resistance Survey India 2014-2016. Available at: https://tbcindia.gov.in/showfile.php?lid=3315

e. **Multidrug-resistant TB (MDR-TB).** A TB patient whose biological specimen is resistant to both H and R with or without resistance to other first-line anti-TB drugs. MDR-TB patients may have additional resistance to any/all FQ or any other anti-TB drug.
f. **Pre-extensively drug-resistant TB (Pre-XDR-TB).** TB is caused by Mycobacterium tuberculosis strains that fulfil the definition of MDR/RR-TB and are also resistant to any fluoroquinolone.
g. **Extensively drug-resistant TB (XDR-TB**). TB is caused by Mycobacterium tuberculosis strains that fulfil the definition of MDR/RR-TB and are also resistant to any fluoroquinolone (levofloxacin or moxifloxacin) and at least one additional Group A drug (presently to either bedaquiline or linezolid [or both]).
h. **Extensive (or advanced) TB disease** refers to the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography.
i. **Severe extrapulmonary TB r**efers to the presence of miliary TB or TB meningitis extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered as severe (adapted from Wiseman et al., 2012 (7)).

A. Approach to Diagnosis of DR-TB in Children:

As there are no clinical disease patterns that can identify the presence of drug resistance in a given case, epidemiological markers, when present, can suggest possible DRTB. However, these markers are not always present. Moreover, first-line drug regimens fail and have an added risk of amplifying resistance to other companion drugs if resistance to Rifampicin and INH is present. Therefore, there has been a shift to identifying the presence of these key resistance in all TB patients at diagnosis (universal DST), replacing the earlier approach of targeted testing for DRTB among the patients more likely to harbour drug resistance strain (presumptive DR-TB cases). Universal DST (U-DST) refers to universal access to rapid DST for at least Rifampicin (and where possible INH). It also includes DST for fluoroquinolones among all TB patients with Rifampicin resistance (preferably before initiation of treatment or as soon as possible).

Epidemiological Markers for DR-TB:

Important epidemiological markers for DR-TB include:

- finding a history of contact with suspect MDR
- details of previous poor treatment (inadequate drugs, dosage and duration) and lack of adherence
- in a patient not responding to therapy, or those with recurrence of disease after previous treatment, as such cases could be harbouring a drug-resistant strain.

- it must be added that the causes of non-response to anti-TB therapy include incorrect diagnosis of TB, poor adherence, paradoxical upgrading reactions, and other untreated coexisting or inter-current co-infections.
- TB among Children living with HIV (CLHIV) or those in contact with someone dying of TB is also found to have a higher likelihood of DRTB.

Confirmation of Drug Resistance:

Confirmation of drug resistance is always by microbiological methods (genotypic and phenotypic). Getting appropriate body fluid samples for pulmonary or EPTB patients is crucial for mandatory microbiological confirmation and drug susceptibility testing. For this, sputum (or other alternative respiratory specimens, e.g. gastric aspirate or lavage for swallowed sputum, induced sputum, bronchoscopic lavage) or other relevant specimens like lymph node aspirates, CSF analysis, pleural or pericardial or peritoneal fluid, tissue biopsies must be collected in all children with presumed DR-TB for NAAT (e.g. Truenat/ Xpert M.TB RIF), LPA and culture and drug sensitivity testing. This may imply a referral to a higher centre to facilitate detailed and sometimes invasive testing.

In a presumptive DR-TB patient, if all efforts for microbiological confirmation have failed or confirmation is not possible due to inaccessible specimen, but the clinical probability of it being DRTB is high (failure of adequate first-line therapy and/or close contact of a proven MDR-TB case), and there is no alternative diagnosis or explanation for non-response the patient may be treated as a clinically diagnosed DR-TB (Probable MDR-TB). In such situations, drug regimen can be decided based on the drug sensitivity pattern of the DRTB contact (likely source case), where available. Moreover, the patients considered to have 'probable' MDR-TB should be presented to and discussed with the DR-TBC Committee for confirming the decision to treat in consultation with a paediatrician.

Furthermore, in children with a severe disease like central nervous system TB or other life-threatening manifestations who have substantial risk factors for DR-TB, treatment as probable MDR-TB can be initiated, pending confirmation, in consultation with the paediatrician in the Nodal DR-TB Centre (NDR-TBC) committee, given their high risk of mortality. Further treatment in such situations can be decided based on their test results as and when available.

Probable MDR-TB Among Children:
The term probable MDR-TB in children would be applied to children wherein DR-TB is clinically suspected strongly, but bacteriologic confirmation is not technically feasible/negative, and the Nodal DR-TB committee takes the decision regarding diagnosis and initiation of treatment.

Criteria for diagnosis of "Probable MDR-TB" include children with signs and symptoms of active TB disease, which in addition have the following risk factors:

- Close contact with a known case of MDR-TB;
- Close contact with a person who died whilst on TB treatment;
- Close contact with a person who failed TB treatment;
- Non-response or Failure of a first-line regimen,
- Previous treatment with second-line medications

AND

Their appropriate specimens fail to demonstrate *M. tb*, and thus the resistance pattern cannot be determined (Culture negative TB), or access to the specimen is not easily

Box 5. Probable MDR-TB Among Children

Confirmed Drug-resistant TB cases:

- A patient is confirmed to have drug-resistant TB only when the results suggest drug resistance are from an NTEP quality assured Culture and DST Laboratory, and an NTEP endorsed testing method (NAAT/LPA/Culture).

Box 6. Confirmed Drug-resistant TB cases

Additional Consideration:

Practitioners need to know which medicines have frequently been used in a given geographical setting or patient group. Moreover, practitioners should strive to test for drug resistance and limit empiric treatment to a minimum despite some uncertainties about DST. The patient's clinical response to treatment should constantly be carefully monitored. If there is poor treatment response, undiagnosed resistance should be considered, as should alternative explanations for failure to respond to treatment (e.g. poor or erratic adherence to treatment, immune reconstitution inflammatory syndrome (IRIS) or the presence of comorbidities.

B. Methods for Drug Susceptibility/Drug Resistance Testing:

I. Drug Resistance Tests Using Molecular Methods: This can be performed on sputum specimens (direct) or culture isolates (indirect) for diagnostic purposes. Presently the following technologies are available for diagnosis of DR-TB through rapid molecular diagnostic testing:

a. Nucleic Acid Amplification Test (NAAT) (viz. Xpert MTB RifTM test using the Gene-Xpert platform /TrueNatTM): These NTEP approved, cartridge / chip-based NAATs can be performed on smear-positive, smear-negative and extrapulmonary specimens as they can detect DNA even with few copies. The tests detect M. tb as well as resistance to Rifampicin in the MTB. The test time is about two hours.

b. **Line Probe Assay (LPA)** refers to molecular test(s) used for (a) detection of MTB complex and rapid diagnosis of R and H resistance (FL-LPA), (b) resistance to class FQ and class SLID (SL-LPA). LPA needs many DNA copies (over 10,000 per ml) for detection and thus can be used directly only on smear-positive specimens. The processing time is **72 hours** each for both first- and second-line LPA. In addition, LPA can be used for genotypic drug sensitivity on an isolate from culture (like MGIT) from any specimen, including smear-negative samples. This mixed-method approach could decrease turnover as the phenotypic sensitivity testing would take weeks compared to a few days with LPA.

c. Xpert M.TB /XDR

This newer version of Cartridge Based NAAT can detect mutations associated with resistance towards H, FQ, SLI and Eto in a single test, using a semi-quantitative nested PCR followed by high-resolution melt technology. It requires GeneXpert platforms equipped with 10-colour modules. Test processing time is about 90 minutes.

- When endorsed, the test is suited to follow molecular tests that detect *M. TB*/Rifampicin resistance.
- It can potentially improve access to rapid drug susceptibility testing, especially for ruling out fluoroquinolone resistance, which is required before starting the shorter oral Bedaquiline-containing MDR/RR-TB regimen.

These methods are PCR-based and cannot be used for determining response to treatment, unlike a smear.

II. Growth-Based Phenotypic Drug Susceptibility Testing: M. tb Culture, though a highly sensitive and specific method for TB diagnosis, requires 2-8 weeks to yield results and hence does not allow rapid confirmation, unlike molecular tests. Culture, however, needs to be used for long-term follow-up of patients on DR-TB treatment and help detect early recurrence in both drug-

sensitive and drug-resistant TB. The growth-based phenotypic culture methods include automated Liquid culture systems, *e.g.,* BACTEC MGIT 960, BacTAlert or Versatrek etc., and solid (Löwenstein Jensen) media.

Mycobacteria growth indicator tube (MGIT) is currently the preferred method for DST under NTEP, and both first and second-line anti-TB drugs sensitivity can be tested by this method. Following drugs can be tested for susceptibility by liquid culture:

- First-line drugs: R, H, E, Z
- Second-line drugs: S, Lfx, Mfx, Km, Cm, Am, Lzd, Cfz*, Bdq*, Dlm *etc.*

Phenotypic testing also determines the critical inhibitory concentrations of various drugs to guide therapy. It could save time by running a molecular genotypic test (LPA) on a culture isolate if the initial specimen was unsuitable due to smear negativity.

Important notes to microbiological testing and result interpretation:

- Ideally, two specimens should be collected from every patient and sent to the NAAT facility, who shall run the NAAT and transmit or test the other aliquot for M. tb culture.
- Samples must be transported immediately after collection to the linked laboratory for appropriate testing. Standard Operating procedure for triple-layer packaging must be strictly adhered to, and the sample must be transported in a cold chain. Samples must not be batched.
- EPTB samples should not be collected in Formalin for bacteriological tests (genotypic as well as phenotypic).
- Airborne Infection Control (AIC) measures must be followed at all times. Biomedical Waste Management must be ensured.
- If R resistance is detected on NAAT, the patient is offered First Line (FL) and Second Line (SL) LPA followed by LC DST as indicated in the algorithm.
- If R resistance is detected with a very low level of M. tb in a patient with low clinical suspicion, it should be confirmed by a repeat specimen for NAAT.
- Suppose R resistance is not detected on NAAT. In that case, the patient is offered FL LPA for detecting resistance to H. All H resistant patients are subsequently offered SLLPA followed by LC DST as indicated in the algorithm.
- Treatment is initiated based on LPA results and modified based on the LC DST results, available later.
- Phenotypic DST for ethambutol, ethionamide may be inaccurate and not reproducible. No agreed DST methods had been established for some other second-line drugs [e.g. cycloserine/terizidone, imipenem- cilastatin/meropenem and P-Aminosalicylic Acid (PAS)].

C. Integrated Drug Resistant TB Algorithms

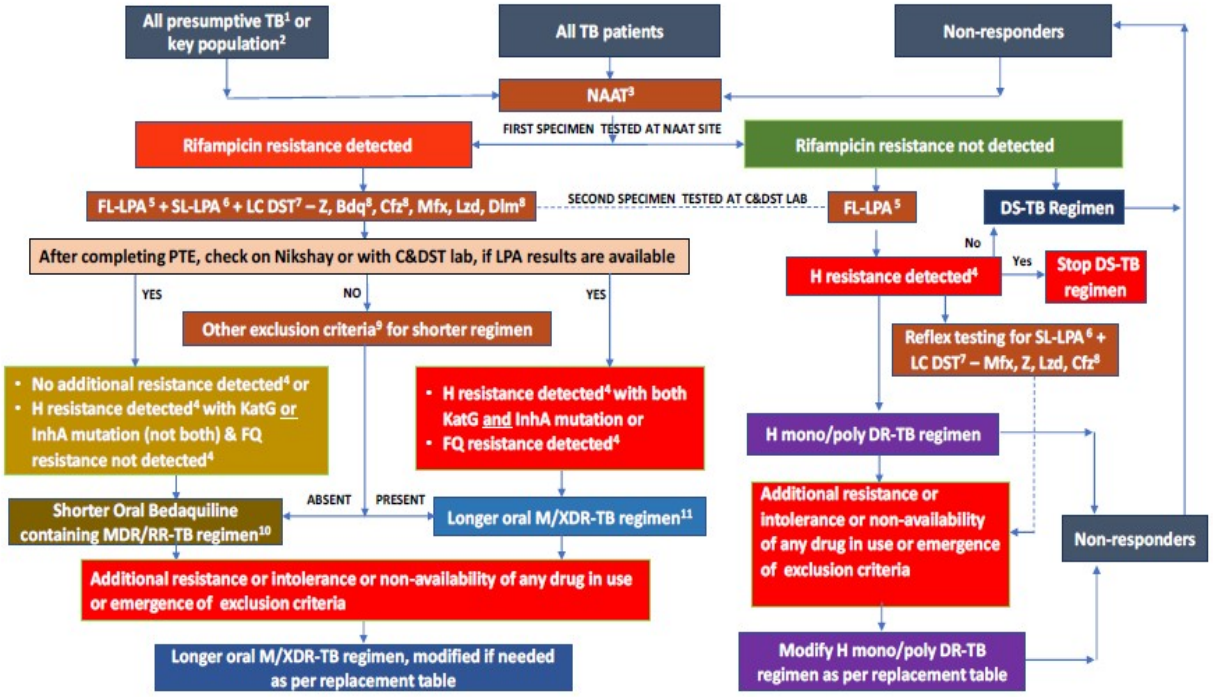


Figure 5. Integrated diagnostic and treatment algorithm for drug resistant tuberculosis

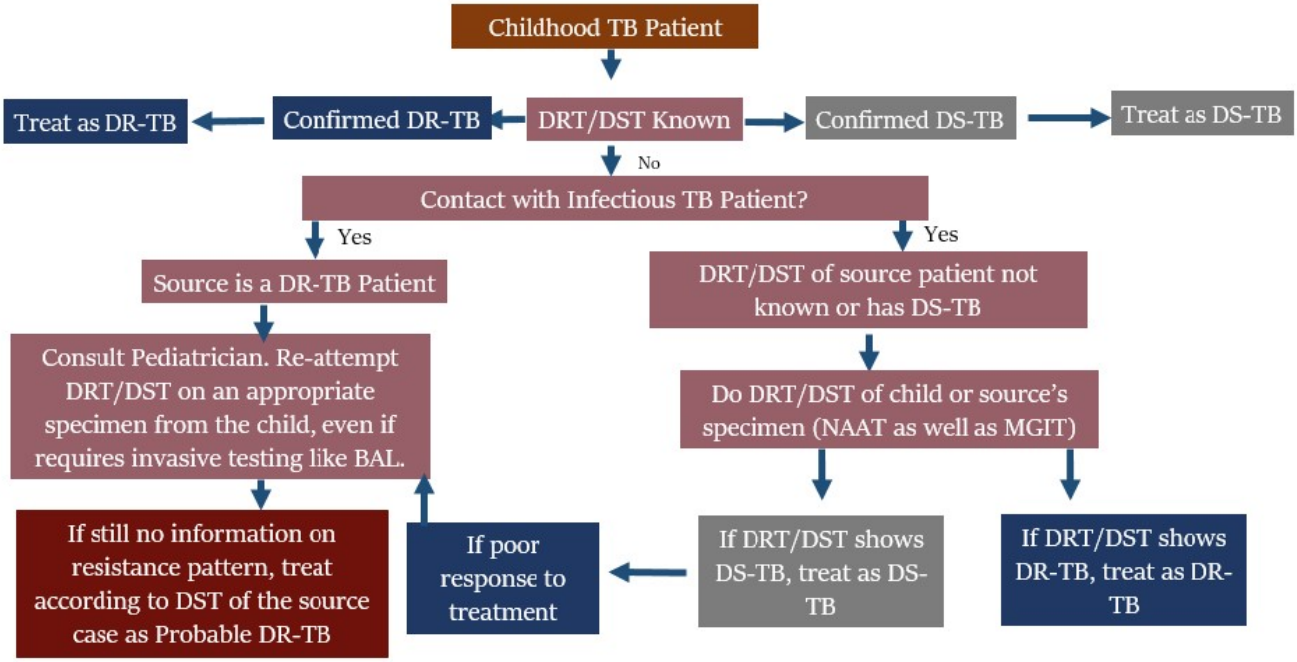


Figure 6. Algorithm approach to diagnosis of DR-TB in children

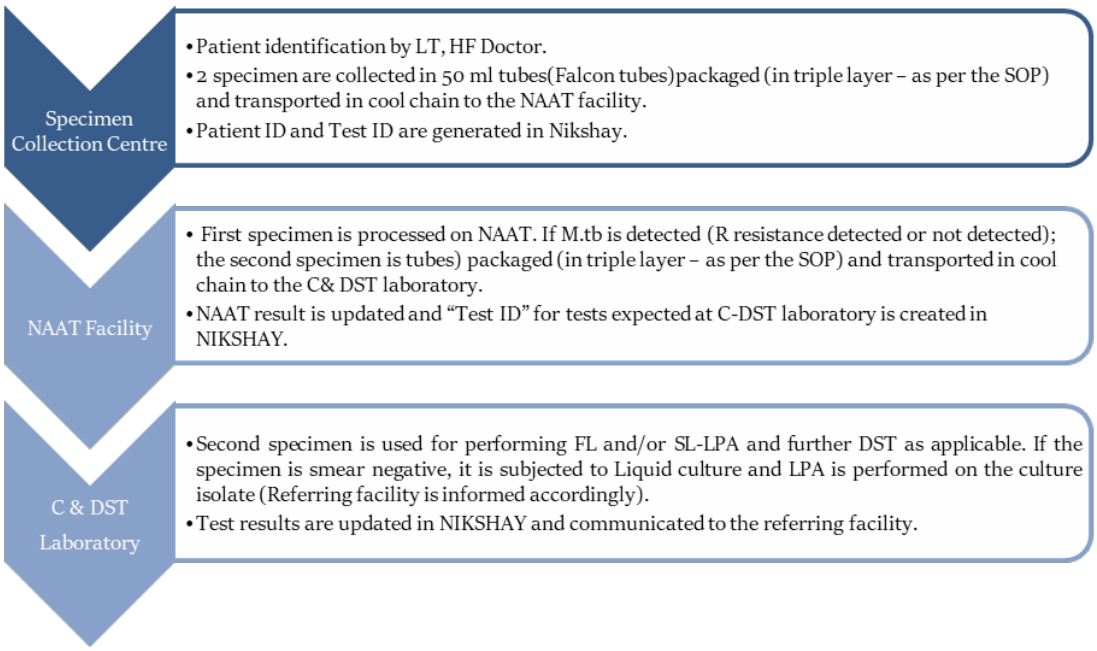


Figure 7. Specimen Flow and Operational Processes

5.1. Treatment of Drug Resistant TB in Children

Compared to drug-susceptible TB (DS-TB) treatment, DR-TB regimens require a longer course, higher pill burden, and higher toxicity profile, resulting in lower adherence and poorer treatment outcomes, including deaths. The principles of designing a WHO-recommended regimen section also applies to the paediatric population.

- Include at least 4-5 effective medicines from Group A and B to which the Mycobacterium tuberculosis strain is known or likely to be susceptible.
- Do not add a single drug to a failing regimen to avoid amplification of resistance.
- Strict monitoring of treatment by clinical examination, radiology and culture response to be undertaken by paediatrician/ expert available/ linked to DR-TBC.

Children aged five to less than 18 years of age and weighing at least 15 kg are eligible for both Shorter or Longer oral MDR/RR-TB regimens. Furthermore, the pre-treatment evaluation carried out at the treatment initiation can be considered valid for one month from the test result. The patient can be re-initiated on a subsequent regimen based on this. In addition, long term follow-up will be done with six-monthly cultures among symptomatic patients till two years after completion of any DR-TB regimen, i.e. months 6, 12, 18 and 24 post-treatment. Lastly, Active Drug

Safety Management and Monitoring (aDSM) treatment initiation form need to be completed for all DR-TB patients at the time of initiation of each new episode of treatment.

5.1.1. Grouping of Drugs

The anti-TB drugs recommended for MDR/RR-TB patients are grouped based on efficacy, the experience of use, drug class and aligned with revised classification as per WHO Consolidated Guidelines for TB Module 4: Treatment of Drug-Resistant TB (2020).

GROUPS & STEPS	MEDICINE	ABBREVIATION
GROUP A: *Include all three medicines*	Levofloxacin OR Moxifloxacin	Lfx Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
GROUP B: *Add One Or Both Medicines*	Clofazimine	Cfz
	Cycloserine OR Terizidone	Cs Trd
GROUP C: *Add To Complete The Regimen And When Medicines From Group A And B Cannot Be Used*	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin or Meropenem	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)	Am (S)
	Ethionamide OR Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

Table 6. Grouping of anti-TB drugs and steps for designing a longer MDR-TB regimen

5.1.2. Standard DR-TB Regimens Available Under NTEP

The NTEP Treatment Expert group (Paediatric), India, has agreed to the following regimens for our country, keeping in view the WHO advice.

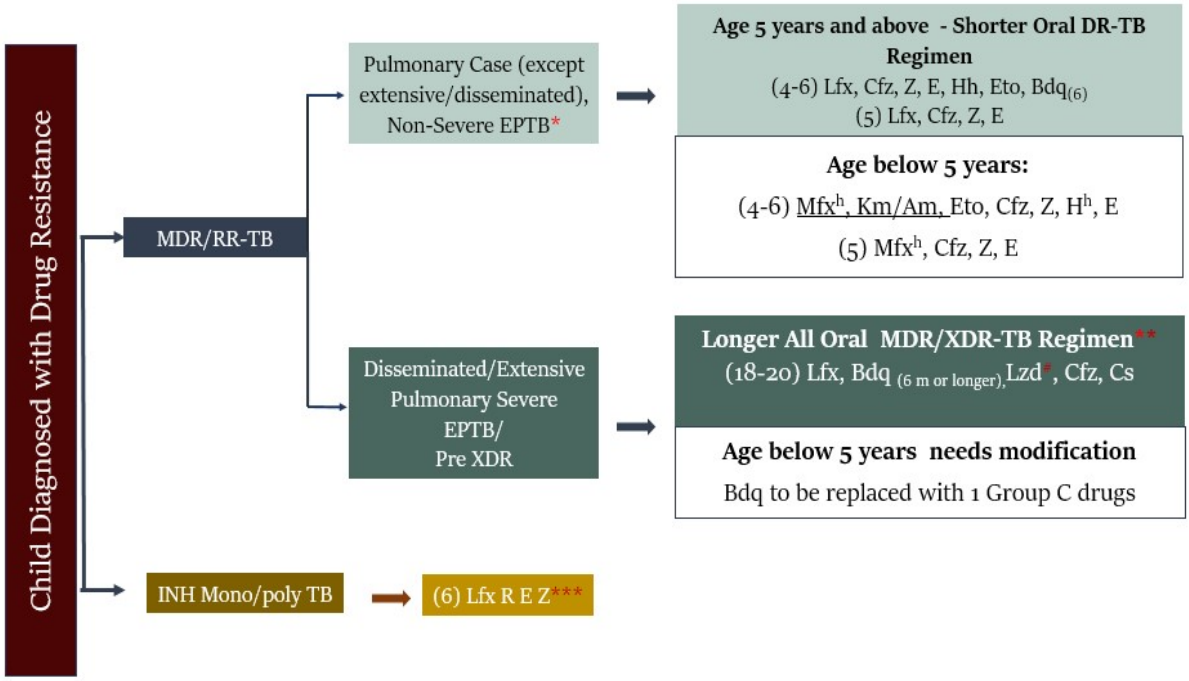


Figure 8. Treatment Algorithm for DR-TB in Children

- * As per the exclusion criteria (mentioned in details in this chapter and Annexure 6) for the shorter MDR-TB regimen, while considering the option of longer oral regimen, shortening the total treatment duration may be considered depending upon the response (12 to 18 months) but not less than 12 months in any case.
- ** Can be given in all children with extensive disease. However, for children under five years of age where neither Bdq nor Dlm is approved yet, the longer oral M/XDR-TB regimen is suitably modified with replacement of Group C drugs for longer oral M/XDR-TB regimen in the sequence of - amikacin, pyrazinamide, ethionamide, PAS, ethambutol, penems.
- ***In conditions like: extensive pulmonary disease; uncontrolled underlying morbidity; extrapulmonary TB (other than isolated pleural effusion or peripheral lymphadenopathy) or any change in the standardized regimen necessitated by drug resistance or intolerability to any drug of the regimen, the therapy is increased to 9 months. For cases with spinal and neuro TB, the total duration is 12 months.
- #dose of Lzd will be tapered to 300 mg after the initial 6–8 months of treatment

5.1.3. Special Considerations for M/XDR-TB in Children

- Always treat in consultation with an expert, preferably paediatrician available/ linked.
- Bedaquiline(Bdq) will be given to children more than five years of age weighing 15kg or more.
- Delaminid(Dlm) will be given to children six years onwards. Although WHO has approved the use of Dlm in the age group 3-5 years, the regulatory approval in India is awaited.
- Delaminid(Dlm) will be considered only as a replacement in a longer oral M/XDR-TB regimen.
- To modify the longer oral M/XDR-TB regimen, the N/DDR-TBC physician must review the resistance pattern, tolerability history, contraindications, and availability of first and second-line drugs to identify the number of drugs from Group A and Group B that need to be replaced.
- In special situations, an extension of Bdq beyond six months and concomitant use of Bdq and Dlm can be done.
- The regimen should preferably be entirely oral. However, injectables may have to be used for efficacy and side-effect profile in certain circumstances.
- The avoidance of an injectable-containing regimen is particularly desirable in children. Given the profound impact that hearing loss can have on the acquisition of language and the ability to learn at school, the use of injectable agents in children should be exceptional under strict monitoring to ensure early detection of ototoxicity.
- For paediatric patients, the drug dosage should be adjusted immediately once the patient's weight crosses the range of weight-band and counselling regarding the change in weight band and the change in the number of pills that need to be consumed.
- Child-friendly (dispersible and palatable) formulations should be used whenever available.
- Bedaquiline tablets suspended in water have been shown to have the same bioavailability as tablets swallowed whole and can therefore be used to treat drug-resistant TB in children until a child-friendly formulation becomes available.
- Clavulanic acid should be included in MDR/RR-TB regimens only as a companion agent to the carbapenems (Imp-Cln and Mpm). When used in this way, it should be given with every dose of carbapenem and should not be counted as an additional effective TB agent.
- Seizures may be more common in children with meningitis treated with imipenem, and meropenem is preferred for cases of TB meningitis and in children.
- The monitoring of DR-TB treatment in children is the same as in adults. However, for probable MDR-TB patients, the paediatrician available at or linked to the N/DDR-TBC must regularly evaluate the child's progress on treatment and initiate any other investigations as deemed necessary.

5.2. (H) mono/poly DR-TB regimen in Children

(6) Lfx R E Z

- Duration is of 6 or 9 months with no separate IP/CP.
- The patient is initiated on (6) Lfx R E Z when found to be resistant to INH (but not Rifampicin) based on the First-line Line Probe Assay (FL-LPA) report. The regimen could be modified subsequently based on SL-LPA results.
- If H mono/poly DR-TB is detected, the FL- LPA deposit is subjected to SL-LPA by the lab and LC-DST to Mfx, Z, Lzd, Cfz*(*Whenever DST is available).
- If there are signs of non-response, the patient must be subjected to NAAT again to rule out amplification of Rifampicin resistance and further LPA and DST.
- In conditions like - extensive disease, uncontrolled comorbidity, extrapulmonary TB or any change in drug of standardized regimen due to additional drug resistance or intolerability to any drug, the regimen is increased to 9 months.
- In exceptional situations of unavailability of loose drug R or E or Z, the use of 4 FDC (HREZ) with Lfx loose tablets may be considered as an option rather than not starting the treatment.
- The dosage of drugs would vary as per the weight of the patients.
- All drugs in the regimen are to be given daily under observation.

5.2.1. Replacement Sequence

Replacement is done in case of additional resistance, intolerance, unavailability or contraindication of the component drugs of the regimen.

SITUATION	SEQUENCE OF USING REPLACEMENT DRUGS
If LFX Can't Be Used	Replace with Mfx^h if SL LPA pattern suggests. Do LC DST for detection of resistance to Mfx^h, Z, Lzd & Cfz*.
If MFX^H Z Can't Be Used	Replace with Lzd. If Lzd also cannot be given, replace with Cfz* + Cs.
If Both MFX^H and Z Can't Be Used	Add 2 drugs of the 3 – Lzd, Cfz*, Cs in order of preference based on resistance, tolerability & availability.
If R Resistance	Switch to appropriate shorter or longer regimen.

*whenever DST is available

Table 8. Standard Replacement sequence of drugs to modify H mono/poly DR-TB regimen

5.2.2 Follow up Monitoring

FOLLOW UP SCHEDULE FOR REGIMEN CLASS H MONO/POLY DR-TB	
DURATION	6 or 9 months (no separate IP/CP)
CLINICAL + WEIGHT ASSESSMENT	Monthly; till the end of treatment
SMEAR MICROSCOPY	• Monthly from month three onwards till the end of treatment. • Conduct SM within 7 days, if the smear at month four or later is positive, rapidly ascertain bacteriological conversion/reversion.
CULTURE	• At the end of month three, end of treatment (month 6 and/or 9 if applicable). • If the culture results of month three is positive, collect one repeat specimen for culture to rapidly ascertain bacteriological conversion/ reversion. If the repeat specimen is culture negative, then specimen collection at the end of treatment
DST	NAAT, SL LPA (Lfx, Mfx, Eto) and LC DST (Mfxh, Z, Lzd & Cfz*) if smear/ culture +ve at month 3, end of treatment (month 6 and/or 9 if applicable).
UPT,CBC/PLATELET[1]; TSH; LFT[2],CXR,ECG[3], S. ELECTROLYTES (K, MG, CA)	As and when clinically indicated
COLOUR VISION TEST	Once in two months (in children)

Table 9. Follow up evaluation schedule of H mono/poly DR-TB patients

- *[1]Lzd containing regimen to rule out bone marrow suppression*
- *[2] HBsAG and other viral markers (Hepatitis A, C & E) to be done in case of Jaundice*
- *[3] In case of baseline ECG abnormality or QTcF ≥450ms for regimen containing Mfx(h) or Cfz, ECG must be done on daily basis for initial 3 days or as suggested by cardiologist. Repeat ECG with long II lead after an hour to reconfirm abnormal ECG.*
- *DST whenever available*
- *Urine Pregnancy Test (UPT)*

5.3. Shorter oral Bedaquiline-containing MDR/RR-TB Regimen

(4-6) Lfx, Cfz, Z, E, H^h, Eto (6) Bdq | (5) Lfx, Cfz, Z, E

Eligibility Criteria

Children, aged five years to less than 18 years of age and weighing at least 15 kg, in consultation with a paediatrician

A. Inclusion Criteria

I. DST based inclusion criteria

- Rifampicin Resistance detected/inferred
- MDR/RR-TB with H resistance detected/inferred based on InhA mutation only or based on KatG mutation only (not both)
- MDR/RR-TB with FQ resistance not detected

II. Non-DST based inclusion criteria

- No history of exposure to previous treatment with second-line medicines in the regimen (Bdq, Lfx, Eto or Cfz) for more than one month (unless susceptibility to these medicines is confirmed);
- No extensive TB disease
- No severe extrapulmonary TB

B. Exclusion criteria

I. DST based Exclusion Criteria

- MDR/RR-TB patients with H resistance detected with both KatG and InhA mutation or MDR/RR-TB patients with FQ resistance detected

II. Other Exclusion Criteria

- those with a history of exposure for > 1 month to Bdq, Lfx, Eto or Cfz. (If the result for FL-LPA, SL-LPA and DST to Z, BDQ & Cfz is not available)
- Intolerance or risk of toxicity from a drug in shorter oral Bedaquiline-containing MDR/RR-TB regimen.
- Extensive TB disease: bilateral cavitary disease or extensive parenchymal damage on chest radiography.
- In children aged under 15 years, presence of cavities or bilateral disease on chest radiography.
- Severe EP-TB disease: the presence of miliary TB or TB meningitis or central nervous system (CNS) TB.
- In children aged under 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression)
- Children below five years

C. Duration of Regimen

- The regimen consists of an initial phase of 4 months that may be extended up to 6 months and a continuation phase of 5 months, giving a total duration of 9–11 months. Bdq is used for a duration of 6 months.
- From start to the end of 4 months: Bdq, Lfx, Cfz, Z, E, Hh, Eto
- From the start of 5 months to end of 6 months – (If IP not extended) – Bdq, Lfx,
- From the start of 6 months to the end of 9 months – Lfx, Cfz, Z, E
- If the IP is extended up to 6 months, then all three drugs Bdq, Hh and Eto, are stopped together.

D. Treatment Extension

If sputum smear microscopy does not become negative by the fourth month of the treatment, subject the patient to FL-LPA, SL-LPA and culture & DST, and the IP should be extended. IP can be extended to the 5th or 6th month based on smear results at the end of the 4th and 5th months of treatment. T (total duration of IP is not more than six months). If any additional resistance to Z/Cfz on C&DST of the baseline sample is detected or to FQ/ inhA mutation of the 4th-month sample is detected, the patient needs to be reassessed at N/DDR-TBC for stopping shorter oral Bedaquiline-containing MDR/RR-TB regimen and initiation of longer oral M/XDR-TB regimen, immediately on receiving the report. The duration of CP is fixed for five months.

Details on erstwhile Shorter Injectable Containing Regimen could be found in Annexure 6.

E. Pre-Treatment Evaluation

CLINICAL EVALUATION	LABORATORY BASED EVALUATION
History and physical examination	Random blood sugar (RBS)
Height & Weight	HIV testing following counselling
	Complete Blood Count (Hb, TLC, DLC, Platelet count)
	Liver Function Tests (including serum proteins)
	TSH levels
	Urine examination – Routine and Microscopic
	Serum electrolytes (Na, K, Mg, Ca)
	Chest X-ray (if not done earlier during diagnosis), ECG

Table 10. Pre-Treatment Evaluation for Shorter oral Bedaquiline-containing MDR/RR-TB Regimen

F. Follow-up evaluation schedule during treatment

REGIMEN CLASS	SHORTER ORAL BEDAQUILINE-CONTAINING MDR/RR-TB REGIMEN
DURATION	9 – 11 months (4-6m IP, 5m CP)
CLINICAL + WEIGHT ASSESSMENT	Monthly in IP or extended IP if previous month S+ve, Quarterly in CP
SMEAR MICROSCOPY	Monthly from 3rd month onwards till end of IP, Monthly in extended IP only if previous month S+ve Conduct SM within 7 days, if the smear at 6 month is positive then ascertain bacteriological conversion/reversion.
CULTURE	At the end of month 3, end of month 6 and/or end of treatment If the culture results of month 6 is positive, collect one repeat sample immediately to rapidly ascertain the bacteriological conversion/reversion If the repeat sample is culture negative, then do end of treatment specimen collection
DST	FL-SL LPA (Lfx, Mfx, Eto) and LC-DST (Z, Bdq*, Cfz*, Mfx, Lzd, Dlm*) if any • culture +ve (end of month 3 or later and end of treatment) or • smear +ve at end of IP, end of extended IP and end of treatment
UPT	As and when clinically indicated
CBC	As and when clinically indicated
TSH & LFT#	At end of IP, then as and when clinically indicated
CXR	At end of IP, then as and when clinically indicated, end of treatment
ECG$	At 2 weeks, then monthly in first 6 months, then as and when clinically indicated
S. ELECTROLYTES	As and when indicated and in case of any QTcF prolongation
(NA, K, MG, CA	
COLOR VISION TEST	Once in two months (in children)

Table 11. Follow-up evaluation schedule for Shorter oral Bedaquiline-containing MDR/RR-TB Regimen

- If smear/ culture remains positive at the end of the third month or by the end of IP respectively or extended IP, a fresh specimen/culture isolate of that time will be subjected to FL-LPA and SL-LPA to check for amplification of resistance to FQ and H (both inhA and katG mutation).
- If no additional resistance is detected, the IP is extended monthly up to a maximum of 6 months.

- If bacteriological reversion is ascertained or if FL-LPA or SL-LPA detects any resistance or if found to be smear/culture positive at the end of six months or later, the patient will be declared as 'treatment failed' and re-evaluated for the longer oral M/XDR- TB regimen.
- Once treated with the shorter oral Bedaquiline-containing MDR/RR-TB regimen for more than one month, a patient will never be reinitiated on it again.

5.4. Longer oral M/XDR-TB Regimen

(18-20) Lfx, Lzd[4], Cfz, Cs (6)Bdq (6 m or longer)

A. Duration of Regimen

18-20 months with no separate IP or CP

B. Eligibility Criteria

- MDR/RR-TB patients who are excluded from shorter oral Bedaquiline-containing MDR/RR-TB regimen.
- Additional resistance to any second-line drugs, especially Lfx, Mfx, Bdq* Lzd*, Cfz*, Dlm* and Z (*whenever available) or intolerance or non-availability of any drug in use.
- Return after Lost-To-Follow Up (LTFU) or failed to shorter oral Bedaquiline-containing MDR/RR-TB regimen or any longer regimen.
- However, as mentioned previously, for children under five years of age where neither Bdq nor Dlm is approved yet, the longer oral M/XDR-TB regimen is suitably modified as per the replacement sequence.

C. Pre-treatment evaluation (PTE)

The list of investigations enumerated for shorter oral Bedaquiline-containing MDR/RR-TB regimen will remain applicable to longer oral M/XDR-TB regimen. Additional investigations specific to group C drugs that may be required in situations where the longer oral M/XDR-TB regimen may need to be modified are as under:

- Blood Urea & Serum Creatinine – if Am need to be added
- Ophthalmologist opinion (for Linezolid)
- Surgical evaluation for consideration after culture conversion is achieved

Once a patient is placed on the longer oral M/XDR-TB regimen for at least four weeks, such a

[4] dose of Lzd will be tapered to 300 mg after the initial 6–8 months of treatment

patient can no longer be switched to the shorter oral Bedaquiline-containing MDR/RR-TB regimen because this 4-weeks treatment would represent exposure to second-line medicines.

D. Treatment Extension

- Total duration of longer oral M/XDR-TB regimen is 18-20 months.
- After month 6 of treatment, the patient is reviewed based on the month five culture result. If the month five culture result is not available at the end of month 6, the decision to taper the dose of Lzd from 15mg/kg body weight to 10 mg/kg body weight based on the month four culture result.
- If the month 5 or 4 culture result (whichever applicable) remains positive, the dose of Lzd (15 mg/kg) and the regimen is extended by one month to month seven and for a maximum till month eight based on monthly culture results of month 6 and 7 respectively and clinical/radiographic response.
- If the month eight culture is also positive, subject the culture isolate to FL-LPA and SL-LPA and Culture & DST.
- If any additional resistance to Group A, B or C drugs in use is detected, the patient needs to be reassessed at N/DDR-TBC to modify the longer oral M/XDR-TB regimen.
- The duration of Bedaquiline is limited to 6 months.
- Extension of Bedaquiline beyond six months is considered in patients in whom an effective regimen cannot be designed, i.e. if only 2 of 5 drugs are available from Groups A & B and an adequate number of Group C drugs are not available due to high background resistance, non-availability or unreliability of DST.
- The maximum duration of treatment is not more than 20 months.
- A treatment duration of 15–17 months after culture conversion is suggested for most patients; the time may be modified according to the patient's response to treatment.
- In XDR-TB patients, the duration of all oral longer regimen is of 20 months.

E. Replacement Sequence:

As per the 2021 Guidelines for PMDT in India following principles apply to the replacement of any of the component(s) in the longer oral M/XDR-TB regimen:

- The drugs replacement is based on efficacy, no demonstrable resistance, prior use, side-effects profile and background resistance to the replacement drug in the country as per the National Drug Resistance Survey (NDRS) report.
- The regimen should preferably be entirely oral.
- Sometimes injectables may be used based on efficacy and side-effect.
- At least 4-5 drugs are to be used in the initial 6 to 8 months, and at least 3-4 drugs in the last 12 months.
- In situations where no drug replacement is required in the first 6 or 8 months of treatment in MDR-TB or XDR-TB patients, continue with at least three drugs after this

depending upon resistance, tolerability, availability, contraindication etc. of any one of Group A or B drugs.

- Replacement sequence of Group C drugs for longer oral M/XDR-TB regimen was recommended in the order of - Delamanid, Amikacin, Pyrazinamide, Ethionamide, PAS, Ethambutol, Penems.
- Combined use of Bdq and Dlm in the regimen is recommended for those M/XDR-TB patients in whom an appropriate regimen cannot be designed using all five drugs from Group A and B.
- Dlm and Am will not be started in the final 12 months of treatment.
- Though Imp-Cln is 4th in the sequence of drugs of group C in WHO guidelines, it will only be used as the last resort for designing the regimens, operational issues of a Peripherally Inserted Central Catheter (PICC) placement for the entire duration of its use, need for admission.
- Table for replacement sequence of using drugs to modify the longer oral M/XDR-TB regimen is placed as annexure (Annexure 5)

F. Follow-up Monitoring

REGIMEN CLASS	LONGER ORAL M/XDR-TB REGIMEN
DURATION	18-20 months (no separate IP/CP)
CLINICAL + WT.	• Monthly up to month 6 or 7 or 8 if previous month S+ve Quarterly in from month 7 or 9 onwards
SMEAR MICROSCOPY	• With culture at C-DST lab. • Conduct SM within 7 days, if any smear at 6 month or later is positive to rapidly ascertain bacteriological conversion/reversion. • C-DST lab to update the result on Nikshay and inform the concerned field staff of collection center on same day.
CULTURE	• Monthly from month 3 onwards to end of 6 months or 7 or 8 if previous month culture +ve. Quarterly from month 6 or 7 or 8 onwards based on previous month culture results. • If the culture results of month 6 or any of the quarterly culture is positive, collect one repeat specimen immediately and send it for culture to rapidly ascertain bacteriological conversion/reversion and if the repeat specimen is culture negative, then the subsequent quarterly or end of treatment specimen collection.
DST	FL & SL-LPA (Lfx, Mfx, Am, Eto) and LC-DST (Mfx, Lzd, Cfz*, Bdq*, Dlm*, Z) if any time culture +ve at end of 6 months or beyond.

UPT	As and when clinically indicated.
CBC/PLATELETS^	Day 15, monthly in first 6 months, 6 or 7 or 8 if previous month S+ve, then as and when clinically indicated
TSH & LFT[#]	LFT quarterly, then as and when clinically indicated. TSH every 6 months
CXR	At end of month 6, end of treatment, as and when clinically indicated
ECG[$]	At 2 wks, monthly in first 6 months and till Bdq/Mfx/Cfz/Dlm are extended, then as and when clinically indicated.
S. ELECTROLYTES (K, MG, CA)	As and when indicated and in case of any QTcF Prolongation

Table 12. Follow up evaluation schedule of longer oral M/XDR-TB regimen during treatment

^ If Lzd is part of the regimen to rule out bone marrow suppression.
 # HBsAG and other viral markers (Hepatitis A, C & E) to be done in case of Jaundice.
$ In case of baseline ECG abnormality or QTcF ≥450ms with longer oral M/XDR-TB regimen that contains Bdq, Mfx, Cfz or Dlm, ECG must be done on daily basis for initial 3 days or as suggested by cardiologist. Repeat ECG with long II lead after an hour to reconfirm abnormal ECG.
** DST whenever available.*

G. Management of Treatment Interruptions and Lost to Follow-up

Patients Who Miss Doses:

All missed doses during IP must be completed before switching the patient to CP. Similarly, all missed doses during CP must be administered prior to ending treatment.

Patients who interrupt treatment for less than two months: The treatment will be continued, and the duration of treatment will be extended to complete the regimen. The follow-up cultures will be done as per the schedule. An additional culture may be considered if the patient returns between one to two months of treatment and has clinically deteriorated.

- If the culture is positive - repeat FL/SL LPA, and LC DST need to be done as per diagnostic algorithm. If additional resistance is detected to any component drugs, the patient will be switched to the longer oral M/XDR-TB regimen with a fresh PTE.
- If the interruption is in IP, the outcome will be accounted for this patient for the longer oral M/XDR-TB regimen only. If the interruption is in CP, the outcome for a

shorter oral Bedaquiline-containing MDR/RR-TB regimen will be declared 'treatment failed'.

Patients who are "lost to follow-up" (interrupt treatment continuously for two months or more) - give an outcome of "lost to follow-up".

- Subject to repeat NAAT & FL/SL-LPA and LC-DST as per the diagnostic algorithm to restart with appropriate treatment.
- Suppose there are signs of impending treatment failure for any MDR/RR-TB patient with or without additional resistance to second-line drugs. In that case, the patient should be switched to the longer oral M/XDR-TB regimen and evaluated further to modify appropriately based on DST results.
- If a patient has received the shorter oral Bedaquiline- containing MDR/RR-TB regimen for more than one month and returns for treatment after continuous interruption of two months or more, the patient is not restarted on a shorter oral Bedaquiline-containing MDR/RR-TB regimen.

H. Paediatric Drug Dosages

DRUGS	DAILY DOSE (PEDIATRIC TILL THE AGE OF 18 YRS)
ISONIAZID[1]	7–15 mg/kg for patients less than 30 kg; max dose 300 mg daily; **High dose**: 15-20 mg/kg
RIFAMPICIN	10–20 mg/kg for patients less than 30 kg; max dose 600 mg daily
PYRAZINAMIDE	30–40 mg/kg for patients less than 30 kg; max dose 2000 mg daily
ETHAMBUTOL	15-25 mg/kg once daily
LEVOFLOXACIN	5 years and under: 15–20 mg/kg split into two doses (morning and evening) Over 5 years: 10–15 mg/kg once daily
MOXIFLOXACIN	7.5–10 mg/kg; **High dose**: 10-15 mg/kg
BEDAQUILINE	200 mg daily for 2 wks; then 100 mg thrice weekly for 22 wks for weight bands 16-30 kg. approved only age >12 yrs
DELAMANID	50 mg twice daily (100 mg) for 24 weeks in 6-11 years of age 100 mg twice daily (200 mg) for 24 weeks for 12-17 years of age.
CYCLOSERINE	15–20 mg/kg
LINEZOLID	<6 years' age: 10-12 mg/kg/d; >6 years age: 15 mg/kg/d
CLOFAZIMINE	2-5 mg/kg 50 mg capsule: Use thrice a week in children weighing upto 5 kg and every alternate day in children between 5-9 y
ETHIONAMIDE/ PROTIONAMIDE	15–20 mg/kg

P-AMINOSALICYLIC ACID	200–300 mg/kg for patients less than 30 kg in two divided doses
KANAMYCIN	15–20 mg/kg once daily (Max 1000mg)
AMIKACIN	15–20 mg/kg once daily (Max 1000mg)
CAPREOMYCIN	15–20 mg/kg once daily (Max 1000mg)
IMIPENEM CILASTATIN	Meropenem is preferred in children.
MEROPENEM	20–40 mg/kg intravenous every eight hours. Meropenem is given with Amoxicillin- clavulanate* 40mg/kg given twice daily based on the amoxicillin component

Table 13. Paediatric Drug Dosages

Chapter 6 ADVERSE EVENTS AND MANAGEMENT OF ADVERSE DRUG REACTION

A symptom-based approach should be followed to manage minor Adverse Drug Reaction (ADR) where the patient is usually able to tolerate ATT drugs and continue medication with symptomatic treatment. However, patients with significant adverse effects should be managed at the hospital level.

Special Considerations:

- If any drug is withheld/ terminated due to ADR, it would be replaced with an appropriate substitute drug.
- Before starting treatment, the patient should be instructed in detail about potential adverse effects produced by the prescribed drug regimen.
- Depending on the severity of ADRs, the following actions may be indicated:
    - if the adverse effect is mild and not severe, continuing the treatment regimen, with the help of ancillary drugs if needed, is often the best option
    - most adverse effects of several second-line drugs are dose-dependent. Therefore, reducing the dosage of the offending drug or terminating it is another method of managing adverse effects;
    - psychosocial support is a crucial component of the management of adverse effects.

6.1. Management of Important Adverse Events

6.1.1. QT Prolongation

Suspected agent(s)	**Bdq, FQ, Cfz**

- ECG monitoring before initiation and during DR-TB treatment is only required while using Bdq or when two drugs known to prolong QTcF (e.g. Mfx, Cfz) are combined in the same regimen.
- QT interval is measured from the start of the QRS complex to the end of the T wave on a standard ECG. The QT is corrected for heart rate, referred to as the QTc and calculated by most ECG machines. Values above QTc Fridericia correction (QTcF) 450ms in men and 470ms in women are categorised as prolonged. Patients with prolonged QTcF are at risk for developing cardiac arrhythmias like torsades de pointes, which can be life-threatening.
- FQ may cause prolongation of the QTcF. While, Mfx and Gfx cause the most remarkable QTcF prolongation, while Lfx and Ofx have a lower risk.

- Low serum levels of potassium, calcium and magnesium are associated with QTc prolongation. Electrolyte levels should be maintained in the normal range in any patient with an elevated QT interval. Also, avoid other drugs that increase the QT interval. Therefore, patients' renal and hepatic function should also be monitored.
- QT prolongation can result in ventricular arrhythmias (Torsades de Pointes) and sudden death. Therefore, ECGs must be used to monitor the QT interval regularly during the use of the suspected drugs.
- Management of increased QTcF: an algorithm for the reintroduction of anti-TB drugs (Bdq/ FQ/ Cfz/Dlm) once prolonged QTc has normalised is shown in the figure below (Figure 9).

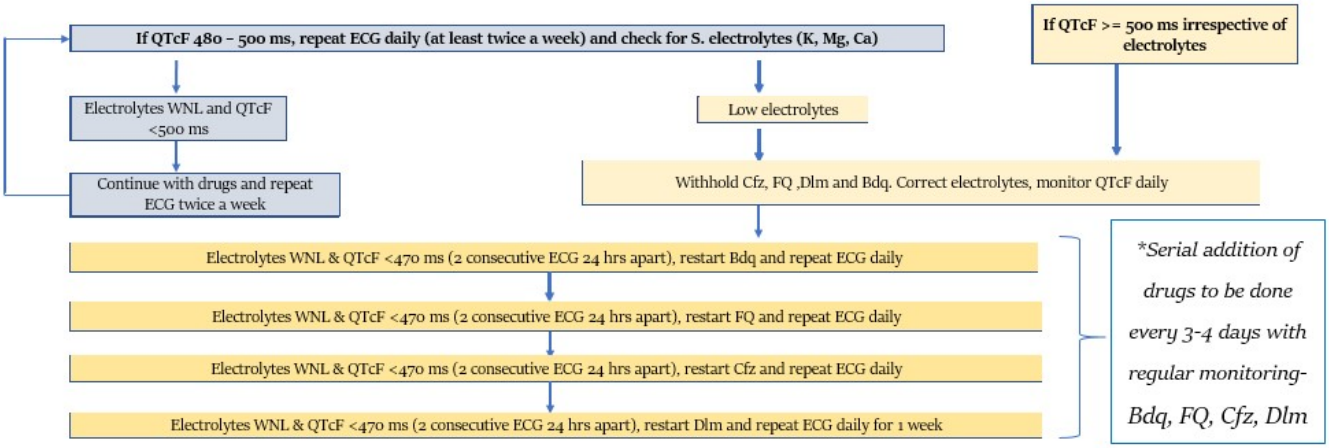


Figure 9. Management of prolonged QTcF during treatment with Shorter/Longer oral MDR-TB regimen

6.1.2. Hepatitis

Suspected agent(s)	**Z, H, R, Eto, PAS, Bdq**

- Very sick patient, i.e., meningitis, sputum smear grade 3+, give ATT e. g. Streptomycin, FQ and Cs.
- The patient is not seriously ill - wait, introduce ATT once enzyme levels are near normal.
- If enzymes are more than five times the upper limit of normal, stop all hepatotoxic drugs and continue with at least three non-hepatotoxic medications (e.g. the injectable agent, FQ and Cs). If hepatitis worsens or does not resolve with the three-drug regimen, then stop all drugs.
- Eliminate other potential causes of hepatitis (viral hepatitis and alcohol-induced hepatitis).

- Once enzyme level improves, reintroduce remaining drugs, one at a time with the least hepatotoxic agents first, while monitoring liver function by testing enzymes every three days. If the most likely agent is not essential, consider not reintroducing it. Management of hepatotoxicity during treatment with DR-TB regimen are described in the figure below (Figure 10).

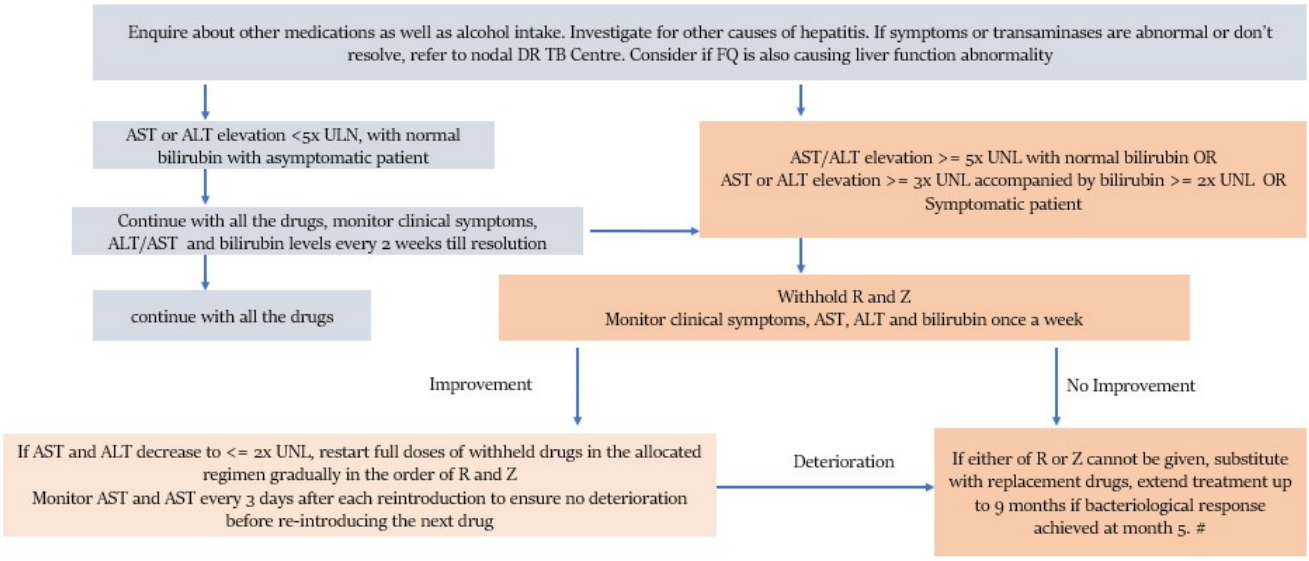


Figure 10. Management of hepato-toxicity during treatment with H mono/poly DR-TB regimen

- **The schedule followed for adult - R is start with 150 mg, repeat LFT after 3 to 5 days, if no increase and no symptoms, increase to 300 mg, repeat same as above and then full dose. For Z process is the same, it is 250 mg initially then 500 mg, 750 mg, 1 gm then full dose.
- # Refer to the nodal DR-TB centre for further management as necessary.

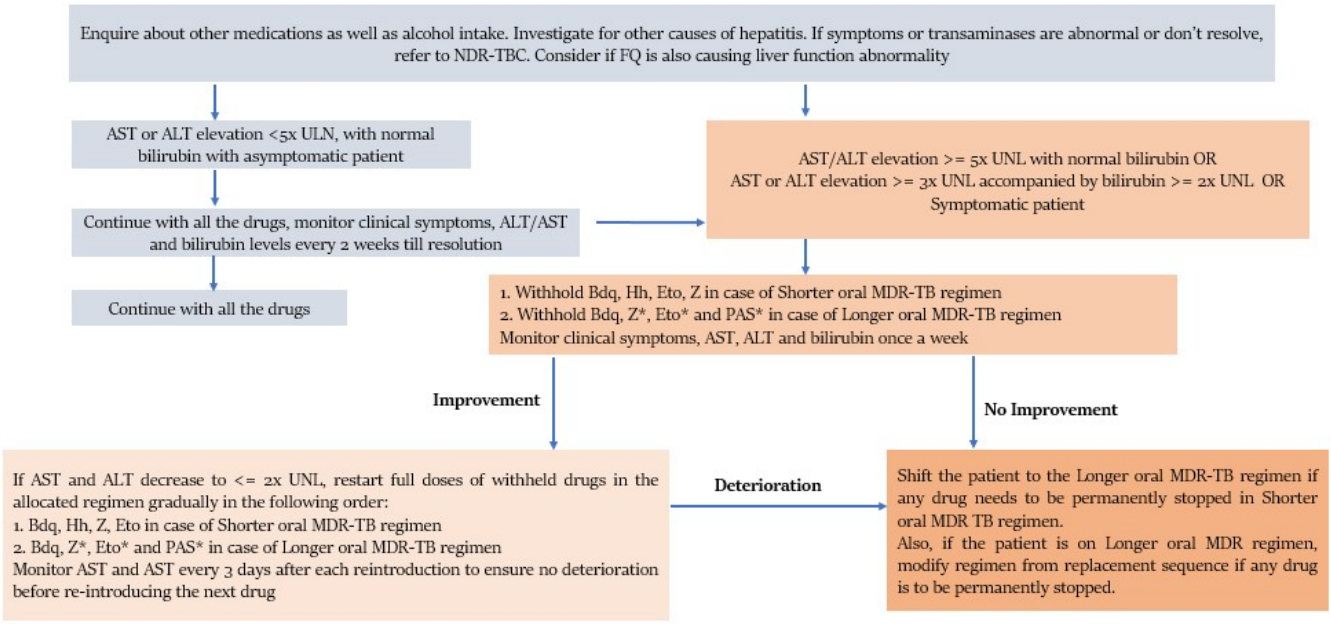


Figure 11. Management of hepato-toxicity during treatment with shorter/longer oral MDR-TB regimen

*If used, introduction is tried from lower doses of each drug with gradually increasing to full dose while monitoring the LFT and symptoms.

6.1.3. Hearing Loss

Suspected agent(s)	Am

- Common cause is aminoglycosides if the reason like wax and middle ear infection is ruled out.
- Document hearing loss and compare with baseline audiogram if available (some degree of hearing loss occurs with most patients starting with a high-frequency loss).
- If early symptoms of hearing loss are documented, change the dosing of the injectable agent to twice/thrice a week.
- Discontinue injectable agent if hearing loss continues despite dose adjustment as it may lead to permanent hearing loss. Add additional drugs to reinforce the regimen.

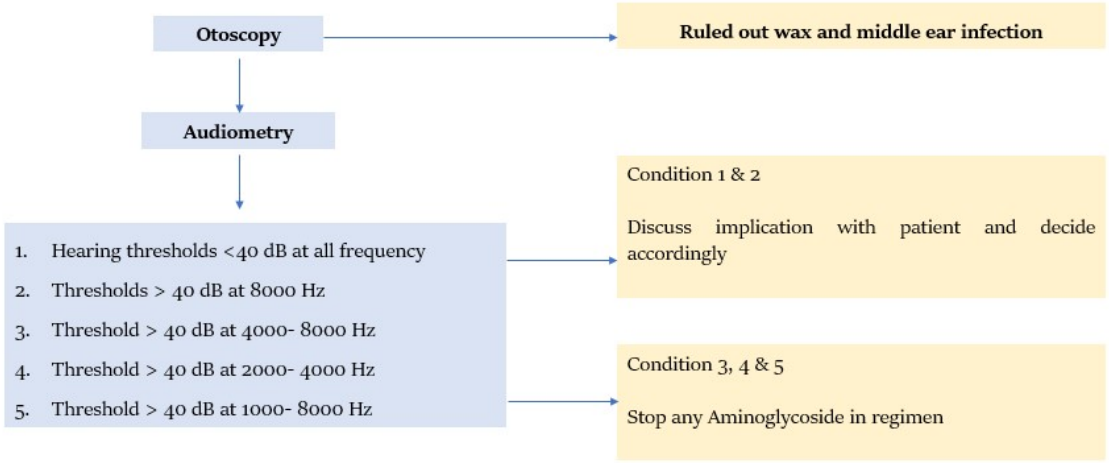


Figure 12. Management of Hearing Loss During Course of Treatment

6.2. Adverse Events, Suspected Agents and Drugs Used in Management of Adverse Event

ADR management is crucial to improve treatment compliance. The majority of the side effects and ADR management is possible with a simple intervention that can be efficiently executed even at the peripheral level. Drugs that can be used for managing common side effects or ADR reported by patients are given in the table below (Table 14).

ADVERSE EVENT	SUSPECTED AGENT	SUGGESTED DRUG TO MANAGE
QTc Prolongation	Bdq, FQ, Cfz	
Rash, Allergic Reaction And Anaphylaxis	Any drug	Hydrocortisone cream, calamine, caladryl lotions
Nausea And Vomiting	Eto, PAS, Z, E, Bdq	Metoclopramide, dimenhydrinate, prochlorperazine, promethazine, bismuth subsalicylate, domperidone
Heart Burn, Gastritis & Abdominal Pain	PAS, Eto, Cfz, Lzd, FQs, H, E, and Z	H2-blockers (ranitidine, cimetidine, famotidine, *etc.*,), Proton pump inhibitors (omeprazole, lansoprazole, *etc.*,) Avoid antacids because

ADVERSE EVENT	SUSPECTED AGENT	SUGGESTED DRUG TO MANAGE
		they can decrease absorption of fluoroquinolone eg. aluminum hydroxide
Diarrhoea Or Flatulence	PAS, Eto	
Hepatitis	Z, H, R, Eto, PAS, Bdq	
Giddiness	Am, Eto, FQ and/or Z	
Metallic Taste	Eto, FQs	
Haematological Abnormalities	Lzd	
Hypothyroidism	Eto, PAS	Levothyroxine
Arthralgia	Z, FQ, Bdq	Ibuprofen, paracetamol, codeine, diclofenac
Peripheral Neuropathy	Lzd, Cs, H, Am, FQ, rarely Eto, E	Amitriptyline
Headache	Bdq, Cs	
Depression	Cs, FQ H, Eto	Selective serotonin reuptake inhibitors (fluoxetine, sertraline), tricyclic antidepressants (amitriptyline)
Psychotic Symptoms	Cs, H, FQ	Haloperidol, thorazine, risperidone, Buromazi thioridazine
Suicidal Ideation	CS,H,Eto	
Seizures	Cs,H, FQ	Phenytoin, carbamazepine, valproic acid, phenobarbital
Tendonitis And Tendon Rupture	FQ	
Nephrotoxicity (Renal Toxicity)	Am	
Vestibular Toxicity (Tinnitus And Dizziness)	Am, Cs, FQs, H, Eto, Lzd	Meclizine, dimenhydrinate, prochlorperazine, Promethazine
Hearing Loss	Am	
Optic Neuritis	E, Lzd, to, Cfz, H, S	
Electrolyte Disturbances-Hypokalaemia And Hypomagnesaemia	Am	

ADVERSE EVENT	SUSPECTED AGENT	SUGGESTED DRUG TO MANAGE
Gynaecomastia	Eto	
Superficial Fungal Infection And Thrush	FQ	Fluconazole, clotrimazole lozenges, Nystatin suspension, itraconazole liquid
Alopecia	H,Eto	
Lactic Acidosis	Lzd	
Dysglycaemia And Hyperglycaemia	Eto, FQ	

Table 14. Adverse Events, Suspected Agents and Drugs Used in Management of Adverse Event

Chapter 7 MANAGEMENT OF TB WITH HIV CO-INFECTION

The HIV and TB epidemics have been entrenching each other with a formation of a vicious loop. HIV infected people are at a greater risk of developing active TB disease than non-HIV infected people leading to an increase in the number of TB patients, which in turn increases TB transmission. The intersection of both epidemics could potentially bring forth a third – Multiple Drug-Resistant Tuberculosis. People Living with HIV (PLHIV) are nearly 18 times (Uncertainty interval: 15-21)[5] more likely to develop TB than people without HIV in the same country. TB accelerates HIV disease progression and AIDS and paves the way for clinical TB and mycobacteremia. HIV and TB make for a fatal combination with extremely high death rates (15–18%) reported among HIV infected TB cases notified under the NTEP. Further, even among cured TB cases with HIV infection, the risk of recurrent TB infection is relatively high. In addition, serious drug interactions between some Antiretroviral drugs and drugs used for TB treatment lead to challenges in treating coinfection.

Since the coinfection rate is high, it is essential from a public health standpoint to screen all those children with HIV for TB and vice-versa. Thus, all patients who have TB should be offered HIV testing after counselling. This is a simple antibody test in children above 18 months of age. Rapid HIV tests that are reliable are available at all ICTC centres across the country. At all Anti-Retroviral Treatment (ART) centres, National AIDS Control Organisation (NACO) ensures strengthening of '3Is' strategy, i.e. Intensive Case Finding (ICF), Airborne infection control (AIC) and Isoniazid preventive therapy (IPT), along with the provision of daily anti-TB treatment (ATT) for PLHIV. NACO and Central TB Division (CTD) are now providing single-window services to prevent and manage HIV-TB coinfection at ART centres to ensure seamless services to CLHIV.

[5] Global tuberculosis report 2021. Geneva: World Health Organization; 2021.

Prevention

- Isoniazid preventive therapy (IPT) for all CLHIV (on ART+ Pre-ART)
- Robust Airborne infection control (AIC) activities
- Awareness generation

Early Detection of HIV-TB

- Provider-initiated HIV testing and counselling (PITC) in TB patients and presumptive TB cases
- Rapid diagnostics for detecting TB and DR-TB in PLHIV
- Intensive Case Finding (ICF) activities at all HIV settings (ICTCs, ART centres, Link ART Centre (LACs), and Targeted Intervention (TI settings): all ICTC clients should be screened for presence of TB and vice-versa

Early Care & Prompt Treatment of HIV-TB

- Promotion of 'Single Window Delivery Services' i.e. ATT from ART centre along with ART drugs
- Prompt initiation of TB treatment
- ART for HIV-TB cases irrespective of CD4 count
- Early initiation of ART (within first 8 weeks) & monitoring of timeliness of ART initiation through expanded ART reporting formats
- Strengthened linkage of HIV-TB patients to ART centres through travel support by NTEP

Box 7. Strategy for HIV-TB Coordination to Reduce Mortality

7.1. Sign and Symptoms in CLHIV for screening for TB

The four-symptom complex below is fairly good starting point for further investigation for TB in CLHIV, as per currently applicable Technical guidelines for ART,2018. However, the ART Medical Officer, would need to evaluate the child first for short duration fevers like malaria, dengue, URI, viral fevers and after excluding these, the child would need evaluation for TB.

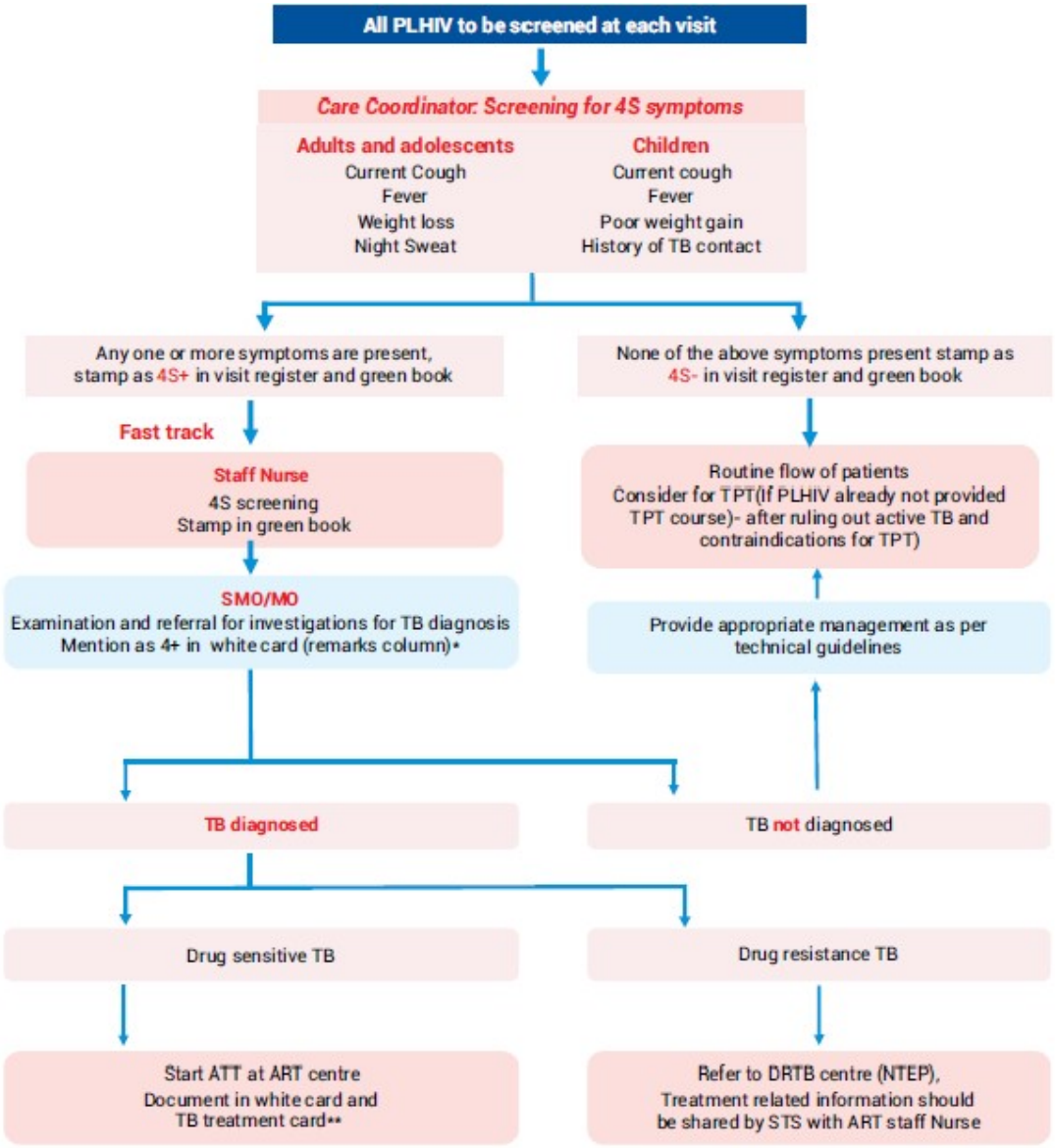


Figure 13. TB Screening Among PLHIV[6]

#Kindly note, the National AIDS Control Programme (NACP) is currently reporting less than 15-year-old patients as children and equal to or more than 15 years old as adults.

** For all PLHIV diagnosed with 'Rif sensitive TB' on NAAT, sample should also be sent for first line LPA.*

If INH resistance is detected, refer to DR TB centre.

*** Information to be captured in NACO IMS and NIKSHAY. HIV-TB line list and HIV-TB register to be autogenerated from IMS*

There are considerable respiratory and other morbidities in CLHIV. Several other diseases or infections could mimic TB-like symptoms. An effort should be made for a microbiological diagnosis in all such cases. This not only allows treatment on robust grounds but also helps by providing information about drug resistance. HIV related other respiratory morbidity makes

[6] National AIDS Control Organization (2021). National Operational Guidelines for ART services, 2021.New Delhi: NACO, Ministry of Health and Family Welfare, Government of India.

interpretation of chest imaging difficult due to overlapping radiological findings between TB and other opportunistic infections or HIV related pathologies. A tuberculin skin test is also impacted by immunosuppression due to HIV infection.

When a patient on ART presents with active TB, there is a possibility of suspecting treatment (ART) failure, mainly if it occurs after six months of starting the ART with other clinical and immunological evidence of HIV progression. Unique problems related to diagnosis of TB HIV co-infection are outlined below.

Overlapping Symptoms

- Chronic pulmonary symptoms due to other HIV related conditions, e.g. Lymphocytic Interstitial Pneumonia, bronchiectasis can mimic TB.
- Weight loss and failure to thrive are both features of HIV and tuberculosis.
- As the HIV disease progresses and the individual becomes more immune-compromised, the clinical presentation is proportionately more likely to be EP or smear-negative than in HIV-uninfected TB patients. This can result in misdiagnosis or delays in diagnosis and, in turn, higher morbidity and mortality.

Radiology

- CXR interpretation: difficult with the presence of other HIV related conditions pneumonia, LIP, bronchiectasis.
- HIV infected patients with active TB proven on sputum culture can have seemingly normal chest radiographs.

Tuberculin Sensitivity Testing (TST)

- Induration >5 mm is read as positive TST.
- Extremely low sensitivity in culture-confirmed TB with HIV cases despite taking cut-offs of 5 mm.
- No consistent evidence that Interferon Gamma Release Assay IGRA is more sensitive than TST.

Microbiological Tests

- Sputum microscopy has poor sensitivity in detecting TB in PLHIV due to fewer organisms in sputum.
- NAAT is the frontline test for the diagnosis of TB among CLHIV. If NAAT is not available, arrangements have to be made to collect and transport specimen to the nearest Nucleic Acid Amplification Test (NAAT) or Mycobacteria Growth Indicator Tube (MGIT) culture site.

Treatment

- Pill burden, Drug interactions, risk of IRIS, and adverse events are critical challenges.

- Deaths during treatment are partly due to TB itself and partly due to HIV related diseases, particularly in the advanced stages of immunodeficiency.
- Further, due to the increased frequency of adverse drug reactions and high pill burden, rigorous monitoring in this particular group of patients is required to ensure adherence to treatment, early identification and treatment of adverse events, and reduce default.

Box 8. Specific Problems in Diagnosis and Treatment of TB in Children Infected with HIV

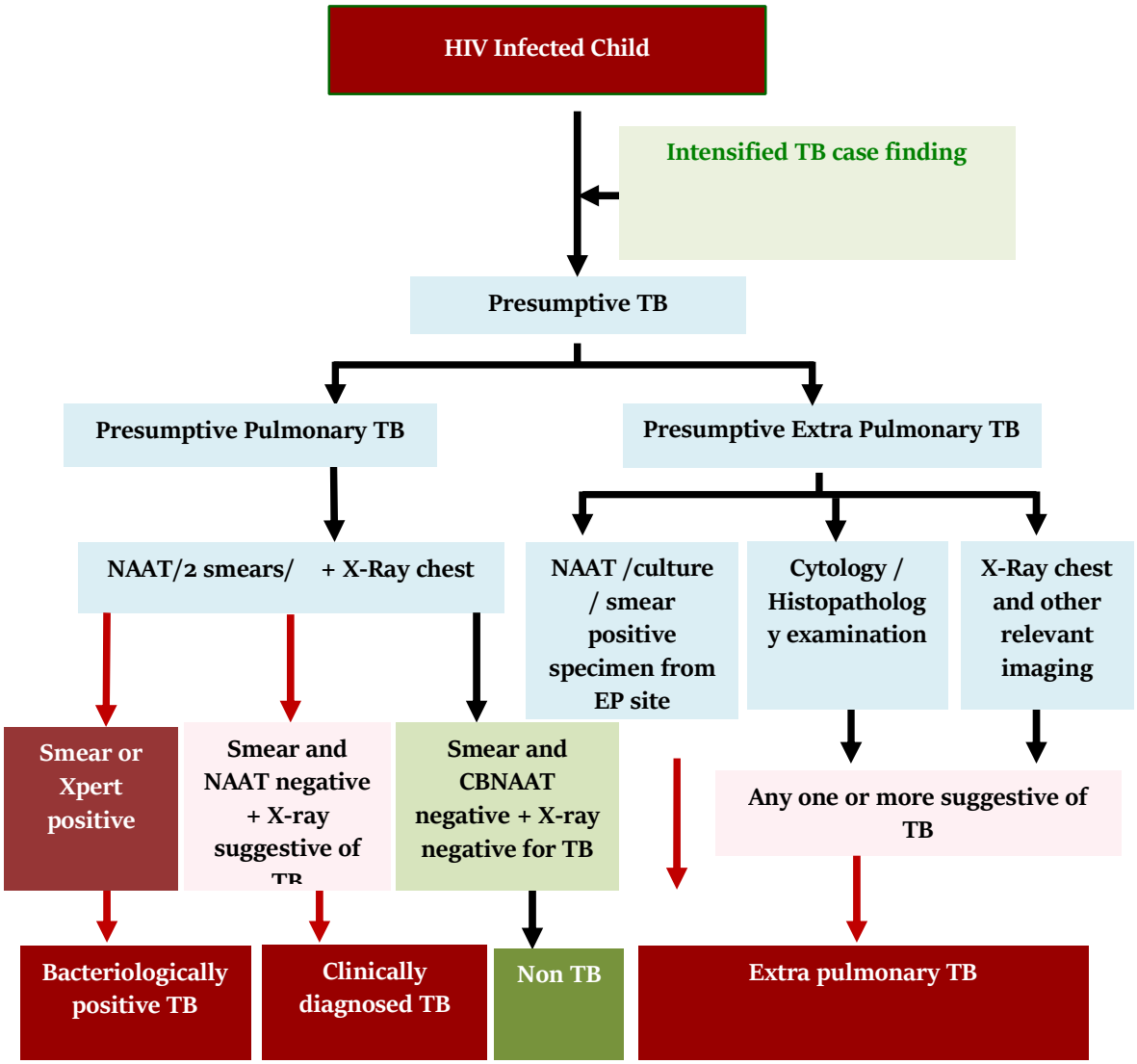


Figure 14. Diagnostic Algorithm of TB in CLHIV

7.2. TB Treatment Recommendations in A Coinfected Patient

The treatment regimen for TB is the same as in HIV non-infected children, and six months of therapy (with intensive and continuation phases) is optimal except with disseminated, intracranial or bony involvement due to TB. At the end of treatment, a further six months of INH

preventive therapy is also advised to reduce the risk of relapse (secondary prophylaxis). Pyridoxine supplementation (10mg/day) should be given till the time INH is prescribed in DS-TB co-infected children.

Giving ART and ATT together is, however, not without problems. Rifampicin is a potent inducer of cytochrome P450, thus increasing the metabolism of NNRTI and protease inhibitors and therefore reducing their drug levels. Newer drugs-like Bedaquiline, are metabolized by the CYP3A4 having multiple drug interactions with protease inhibitors and non-nucleoside reverse-transcriptase inhibitors (NNRTI). There can also be adverse events, especially hepatotoxicity. The possibility of developing Immune Reconstitution Inflammatory Syndrome (IRIS) is always there more so when ART is initiated early. Moreover, high pill count may also affect patients' acceptance and lead to increased loss to follow-ups. The ART in TB cases should be as per the latest NACO guidelines in place and with the involvement of the local ART facility.

7.2.1. Initiation of ART in PLHIV with TB Coinfection

All PLHIV diagnosed with active TB are to be initiated on ART regardless of CD4 count after initiation of TB treatment as per the NTEP guidelines. Start ATT first, initiate ART as soon as TB treatment is tolerated (between 2 weeks and 2 months), keeping in mind the time needed to accept the diagnosis, counselling needs, pill burden, drug interactions/ additive toxicities with ATT, and TB associated Immune reconstitution inflammatory Syndrome (TB-IRIS). Lastly, caution is needed for PLHIV with TB Meningitis, since immediate ART is associated with more severe adverse events than initiating ART two months after the start of TB treatment.

Current ART regimen	**ART modification while receiving rifampicin-based regimen For TB**
DTG based regimen	Double the dose of DTG. DTG dose will need to remain twice daily for two weeks after the last dose of rifampicin
LPV/r-based regimen	Super boosting of LPV with ritonavir (the ratio of LPV:r is 1:1). Super-boosting of LPV with ritonavir to continue for two weeks after stopping rifampicin
EFV based regimen	No modification is required
DTG + LPV/r regimen	Double the dose of DTG (DTG 50mg twice daily). In addition, super boosting of LPV with ritonavir (the ratio of LPV: r is 1:1). Both double dose of DTG and Super-boosting of LPV with ritonavir to continue for two weeks after stopping rifampicin

Dolutegravir (DTG); Lopinavir (LPV); ritonavir (r); Effavirenz (EFV)

Table15. Modification of ART regimen in CLHIV receiving Rifampicin based ATT

Weight and age of CLHIV	Recommended Regimen in TB coinfection in CLHIV
Weight- less than 20kg or Agebelow 6 years	FDC of Abacavir + Lamivudine twice daily as per weight band + Lopinavir /ritonavir + super-boosting with additional ritonavir,twice daily as per weight band
Weight between 20-30kg and Age: between 6-10 years	FDC of Abacavir +Lamivudine twice daily as per weight band + DTG 50mg twice daily
Weight above 30 kg and Age: above 10 years	FDC of Tenofovir + Lamivudine + Dolutegravir once daily with anadditional dose of Tab Dolutegravir 50 mg after 12 hours
Note: DTG dose will need to remain twice daily for two weeks after the last dose of rifampicin super-boosting of LPV with ritonavir to continue for two weeks after stopping rifampicin	

Table 16. ART Regimens in CLHIV on First-line ART with TB coinfection

7.2.2. PLHIV already on ART at time of Diagnosis of Active TB

The following points are to be considered in PLHIV if TB is diagnosed in patients already receiving ART:

- In PLHIV who are already on ART at the time of TB diagnosis, ART modification needs to be done to maintain optimal efficacy of ATT as well as ART.
- When a patient on ART presents with active TB, there is a possibility of failure of treatment (ART). The NACO recommends the following guiding principles in this context:
    - If an episode of TB occurs within the first six months of the initiation of ART, it should not be considered a failure of the treatment. The ART regimen should be adjusted for co-administration with rifampicin / bedaquiline-containing regimens.
    - If an episode of TB develops more than six months after the initiation of ART, and data on the CD4 count (and viral load), are available, the decision on whether the diagnosis of TB represents ART failure should be based on the CD4 count and viral load data.
- The development of an episode of pulmonary TB after six months of ART, without other clinical and immunological evidence of disease progression, should NOT be regarded as representing ART failure.
- Extrapulmonary TB should be indicative of ART failure, although simple lymph node TB or uncomplicated pleural disease may be less significant than disseminated TB. Close monitoring is needed, and adherence support should be reinforced.

7.2.4. ART among CLHIV with DR-TB Coinfection

Second-line anti-TB drugs should be initiated first, followed by ART as soon as second-line anti-TB drugs are tolerated. Generally, this should be within the first two weeks of initiating DR-TB treatment. On the other hand, undue delay in starting ART could result in a significant risk of HIV related death amongst DR-TB patients. Patients who are already on ART during DR-TB diagnosis can be continued on ART when DR-TB therapy is initiated.

7.2.5. Drug Interactions of Second Line Anti-TB Drugs with ART

Bdq should be used with caution in PLHIV infection treated with Anti-Retroviral (ARVs) that exhibit drug-drug interactions with it (efavirenz) or prolong QT interval (lopinavir/Ritonavir). Bdq has been used in large cohorts of patients. While experience is growing and drug monitoring is still required, the concern is less due to cohort data reviewed from South Africa. However, frequent clinical and cardiac evaluation is necessary for these patients.

- Dolutegravir can be used safely with the new TB drugs Bedaquiline and Delamanid. PLHIV already on NRTI+DTG regimen may be continued with Bedaquiline / Delamanid containing DR-TB regimen.
- PLHIV on NNRTI/PI-based ART regimen need substitution of PI with DTG in the ARV regimen, when co-prescription with BDQ/DLM containing DR-TB regimen is required.
- TB-HIV co-infected PLHIV requiring a PI-based second/third-line ART, need coordination for considering a non-BDQ/DLM DR-TB regimen.
- In case an effective DR-TB regimen cannot be made without BDQ/DLM, the necessary DR-TB regimens using new TB drugs may be given with PI-based ART but with intensive monitoring for toxicities of BDQ/DLM.
- PLHIV on ARV regimens with boosted PI, if treated with Bedaquiline-based ATT, should be monitored closely.
- All TB-HIV co-infected PLHIV diagnosed with drug-resistant TB should be referred to the linked DR-TB centre for starting treatment for DR/MDR-TB.

Drug-drug interaction studies of Delamanid (Dlm) with tenofovir, efavirenz and lopinavir/Ritonavir, respectively, suggested that no dose adjustments were needed when Dlm was used with any of these ARV agents. However, PLHIV, receiving Dlm as part of DR-TB treatment, should have their ART regimens designed in close consultation with HIV clinicians and ART specialists.

7.2.6. Cotrimoxazole Prophylaxis Therapy (CPT) in HIV-TB cases

Cotrimoxazole is a fixed-dose combination of sulfamethoxazole and trimethoprim, given routinely to prevent opportunistic infections in HIV-infected persons. It has been shown to reduce morbidity and mortality in HIV-infected patients in general and HIV-infected TB patients in particular.

7.2.7. Monitoring During Treatment

HIV-infected children on ATT should have LFTs at baseline, day 15, month one and month three. After three months, a symptom-directed approach is helpful. If symptoms of drug toxicity develop, a physical examination and liver enzyme measurement should be repeated. Guidelines for ATT induced liver disease remain the same as in any other child.

7.2.8. TB Immune Reconstitution Inflammatory Syndrome (IRIS)

After ART initiation, HIV-1 replication is significantly reduced, and viral load rapidly falls, resulting in increased CD4 cell function & improved immunity. The host immune response to the pathogen then produces the clinical manifestations in a subset of patients. These are usually two types of situations (a) paradoxical IRIS: the TB symptoms that start abating on ATT show exacerbation after the patient is started on ART. (b) Unmasking IRIS: usually, there are no clinical features of TB before starting ART. After ART is initiated, an excellent initial response (CD4, viral load) is seen, and then the TB manifestations become manifest.

IRIS is also a diagnosis of exclusion. It is essential to rule out other causes of similar clinical presentation like poor adherence to TB therapy, failure of TB therapy due to drug resistance, another opportunistic infection or neoplasm, drug toxicity or drug reaction.

Anti-tuberculosis therapy and ART should be continued in every case. Mild IRIS should be managed with symptomatic treatment, e.g. aspiration of large fluctuant lymph nodes or subcutaneous abscess may provide relief. In moderate to severe IRIS, short term therapy with corticosteroids can be given (Prednisolone in a dose of 1.5 mg/ kg orally for two weeks followed by 0.75 mg/ kg orally for two weeks and then tapered off). Treatment for paradoxical IRIS is initiated after excluding all other clinical mimickers.

7.2.9. BCG in children with HIV

BCG is useful for CLHIV born in TB-endemic countries. BCG vaccination should be given at birth to all asymptomatic HIV exposed infants. However, if BCG has not been given at birth, it should not be given in symptomatic HIV-infected older infants and children.

Chapter 8 MANAGEMENT OF A NEONATE BORN TO A MOTHER WITH TUBERCULOSIS

There are several ways a newborn can be exposed to TB with an absolute but variable risk of transmission of infection. These situations include when the mother has active TB (both pulmonary or extrapulmonary) when the baby is born, or the mother has completed treatment for TB (pulmonary or extrapulmonary) while carrying this baby or else neonate exposed to a Health care worker/another contact with Pulmonary TB. ATT should be given to pregnant women having TB as most First Line Drugs (FLDs) (except aminoglycosides) are safe, and women's health is paramount.

Safety of ATT During Pregnancy

- FLDs are Safe (except aminoglycosides), particularly after the first trimester
- Aminoglycosides are unsafe and not recommended
- Offers no transplacental protective benefit to the foetus

Box 9. Safety of ATT During Pregnancy

The risk of transmission of infection to the newborn is affected by many factors like maternal disease (high with miliary, meningeal or pulmonary disease; low with pleural effusion or lymph node and unknown with HIV co-infection) and therapy (low risk if completed treatment or even if taken two weeks of treatment), closeness and cough etiquette of contact, isolation and barrier nursing, and use of preventive therapy.

The newborn should first be evaluated for the presence of disease as early as possible. As the symptoms can be subtle, a good clinical examination and chest radiograph is needed. Other investigations, including USG abdomen or gastric aspirate, may be indicated based on symptoms and examination.

8.1. Preventive Therapy to Neonate

TB Preventive therapy is recommended for neonates born to mothers with any form of active TB in pregnancy or after birth. The neonate is exposed to an infectious case of TB after birth. Active disease should be ruled out in such a neonate before starting preventive therapy. INH preventive therapy is given in a dose of 10 mg/kg for six months, and Pyridoxine may be prescribed.
However, if the neonate has been exposed to an MDR contact, then TB preventive therapy is not recommended. The efficacy of 2nd line drugs in preventing TB is not unequivocally established, and also these drugs can be fairly toxic.

Modern chemotherapy is so efficacious in drug-sensitive cases that separation of the mother and infant is no longer considered mandatory, provided the mother's therapy is started, and the baby is on IPT. Breastfeeding can continue and is safe. Mother, if still under treatment, should practice strict personal and cough hygiene. ATT excreted in a small amount in the milk has no therapeutic or adverse effect on the baby.

Separation should be practised if only the mother is ill enough to require hospitalization, if she has been or is expected to become non-adherent to her treatment, or if she is infected with a drug-resistant strain of *M. tuberculosis*. Also, consideration should be given to sick mothers' health, nutrition and rest. During barrier nursing, expressed breast milk feeding is a safe option even when the mother is on Anti-TB drugs.

Vaccination with BCG appears to decrease the risk of tuberculosis in exposed infants. Hence, all children born to mothers with TB should receive BCG at birth even if they are isoniazid preventive therapy. Prior TST testing is not recommended for deciding preventive therapy for exposed neonates.

8.2. Perinatal Tuberculosis

There are two main infectious routes for congenital TB *viz*. Transplacental route: forming a primary complex in the liver of infant with secondary hematogenous spread; and, through aspiration or ingestion of infected amniotic fluid: leading to a primary focus in lungs or GIT. Congenital TB is acquired during intrauterine life or before complete passage through the birth canal. Perinatal TB is the preferred term that encompasses true congenital and neonatal forms of the disease. While diagnostic criteria like modified Cantwell's criteria can be used to diagnose congenital conditions, these also have limitations. The distinction between true congenital cases and those acquired postnatally is of pure epidemiological significance and may not be essential. Modes of presentation, treatment, and immediate prognosis do not differ considerably between two groups, and it may be difficult to differentiate at times between these groups.

Congenital and perinatal forms of TB mimic common neonatal illnesses and have a uniform poor outcome. Many patients die without a diagnosis, especially in conditions where the index of suspicion is low, or the microbiological examination is unyielding. Extensive and invasive investigations are difficult to carry out, especially in small hospitals and sick patients. The treatment regimen of perinatal TB is similar to paediatric TB.

Chapter 9 MANAGEMENT PREVENTION OF TB

TB Infection

- *India has the highest burden of TB infection (TBI) globally.*
- *5–10% of those infected will develop active TB disease over the course of their lives, usually within the first two years after initial infection.*
- *In India, 71% of Household Contact (HHC) of pulmonary TB patients had baseline TBI.*
- *The risk of TBI increases 16-21 times in case of HIV coinfection with or without ART.*
- *Eligibility for Tuberculosis Preventive Treatment (TPT) relies on ruling out active TB and risk versus benefit assessment.*

Box 10. TB Infection

Children are more susceptible to TB infection, more likely to develop active TB disease soon after infection, and more likely to develop severe forms of disseminated TB. The risk of infection with tuberculosis is most significant if the contact is in close proximity and a sputum smear-positive patient (microbiologically confirmed pulmonary case). Factors that predict likely transmission of TB are the anatomical site of disease, positive sputum bacteriology, radiographic findings, behaviours that increase aerosolisation of respiratory secretions, age, HIV coinfection and effective therapy. Moreover, studies also suggest that increased grades of smear positivity of source cases are associated with an increased risk of infection in child contacts. In resource-limited settings, contact screening focuses on contacts of smear-positive cases because of the greater risk of infection in this group and limited capacity for screening. However, cases of smear-negative pulmonary TB can also transmit infection.

Contact history (including closeness and type of source case of TB disease) is essential for children with suspected TB disease. Studies also show that the risk of infection was much higher if the source case was a primary caregiver like mother, aunt or grandmother. Furthermore, current evidence shows that the risk of getting infection amongst the HIV negative household contacts of pulmonary smear-positive cases was high irrespective of their age group. The highest risk was among younger children <5 years of age. The risk of developing the disease was highest among children <five years of age and almost twice that of the other age groups. Therefore, a medical officer/paediatrician should evaluate children up to five years of age, who are close contacts of a microbiologically confirmed pulmonary TB patient within the past three months, for active TB. INH preventive therapy should be given irrespective of their BCG or nutritional status after excluding active TB.

The dose of INH for preventive therapy is 10 mg/kg body weight administered daily for a minimum period of six months. The INH tablets should be collected every month. The contacts should be closely monitored for TB symptoms.

Strategies to prevent TB include:

- Early detection and treatment of infectious cases;
- Airborne infection control practices;
- Contact screening and TB preventive therapy (TPT), and;
- BCG vaccination.

General Measures to Prevent the Spread of Infections

- Keeping windows and doors open, as far as feasible, to allow fresh air into patients' homes
- Maintaining spatial separation of at least 3 feet
- Using a surgical face mask/ cloth over mouth by the patient
- Covering mouth/nose when coughing/sneezing
- Using tissues and promptly disposing them in the trash or using clean washed towels/cloth that is kept separate and washed and sun-dried daily.
- Performing hand hygiene if hands get soiled with respiratory secretions by the patient

Contact Screening

- All close contacts, especially household contacts, should be screened for TB.
- In the case of paediatric TB patients, reverse tracing to search for any active TB case (likely source) in the child's household must be undertaken.
- Particular attention should be paid to contacts with the highest susceptibility to TB infection, e.g. children <five years, contacts with known or suspected immune-compromised status, particularly HIV.

9.1. Children Living with HIV (Adolescents and Children)

TPT reduces the overall risk for TB by 60-90% among PLHIV. The following are the recommended actions:

- Adolescents and children (>12 months) living with HIV should be screened for TB using a four-symptom complex, and TPT can be provided to those without symptoms or after ruling out active TB in those with TB symptoms. TPT should be given to all these individuals irrespective of the degree of immunosuppression, whether on antiretroviral treatment (ART), previous TB treatment, or pregnancy in women.

- Infants aged < 12 months living with HIV who are in contact with a patient of pulmonary TB and are investigated for TB should receive TPT with six months of isoniazid (6H) after active TB is ruled out.

All household contacts of pulmonary* TB patients

- All HHC of pulmonary*[7] TB patients should be given TPT after ruling out TB regardless of their age.
- In children HHC under five years of age, TPT will be offered after ruling out active TB without TBI testing.
- In children, HHC >five years and adolescents, chest X-Ray and TBI testing would be offered wherever available. All efforts need to be made to ensure that CXR & TBI testing is made available.
- However, TPT must not be deferred in their absence. (This includes close contacts of pulmonary* TB patients at the workplace and other settings, regardless of their age).

Expansion to Other Risk Groups

Children with clinical risk factors on immunosuppressive therapy, anti-TNF treatment, dialysis, preparing for organ or hematologic transplantation having silicosis should be tested and treated for TBI because of their increased risk for progression to active TB disease.

In addition to the above, INH preventive therapy should be considered in the following situation: A child born to a mother diagnosed with TB in pregnancy should receive prophylaxis for six months, provided congenital TB has been ruled out. BCG vaccination can be given at birth even if INH preventive therapy is planned.

[7] *bacteriologically confirmed pulmonary TB patients will be prioritized for enumeration of the target population for TPT

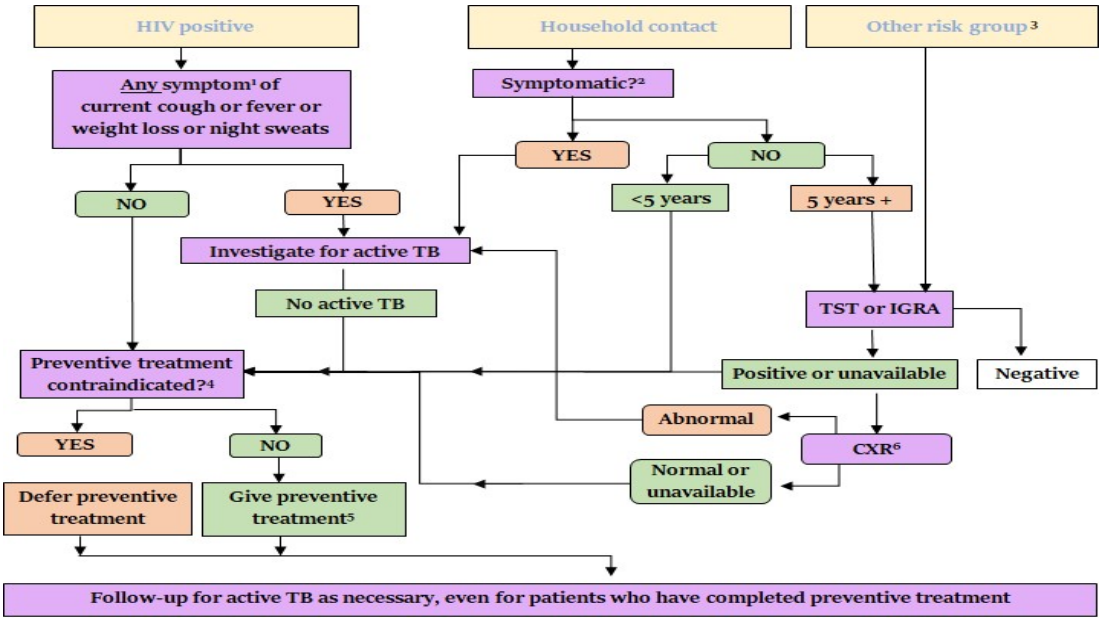


Figure 15. Algorithm for TB screening and TPT in India

1. *If <10 years, any one of current cough or fever or history of contact with TB or reported weight loss or confirmed weight loss >5% since last visit or growth curve flattening or weight for age <-2 Z-scores. Asymptomatic infants <1 year with HIV are only treated for TBI if they are household contacts of TB. TST or IGRA may identify PLHIV who will benefit most from preventive treatment. Chest radiography (CXR) may be used in PLHIV on ART before starting TPT.*
2. *Either cough, fever, night sweats, haemoptysis, weight loss, chest pain, shortness of breath, or fatigue. In children <five years should also be free of anorexia, failure to thrive, not eating well, decreased activity or playfulness to be considered asymptomatic.*
3. *Including dialysis, anti-TNF agent treatment, preparation for transplantation, silicosis or other vulnerable risk groups where testing must precede before TPT.*
4. *Including acute or chronic hepatitis; peripheral neuropathy (if isoniazid is used); regular and heavy alcohol consumption. Pregnancy or a previous history of TB are not contraindications.*
5. *The regimen is chosen based on considerations of age, strain (drug-susceptible or otherwise), risk of toxicity, availability and preferences.*
6. *Chest X-Ray may have been carried out earlier as part of intensified case finding.*

9.2. TB Preventive Therapy (TPT)

• People Living with HIV (± Art)
  ○ Adults and Children >12 Months
  ○ Infants <12 Months with HIV in Contact with Active TB
• HHC Below 5 Years Of Pulmonary* TB Patients
	TPT to all after ruling out active TB disease	• 3-month weekly Isoniazid and Rifapentine (3HP) in persons older than 2 years
		• 6-months daily isoniazid (6H)

• HHC 5 Years And Above Of Pulmonary* TB Patients#	TPT among TBI positive# after ruling out TB disease	
Other Risk Groups Individuals Who Are: • On Immunosuppressive Therapy • On Anti-TNF Treatment • On Dialysis • Preparing for Organ or Hematologic Transplantation • Having Silicosis	TPT after ruling out TB disease among TBI positive	

Box 11. TB Preventive Therapy (TPT)

- **bacteriologically confirmed pulmonary TB patients would be prioritized for enumeration of the target population for TPT*
- *#CXR and TBI testing would be offered wherever available, but TPT must not be deferred in their absence*
- *Until 3HP is widely available under the programme, all states must intensify the monitoring to saturate the TPT coverage in PLHIV and children < 5 years who are in contact with an index TB patient using 6H and move to 3HP whenever available.*

6 MONTHS OF DAILY ISONIAZID MONOTHERAPY (6H)	Age 10 years & older: 5 mg/kg/day[d] Age <10 years: 10 mg/kg/day (range, 7–15 mg)					
THREE MONTHS OF WEEKLY RIFAPENTINE PLUS ISONIAZID (12 DOSES) (3HP)	**Age 2-14 years[c]**					
	Medicine, formulation	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg
	Isoniazid, 100 mg[a]	3	5	6	7	7
	Rifapentine, 150 mg	2	3	4	5	5

	Isoniazid + rifapentine FDC (150 mg/150 mg)[d]	2	3	4	5	5
	Age >14 years[c]					
	Medicine, formulation	30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg
	Isoniazid, 300 mg	3	3	3	3	3
	Rifapentine, 150 mg	6	6	6	6	6
	Isoniazid + rifapentine FDC (300 mg/300 mg)[b]	3	3	3	3	3

Table 17. TPT Regimen Options and Recommended Dosages of Medicines

a. 300 mg formulation can be used to reduce the pill burden

b. Expected to become available shortly

c. Dosage may differ among adults and children in overlapping weight-bands

d. Maximum dose of H, if given daily, would be 300 mg/day.

9.2.1. Policy for TPT in DR-TB Contacts in India

Preventive treatment among paediatric HHC of MDR-TB index patients (in whom FQ resistance has been ruled out) and among HHC of H resistant index patients (in whom R resistance has been ruled out), use of 6Lfx and 4R respectively to be introduced in a phased manner for all age groups.

The following are the salient features:

- Once a DR-TB patient has been identified, all household contacts are counselled, screened and evaluated to rule out active TB;
- It is critical to know the DST pattern of the index DR-TB patients to guide the TPT regimen choice in those found eligible to receive TPT for among DR-TB contacts.
- NAAT is used upfront among contacts with symptoms or abnormal chest X-ray to diagnose TB;
- If the result is M.*tb* detected with no resistance, the treatment for DS-TB is initiated;
- If the result is M.*tb* detected with H and R resistance, manage as per DR-TB guidelines;
- If the result is M.*tb* not detected, in HHC <5 years, assess for TPT and check for any contraindications;
- If the result is M.*tb* not detected, in HHC >5 years of age with TBI test positive or unavailable and chest X-ray is normal or unavailable check for any contraindications;
- If contraindications to TPT drugs exist, defer TPT and if no contraindication exists, offer TPT regimen as appropriate based on DST pattern of the index patient; and
- Follow-up for active TB as necessary, even for patients who have completed preventive treatment irrespective of TPT offer.

- The efficacy of TPT is highest if at least 80% of the doses are taken within the duration of the regimen.

REGIMEN	DOSE BY AGE AND WEIGHT BAND
SIX MONTHS OF DAILY LEVOFLOXACIN (6LFX) FOR CONTACTS OF R RESISTANT FQ SENSITIVE PATIENTS[#]	Age > 14 years, by body weight: < 45 kg, 750 mg/day; ≥ 45 kg, 1g/day Age < 15 years (range approx. 15–20 mg/kg/day), by body weight: 5–9 kg: 150 mg/day 10–15 kg: 200–300mg/day 16–23 kg: 300–400mg/day 24–34 kg: 500–750mg/day
FOUR MONTHS OF RIFAMPICIN DAILY (4R) FOR CONTACTS OF H RESISTANT R SENSITIVE PATIENTS*	Age 10 years & older: 10 mg/kg/day[**] Age <10 years: 15 mg/kg/day (range, 10–20 mg)

Table 18. TPT Regimen Options and Recommended Dosages of Medicines for Contacts of DR-TB Index Patients

- [#] Levofloxacin 100 mg dispersible tablets available for children. Children receiving 6Lfx should be watched for joint abnormalities.
- In children from 0-14 years, 4R should only be used after ruling out active TB in limited geographies/populations for evidence generation to guide future scale up for country wide implementation.
- [**] *Maximum dose of R would be 600 mg/day.*

9.3. Role of Pyridoxine and its Availability

Peripheral neuropathy that develops secondary to a deficiency of vitamin B6 (pyridoxine) during TB treatment infrequently occurs among patients taking standard doses of H for TPT. It is easily recognised (as symmetrical numbness and tingling of the extremities) and usually easily reversible upon H withdrawal and giving high-dose pyridoxine therapeutic dose (100–200mg/day).

Individuals at risk for peripheral neuropathy, such as those with malnutrition, chronic alcohol dependence, HIV infection, renal failure, diabetes, pregnancy or breastfeeding, should receive

vitamin B6 supplements when taking an H-containing regimen. The standard dose of pyridoxine, when used prophylactically for prevention of neuropathy among patients taking isoniazid, is 10 mg/day in children and 25 mg/day in adults.

Nonetheless, TPT should not be withheld if pyridoxine is not available. Alternatively, the multi-vitamin/B-complex formulations with the requisite prophylactic dose of pyridoxine available within the general health system may be considered.

9.4. BCG Vaccination

BCG – (Bacille Calmette Guerin) is a weakened (attenuated) version of Mycobacterium bovis, closely related to Mycobacterium tuberculosis. It is routinely given at birth or soon after that as an intradermal injection in the country. It is a single dose vaccine and can be given safely to older children too, where the dose at birth is missed.

The efficacy of BCG vaccine is variable and ranges from substantial protection, in the UK MRC trial (RR 0.22; 95% CI, .16–.31), to the absence of clinically significant benefit in the Chingleput trial (RR, 1.05; 95% CI, .88–1.25). There are marked differences in estimated efficacy according to the geographic latitude at which tests were conducted—greater efficacy in trials conducted at latitudes farthest from the equator. Furthermore, efficacy is better in school-age children with prior testing (74%) and neonatal vaccination (60%). It is estimated that for the prevention of meningeal and miliary TB, overall protection by BCG is around 85%, and with neonatal vaccination, it is approximately 90%.

9.4.1. Complication - BCG lymphadenitis

BCG lymphadenitis appears as an isolated axillary (or supraclavicular/cervical) lymph node enlargement with BCG history on the same arm. There is usually no tenderness or raised temperature over swelling (except in impending rupture) and no fever or other constitutional symptoms.

BCG adenitis has the following characteristic features:

- A preceding history of vaccination on the same side
- It can appear anytime within the first year or so
- More often with subcutaneous or injection high up on the shoulder
- Injection given high up on the shoulder can cause ipsilateral supraclavicular adenopathy too,
- Never has associated systemic signs in healthy children

TST, FNAC cytology, smear for AFB or NAAT does not help distinguish BCG lymphadenitis from TB LN. However, clinical differentiation from TB lymphadenitis may not be difficult, as isolated axillary glandular TB cases are sporadic.

Course of Untreated Lymphadenitis

Non-suppurative lymphadenitis regresses spontaneously over a few weeks to months; it can take 6-8 months. However, in a few cases, progressive enlargement and evolution into abscess formation can occur. Suppuration may develop in 30% to 80% of cases of BCG lymphadenitis.
On the other hand, suppurative lymphadenitis can regress spontaneously, but the most likely outcome in these cases is the development of spontaneous rupture and sinus formation. Finally, healing of the sinus occurs through cicatrisation, but the process usually takes several months.

Management of Lymphadenitis

Non-suppurative BCG lymphadenitis should be allowed to regress spontaneously. If already suppurated or suppuration develops, needle aspiration may prevent rupture and subsequent large ulceration. However, repeated aspiration on refilling may be required, and gradually the pus starts thinning out and decreasing in volume. Sometimes, if the pus is thick, incision and drainage may be needed. Moreover, surgical excision is resorted for cases with multiloculated or matted glands.
Lastly, antibiotics and ATT are ineffective in hastening regression or preventing suppuration in BCG lymphadenitis and should not be used.

Immunosuppressed children can develop disseminated BCGiosis, which will require therapy. However, BCG is inherently resistant to Pyrazinamide.

Chapter 10 TB CASES AND THEIR TREATMENT OUTCOMES

10.1. Treatment Outcomes

The treatment outcome definitions make a clear distinction between two types of patient groups (cohort):

1. Patients treated for drug-susceptible TB
2. Patients treated for RR/MDR-TB and XDR-TB

10.1.1. Treatment Outcomes for Drug-susceptible TB Patients

Cured: microbiologically confirmed TB patients at the beginning of treatment who was smear or culture negative at the end of the complete treatment.

Treatment Completed: A TB patient who completed treatment without evidence of failure or clinical deterioration BUT has no record to show that the smear or culture results of biological specimen in the last month of treatment were negative. This could be either because the test was not done or because the result is unavailable or the test is not feasible, e.g. in some forms of EPTB. There may be practical difficulties in repeating the biological specimen at the end of therapy.

Treatment Success: TB patients either cured or treatment completed are accounted in treatment success.

Failure: A TB patient whose biological specimen is positive by smear or culture at the end of treatment

Failure to Respond: A case of paediatric TB who fails to have a microbiological conversion to negative status or fails to respond clinically/ or deteriorates after four weeks of compliant intensive phase shall be deemed to have failed response provided alternative diagnoses/reasons for non-response have been ruled out

Lost to Follow Up: A TB patient for whom no treatment was interrupted for two consecutive months or more

Non-Evaluated: A TB patient for whom no treatment outcome is assigned. This includes the former "Transfer-out."

Treatment Regimen Changed: A TB patient who is on a first-line regimen and subsequently has been diagnosed with DR-TB and, therefore, switched to a drug-resistant TB regimen before being declared as failed.

Died: A patient who has died during the course of anti-TB treatment.

10.1.2. Treatment Outcomes for RR-/MDR-TB and XDR-TB Patients

Interim Outcome

Bacteriological Conversion: After bacteriological confirmation of TB, at least two consecutive cultures (applicable for DR-TB and DS-TB) or smears taken on different occasions at least seven days apart (applicable for DS-TB only) are found to be negative.

Bacteriological Reversion: At least two consecutive cultures (applicable for DR-TB and DS-TB) or smears (applicable for DS-TB only) taken on different occasions at least seven days apart are positive either after the initial conversion or for patients without bacteriological confirmation of TB.

- For defining treatment failed, bacteriological reversion is considered only when it occurs in the continuation phase.
- Time-to-culture conversion is calculated as the interval between the date of DR-TB treatment initiation and the first of these two negative consecutive cultures taken seven days apart (date of sputum specimens collected for culture should be used).

10.2. Final Outcomes

Treatment Failed: A patient whose treatment regimen needed to be terminated or permanently changed[8] to a new regimen option or treatment strategy.

Cured: A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy with evidence of bacteriological response[9] and no evidence of treatment failed.

Treatment Completed: A patient who completed treatment as recommended by the national policy whose outcome does not meet the definition for cure or treatment failed.

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[8] *Reasons for the change include:*

*a) No clinical or bacteriological response**

b) Adverse drug reactions (ADRs),

c) Evidence of additional drug resistance to medicines in the regimen.

[9] *Bacteriological response – bacteriological conversion with no reversion.*

Died: A patient who died[10] before starting or during the course of treatment.

Lost to Follow up: A patient who did not start treatment or whose treatment was interrupted for two consecutive months or more.

Not Evaluated: A patient for whom no treatment outcome was assigned[11].

The following must be noted:

- In case of change in regimen within the scope of guidelines for the purpose, from shorter to longer or vice-versa in the initial months before any definitive treatment outcome applies, the outcome of only the changed regimen needs to be reported. The patient needs to be moved out of the denominator of the previous regimen.
- Patients who are still on treatment due to frequent short interruptions (less than two consecutive months) due to the patient or provider requirements can be reported as not evaluated for an outcome not assigned at the time of reporting to NTEP. Still, the data can be cleaned and updated later when the outcome is available.

[10] *Patient died of any reason*

[11] *This includes cases "transferred out" to another treatment unit whose treatment outcome is unknown and excludes lost follow up.*

Chapter 11 PROGRAMME MANAGEMENT UNDER NTEP

11.1. Recording and Reporting:

The reporting system used for monitoring TB control is NIKSHAY – a case-based, web-based surveillance tool, developed indigenously. This digital repository of program data allows the program managers to make informed decisions on a real-time basis for better TB control. Nikshay is also the only recommended tool for the private sector to notify TB cases. Nikshay can be accessed via the web or conveniently through the mobile App for ease of notification.

Furthermore, Directory Services are incorporated in Nikshay for ease of communication and patient linkage. In addition to existing treatment adherence strategies, Information Communication Technology (ICT) enabled strategies that help support treatment adherence reporting are included.

PHI Level:

At the PHI Level, after diagnosis of a case of TB, the patient is registered in the TB notification register and notified in Nikshay on a real-time basis. Subsequently, the patient is initiated on treatment by starting a treatment card for the episode. Each patient record consists of patient enrolment, request for TB diagnostic test/s and updating results, filling up treatment card, drug dispensation, follow up, contact investigation, comorbidities and treatment outcomes. All modules should be updated promptly during the anti-TB treatment of the patient. PHI-wise patient registration status can be monitored at the TB Unit (TU) level by the Officer of TB Unit (Block Medical Officer) (MOTU) and the District TB Officer (DTO) at the district level. Private TB patient notification is to be mandatorily done in Nikshay. Facilities registered under Nikshay can either notify directly using the web portal or mobile App or report to the nodal officer, i.e. the DTO. The notifications received by the nodal officer are entered in Nikshay using the respective TU ID and password. At the PHI level, Public Health Action (PHA) is initiated by Senior Treatment Supervisor (STS) or Health Visitor, and details of the same, i.e. date of a home visit, list of household contacts, number of symptomatic contacts, chemoprophylaxis status, linkage to HIV counselling and testing, linkage to CDST services are entered. The programme recommends public health action to be undertaken, and details entered within two weeks of notification (date of diagnosis).

Dynamic Reports at the DTO and TU Level:

A variety of reports can be generated at all levels in Nikshay. The period of the reports currently available for generation is on a quarterly or monthly basis. The reports based on case notification, treatment initiation, outcome, UDST status of patients, DST report, etc., can be generated as per day - 1 (i.e. data recorded in Nikshay till the previous day).

The case-based entry at the PHI level for the TU forms the basis for generating all reports at the TU level. In case of missed or delayed Nikshay entry, or incomplete updating of the modules at the PHI level, the corresponding report does not reflect the actual performance of the PHI or the TU. It is, therefore, mandatory that all data be updated in respective modules on a real-time basis for accurate reporting.

Results of patients undergoing culture and drug susceptibility testing from a C&DST or Intermediate Reference Laboratory (IRL) or any accredited lab can be recorded in Nikshay by the respective laboratories, and the results are available without delay for treatment decision making at the DTO/TU/PHI levels. Details of patients requiring admission at the drug-resistant TB centre are also available for further action. Lastly, patient reports for Direct Beneficiary Transfer (DBT), i.e. DBT Benefit report and DBT beneficiary reports are also available in Nikshay, which have the real-time status of patients' payment status.

State Level:

All the reports that are available at the TU and PHI are also generated at the State level. The reports of all districts are monitored at the state level based on the monitoring indicators designed for the program and scoring of districts against the same. State reviews the program and provides feedback on areas for improvement – e.g. case finding, case holding, treatment outcomes, DST patterns, DBT etc. The district-specific action plan is formulated to improve performance and address gaps in program management. The reports from the districts can be reviewed for any given period from the state, as this is a real-time program monitoring tool.

National Level:

Scoring of the States is done on a quarterly tenure based on the Monitoring Indicators developed by the program. Reports from all states are reviewed at CTD, and timely feedback is provided to the states for undertaking corrective action. The input to States is shared as a monthly report which is auto-generated from Nikshay. Feedback on specific thematic areas is shared in the mail on a need basis and during review meetings.

11.2. Supervision and Monitoring:

In addition to routine supervisory activities as listed under NTEP, the medical officer should undertake the following actions concerning paediatric TB patients:

Correct Diagnosis and Treatment Initiation:

The Medical Officer should elicit detailed history and review all relevant records to ensure that an accurate diagnosis has been made and appropriate treatment initiated. Where required, a specialist opinion may be taken. Children with EPTB may need other drugs, and a follow up with the specialist. A shared care model should be followed. While a monthly specialist visits in IP and bimonthly in the CP may be sufficient for most cases, any persistent symptom, a sign of non-response or complication, or a serious adverse event should prompt a visit to the paediatrician for review.

Completeness of Treatment Card:

The medical officer should ensure that all details of the treatment card are duly filled and simultaneously entered in Nikshay. Address and phone numbers of patient, contact person, treatment supporter should be entered in relevant records. Updating of patients' weight, details of follow up visits, retrieval actions done in case of missed doses are also to be supervised.

Moreover, efforts taken by the STS and Health visitor in tracing the index case and contact screening should be closely supervised and documented in the remarks column of the treatment card. Supervisory home visits should be undertaken frequently to monitor adherence, document adverse drug reactions and growth monitoring. Lastly, public health actions initiated for privately notified paediatric patients should prioritise all efforts supervised to ensure a successful treatment outcome.

Preventive Therapy:

Medical officers should monitor all children started on IPT and verify correct dosage and timely refills.

11.3. Advocacy Communication and Social Mobilization

Advocacy, Communication and Social mobilisation activities in paediatric TB should be carried out at individual and community levels. Activities should create awareness among people about childhood TB (signs and symptoms) diagnosis and treatment to increase accessibility and utilisation of services. It should be remembered that ACSM activities are not a substitute for TB control activities. These are supportive services to enhance the quality of services, widen the reach of activities, facilitate the implementation of TB care services, mobilise the civil society, and actively engage panchayat raj institutions in the care and control of TB among children.

Inter sector Coordination:

To address the gaps in Paediatric TB coverage, NTEP collaborated with Child Health and Adolescent health programmes of the Ministry of Health and Family Welfare, the Rashtriya Bal Swasthya Karyakram (RBSK), and Rashtriya Kishor Swasthya Karyakram (RKSK) and developed a framework to address tuberculosis among children and adolescents. Its adoption will help increase paediatric case detection.

Indian Academy of Paediatrics (IAP) has also been engaged to manage paediatric TB patients accessing the private sector through involvement in policy divisions and support in the capacity building of all its members.

Death Audit

The Medical Officer should conduct an in-depth audit of all the deaths occurring amongst the TB patients irrespective of initiation of treatment. Similarly, DTO should conduct a death review of all MDR-TB patients who died. This would be beneficial in understanding the cause leading to the deaths and guide the programme in taking appropriate action to prevent them.

Chapter 12 OPERATIONAL MANAGEMENT OF PAEDIATRIC TB PATIENTS SEEKING CARE IN THE PRIVATE SECTOR

This chapter aims to outline the sequence of flow of paediatric TB patients seeking care in the private sector from notification to successful treatment completion; the mechanism of establishing linkages between the public and private sectors; and to briefly introduce the concept of purchasing services.

The programme recognizes that although free quality diagnostic, treatment, and patient support services are available in the public health sector, a significant number of patients seek health services from the large unorganized private health sector. Under NTEP, 28-30% of the total notification is contributed by the private sector. For paediatric TB, this proportionate share is higher than 40%. Consequently, reaching out to these patients is essential, primarily to deliver essential public health services to prevent the spread of disease and the emergence of drug resistance, support them in their treatment, and address comorbidities that adversely affect treatment outcomes.

A paediatric TB patient seeking care in the private sector may come into the programme's purview through notification or referral. Both these scenarios and the steps to be followed in their operational management are listed below:

Scenario 1- Patient Notified from the Private Sector:

It is assumed that a Paediatric TB patient who has been notified on Nikshay from the private sector is seeking care from a health facility already engaged by the programme. The NTEP or public health department could establish this engagement directly or through a Patient-Provider Support Agency (PPSA) or other Non-Government Organization (NGO) or Partner agency. The local public health staff and NTEP staff are responsible for reaching out to the private provider (PP) directly or through a PPSA and ensuring that the TB Care cascade is followed for the patient as per NTEP guidelines or Standards of TB Care.

Scenario 2- Paediatric-TB Patient Referred for Treatment from the Private Sector:

With microbiological confirmation in the private sector-

At times, Paediatric TB patients diagnosed in the private sector will wish to avail services from the public sector (NTEP). NTEP strongly recommends microbiological confirmation of all patients before initiation of treatment and discourages any empirical treatment. For such patients, results from private laboratories will be considered acceptable if they are from an NTEP certified laboratory. For patients who do not have consequences in accordance with the above, microbiological confirmation would be offered under NTEP.

With the clinical confirmation of TB in the private sector-

In presumptive or clinically diagnosed TB patients from the private sector, all attempts should be made by public sector facilities to confirm the diagnosis of TB microbiologically; however, if no microbiological confirmation is possible due to lack of specimen, as is seen often in paediatric TB- the decision to treat for TB based on clinical symptoms and chest X-Ray findings may be taken by the treating clinician. The term probable MDR-TB in children would be applied to children wherein DR-TB is clinically suspected strongly. Still, bacteriologic confirmation is not technically feasible/negative, and the Nodal DR-TB committee decides on diagnosis and initiation of treatment. The criteria for diagnosis of Probable MDR-TB is detailed in Chapter 5 of these guidelines.

With treatment initiated in the private sector-

When patients may have consumed some duration of anti-TB drugs, such prior anti-TB treatment is not likely to be uniformly reliable as far as the quality or quantity and the duration of drugs consumed. Given that uncertainty, the basic principle is that duration of the TB regimen under NTEP need not be reduced. However, where prior treatment is well-documented, adequate and effective, the treating clinician can adjust the duration after detailed patient review, approval and documentation of decisions taken.

If such a referral from the private sector has taken place without notification on Nikshay, the patient would be freshly notified after due confirmation of the diagnostic results. In such situations, the local public health staff such as STS, TB Health Visitor (TBHV), Public-Private Mix (PPM) coordinator at the district level, and PPSA (where operational) should reach out to the private health facility to establish linkages with the programme.

In both scenarios (notification/referral), if the patient's family prefers to continue clinical services from the private provider, the health staff/NTEP staff should support it by coordinating with the treating clinician(s) and hospital management. All paediatric patients are also eligible for receiving public health action (detailed later), irrespective of where they seek TB care.

12.1. Services for Paediatric TB Patients in the Private Sector:

As detailed in the previous chapters, the TB/DR-TB care cascade for paediatric TB patients is to be ensured for every paediatric patient notified or referred from the private sector. This includes DST (first-line or second-line drug resistance testing as per NTEP guidelines), counselling, Pre-treatment evaluation, treatment initiation and adherence support, follow up clinical assessment, bacteriological, radiological and biochemical testing at prescribed intervals, interrupter retrieval, active drug safety monitoring and management, comorbidity management, Nikshay Poshan Yojana (NPY), contact tracing and TB preventive therapy for contacts as applicable, reporting of treatment outcomes and post-treatment follow up.

To avail services under NTEP, an efficient specimen collection and transport system should be established from the private/other providers to the nearby TB Detection Centre (TDC) or NTEP certified NAAT/DST laboratory.

A strong and sustainable partnership between the programme and providers is necessary to establish linkages to ensure the availability of the services mentioned above for any paediatric TB patient in the private sector. These services may be extended through:

Local Public Health Facilities:

TB services for paediatric TB patients seeking care in the private/other sectors can be accessed from NTEP at all levels of the health system- from the field level care offered through the network of Health & Wellness Centres (HWCs) under Ayushman Bharat to tertiary care available in Medical Colleges, Nodal DR-TB Centres, or Centres of Excellence. It would be the responsibility of the DTOs to reach out to all private providers of the respective district and make them aware of the free of cost services including drugs, diagnostics and patient support available through the public sector. Although the decision to avail of these services depends on the patient's willingness and the provider; the availability of these services should always be explained to the private providers. Similarly, patients should be aware of free services through private providers and communities (like TB champions). PPSAs should support the DTO (if present), PPM coordinators, STS, TB-HV in this task. Lastly, private practitioners should be made aware of the newer protocols in the management of paediatric TB.

Purchasing Services from the Private Sector:

One of the options for such linkages available within the programme is the Guidance Document on Partnerships (2019). The Guidance provides purchasing services for diagnosis, specimen collection, transportation, laboratory services for C-DST of first and second-line drugs.
To increase paediatric TB services' capacity and utilize experts and health institutes in expanding access, the State should consider engaging private health institutes or providers. These can also be purchased for public sector patients if needed explicitly in any particular geography.

Moreover, any component in the paediatric TB care cascade or a mix of different elements (such as specimen collection, specimen transportation, drug transportation) can be "bundled" together or included as an activity for PPSAs. States and Districts may conduct a 'needs assessment' to find services that require focus in their respective geographies. Particularly for the private sector, additional efforts for engagement may require more targeted advocacy and communication material for the providers and the patients' families. Likewise, other channels for specimen management, X-rays, drug supply may be established for paediatric TB in the private sector. States may assess their needs and purchase a whole package of services as a bundle or individual activities in the range of services needed for paediatric TB management. A summary of the various partnership options which can be adopted are listed below:

PARTNERSHIP OPTION	SERVICES
PATIENT PROVIDER SUPPORT AGENCY (PPSA)	1. Private provider empanelment and engagement 2. Linkages for specimen transportation and diagnostics 3. Patient management (public health action, counselling, adherence support) Logistics of Anti-TB drugs The PPSA is an example of a "service bundle" that covers a whole range of activities for end-to-end management of private sector
PUBLIC HEALTH ACTION	1. Counselling and adherence management 2. Contact tracing and chemoprophylaxis 3. HIV counselling, testing and treatment linkage 4. Drug susceptibility testing (DST) and linkage for DR-TB services 5. Blood sugar testing and linkages for diabetic care 6. Linkages for Nikshay Poshan Yojana
SPECIMEN MANAGEMENT	1. Collection of sputum samples 2. Collection of respiratory (excluding sputum) and EP specimen 3. Transportation of specimen
DIAGNOSTICS	1. X-ray centres 2. Smear Microscopy (Ziehl–Neelsen/Fluorescence Microscopy)/Molecular diagnostics 3. Culture (stand-alone) / Line Probe Assay / Culture and Drug Susceptibility Testing 4. Pre-treatment and follow-up investigation 5. Latent TB infection (LTBI) test
TREATMENT SERVICES	1. TB management centre 2. DR-TB treatment centre (outdoor) 3. DR-TB treatment centre (indoor) 4. Specialist consultation for DR-TB patients
DRUG ACCESS AND DELIVERY SERVICES	1. Drug supply chain management 2. Improving access to anti-TB drugs for TB patients notified by the private sector
ACTIVE TB CASE FINDING AND TB PREVENTION	1. Active TB case finding 2. 2. TB prevention package for vulnerability mapping and LTBI management

ADVOCACY, COMMUNICATION AND COMMUNITY EMPOWERMENT	1. Advocacy 2. Communication 3. Community Empowerment

Table 19. Partnership Options

The details of these partnership options and mechanisms for contracting private service providers are available in the Guidance Document on Partnerships 2019. If included in PPSAs or through other partnership options, States/Districts must budget it as a separate activity in their Memorandum of Understanding (MoUs) or agreements.

12.2. Augmentation of Paediatric TB services through a Hub & Spoke Model:

As the services for Paediatric TB are specialized, there may be cost efficiency in setting up a hub and spoke model where smaller 'spoke' health facilities are suitably linked through a referral network to a central 'Hub'. State/District NTEP may identify a few health facilities to function as hubs or referral centres and organize referral linkages from identified spokes to the hub for management of paediatric TB as per guidelines. This selected hub may be a public sector health facility or a private-sector health facility under an MoU with NTEP (as mentioned above).

FUNCTIONS OF HUB	FUNCTIONS OF SPOKES
1. Specimen collection and diagnosis as per the latest recommendations 2. Manage and treat paediatric TB patients as per guidelines and standards 3. Follow up examination 4. Manage ADR 5. Maintain treatment register 6. Report in NIKSHAY	1. Specimen collection and diagnosis as per the latest recommendations, if possible. 2. Referral to Hub for specimen collection and diagnosis/ Chest X-Ray. 3. Notify every TB patient in Nikshay 4. Maintain referral register 5. Facilitate follow-up examination of patients 6. Counselling for adherence support 7. Report in NIKSHAY

Table 20. Functions of Hub and Spokes Models

DTO should make efforts to make the services from the hub to be free of cost. A person (hub agent/TB Mitra) may be supported to coordinate TB patients and engagement with NTEP. Cost of such personnel support to be incorporated within the package of engagement that includes the fee for consultation, indoor and investigations.

12.3. Enablers and Incentives:

Incentives Available Under NTEP			
	Particulars	**Amount**	**Eligibility**
1.	Informant incentive for referring presumptive TB patients to public facility	INR 500 per patient detected with TB on referral to a government health facility by said informant	Available for confirmed TB patient
2.	Private Provider Incentive	INR 500 per TB patient notified and INR 500 on reporting treatment outcome per patient	Private Providers (Private Practitioner, Hospital, Laboratory, and Chemist) who notify/inform (refer) TB patients to NTEP on Nikshay and declare the outcome.
3.	Treatment supporter incentive	INR 1000 per DSTB patient & Patients on H-Monopoly and INR 5000 per DRTB patient for 'Treatment Supporter' on completion of treatment	On the update of Outcome for Drug-sensitive TB patients INR 2,000 on completion of Intensive phase (IP) and INR 3,000 on completion of continuation phase (CP) of treatment for Drug-Resistant TB patients
4.	Transportation support for patients from tribal area	INR 750 as one- time support	Upon notification for TB patient notified from notified Tribal areas
5.	Transportation support for DRTB patients	As per rates defined by State Government	All DR-TB patients
6.	Injection prick charges for DRTB patients	INR 25 per injection	For persons who are not supported by government for providing injection to DRTB patient

7.	Nikshay Poshan Yojana - To provide nutritional support to TB patients at the time of notification and subsequently during the course of treatment	INR 500 for a treatment month paid in instalments of up to INR 1000 as an advance	All unique TB patients notified on or after 1st April 2018 (including all existing TB patients under treatment for at least one month from this date)

Table 21. Incentives Available Under NTEP

12.4. Sensitization and Capacity Building of Private Providers:

Regular sensitization and training should be conducted for all private providers on paediatric TB diagnosis, treatment and patient support. Private providers may also be given access to e-modules in Swasthya e-Gurukul, which provide an understanding of treatment and management of paediatric TB patients. Channels for communication between the private providers and specialists and NTEP should be established for teleconsultation like difficult to treat clinics to aid in making clinical decisions that are in line with Programme Guidelines. A list of contact details of local public health staff/officers and PPSA (where present) should be made available to all private providers. Use of Nikshay Sampark (Toll-free number: 1800-11-6666) for feedback and concerns should also be promoted from private providers and patients.

Key Points to Remember:

- A paediatric TB patient notified in the private sector must receive all services and benefits available for public sector patients. Access to testing, public health action, patient support enablers and drugs must be ensured for all patients in the private sector.
- Linkages must be well established between the private sector health facility and the local public health authorities at the TU/District level to ensure a smooth flow of information and services for the patient's benefit.
- Depending on the context and need, eligible services may be procured from private sector service providers to ensure minimal out of pocket expenditure to the patient.
- Access to Nikshay ID, Recording and Reporting (R&R) formats, IEC Material, drugs and incentives for private providers must be ensured.
- The local public health authorities should establish linkages with the private sector- a coordinated effort of all State/District PPM Coordinators, STS, TB-HV, and staff from PPSA (if present) is needed.
- Management of specific conditions such as DR-TB may be accessed from their respective NTEP Guidelines available on https://tbcindia.gov.in/

Box 12. Key Points on Operational Management of Paediatric TB Patients Seeking Care in the Private Sector

Chapter 13 OPERATIONAL Involvement and Collaboration with of Other Sectors/Ministries

13.1. Involvement of Indian Academy of Paediatrics

Central TB Division, MoHFW has signed a Memorandum of understanding with the Indian Academy of Paediatrics (IAP) on 10th October 2019 to effectively engage with the paediatricians to notify TB cases and train 18,000 Pediatricians and 2000 medical officers under NTEP on Standards of TB Care in India through 300 district level CMEs and motivate them to be involved under the program through offering access to diagnostics and drugs under the programme. Communication material for Pediatricians has been developed and is being used in training. The funds for the entire activity are provided by CTD to IAP National level and therein to the IAP zonal level.

13.2. Medical Colleges as Paediatric Centre of Excellence(pCOE-TB)

Purpose and Scope:

To set up a network of pediatric Centres of Excellence for TB (pCoE-TB) at the National and Regional level across the country for supporting the National TB Elimination Program in TB control activities in the Paediatric age group.

Objectives:

The Paediatric Centres of Excellence would serve the following broad objectives:

a. Serve as Model centres for TB care, support and treatment
b. Increase capacity, knowledge, skills, and abilities for Paediatric TB prevention and control through communication, education, and training activities targeting all public and private sector paediatricians and providers of paediatric care s in the operational states/regions.
c. Improve sustainable evidence-based TB clinical practices and patient care networking and provision of expert medical consultation
d. Monitoring the clinical and programmatic outcomes of Paediatric TB patients.
e. Build capacity of the health system to carry out operational research in TB diagnosis, treatment and prevention aspects

Responsibilities and Support provided by NTEP - National Implementer of the programme:

1. The CoE mechanism would be directly under the observation of the Central TB Division, with monitoring components integrated with existing review mechanisms at the National, Regional, State level, including the Taskforce mechanism.
2. Representation from Regional pCoE would be ensured in the National Technical Expert Group (NTEG) on Paediatric TB
3. The faculty in the Centre of Excellence would be prioritized for participation in training activities, especially on updates and new interventions
4. Participation would be ensured in the review meetings across various levels under the programme
5. Support would be provided to collaborate with NTEP partners and research agencies for developing and implementing research projects
6. pCoE-TB serves as a nodal hub centre and is connected via the video-conferencing ECHO platform to facilitate knowledge exchange within the network. The requisite software would be available free of cost to CoE, as per MoU with ECHO India, to host the VC session. The referral sites (spokes) may join the session using Tablets provided by NTEP or mobile phones.
7. National and Regional pCoE would be nominated by the Central TB Division.

Responsibilities of facility established as Paediatric Centre of Excellence for TB (pCoE TB)

A. The Paediatric CoE would comply with the following requirements:

1. The Paediatrician/medical officer and health worker are trained in Updated NTEP guidelines.
2. Provide comprehensive diagnostic (including pre-treatment evaluation), and treatment services are per NTEP programmatic guidelines.
3. Provide comprehensive paediatric TB related services, including advanced case management and management of complications.
4. Serve as the nodal centre to provide training and mentorship to health care workers, including doctors, nurses, counsellors and pharmacists from referral health facilities. This includes organizing initial training, re-training and update training.
5. Conduct field-based training to paediatric care providers in the catchment geographies where required.

6. Conduct mentorship visits to paediatric health facilities where required.
7. Conduct onsite sensitization to all staff of the paediatric CoE to promote and strengthen the pCoE functioning.
8. Enable access to catering population through multiple modes of conveyance.
9. Undertake research projects in collaboration with NTEP and its partners.

B. pCoE would manage Communities of Practice, thematic e-group of paediatricians and other paediatric service providers from both public and private sector for fast-tracking the dissemination of technical and research updates and providing ongoing technical support to those in need.

1. Establish an ECHO HUB site and conduct ongoing training and distance learning sessions for paediatric providers from the public and private sector.
2. Serve the broad objectives of a pCoE mentioned under section V of this document.
3. pCoE activities may be budgeted in the Annual PIP, based on the training load, additional training for newer initiatives and revision of guidelines. The equipment requirements for the ECHO hub site may be proposed as one time in the Annual PIP as per the norms shared, and the maintenance cost may be added for the second year onwards.
4. The norms for TA/DA, Honorarium, Refreshment, Course Material, Vehicle hire, Accommodation, Venue Hiring Incidental expenses should be as per State / NHM norms.
5. Funds for travel to various training/meetings may be borne by institute or organization, and if not available, State funds under NTEP may be used for the above purposes as per State / NHM norms.

C. The pCoE is expected to achieve the following outcomes:

a. Increased availability of trained resources for the management of paediatric TB in the country through periodic training of paediatricians by CoEs.
b. Improved clinical management of paediatric TB by serving as a knowledge centre and providing ongoing hands-on mentorship and online technical support.
c. Generate evidence on paediatric TB clinical and programmatic needs.

13.3. Ministry of Child Health

The National Tuberculosis Elimination Programme and the two significant national programmes working with children in the country, namely, Rashtriya Bal Suraksha Karyakram (RBSK) and Rashtriya Kishore Suraksha Karyakram (RKSK), have come together and developed an Inter-sectoral collaboration framework to accelerate this drive. These two programmes will work with the NTEP and support screening and preventive services through existing outreach activities. They will ensure every child suspected of TB is referred to the nearest healthcare centre for timely diagnosis and management of tuberculosis.

Goal:

To reduce morbidity and mortality associated with TB in children and adolescent population through

- Prevention
- Early detection
- Prompt and complete management of TB

Strategy:

- Enhancing community awareness about TB in children and adolescent population.
- Generating demand and promoting disease prevention and early health-seeking behaviour.
- Increasing the early detection of TB symptoms in children and further tracking for timely TB diagnosis and treatment initiation.

Collaboration with Child Health Nutrition Division (CNH):

Malnutrition and TB form a vicious cycle, where malnutrition predisposes a child to acquire TB, while TB could exacerbate undernutrition. In high TB burden countries, 2-24% of acutely malnourished children have been diagnosed with TB. As undernutrition is one of the significant risk factors for TB infection and compounded by low immunity in children under the five-year age group, children who are sick and have Severe Acute Malnutrition are more predisposed to develop primary TB disease. Furthermore, children with SAM and TB are 40% more likely to die than severely malnourished children without active TB disease. Following are the suggested interventions for collaboration between NTEP and NRC (Nutrition Rehabilitation Centres).

Suggested NTEP Collaboration Points

a. Screening - Screening for presumptive TB by eliciting verbal case-history and through examination.

b. Sample Collection & Transportation - As children under five years of age are usually unable to produce sputum, the sample from a presumptive pulmonary TB child may be collected by the paediatrician if available at the NRC - either via Gastric Aspirate / Lavage or Induced Sputum. The sample needs to be collected in a Falcon Tube in normal saline (to be provided by NTEP). Formalin should NOT be used as a preservative. The collected sample may be sent by the concerned NRC staff to the nearest linked NTEP diagnostic facility (this may be co-located with the NRC or to a linked facility identified and mapped by both the programs). Alternatively, the linked NTEP facility may also be informed to collect the sample from the NRC.

c. NTEP Referral - After identifying the presumptive TB case, the child needs to be linked to a

NTEP facility for further management. This may be either co-located with the NRC or can be a nearby health facility identified by the NTEP.

d. Recording and Reporting - All collaborative activities need to be documented using standard records and reports and at prescribed intervals.

13.4. Other Partners

SAATHII

Catalysing Pediatric TB Innovations (CaP TB) was implemented by Solidarity and Action Against The HIV Infection in India (SAATHII), funded by Unitaid/ Elizabeth Glaser Paediatric AIDS Foundation (EGPAF) from October 2017 – September 2021 with the private sector paediatric providers, children and adolescents (0-18 years) with TB. The goal of this project was a reduction in mortality and morbidity due to paediatric TB by generating evidence on the impact of intensified case finding (ICF) on presumptive TB and TB identification and engagement of paediatricians from the private sector; strengthening the capacity of public health staff on paediatric TB diagnosis and management in Ahmednagar, Maharashtra, India. The geographies covered in this project were 15 districts across three states; Maharashtra, Andhra Pradesh, and Telangana, with the expected impact of increased paediatric TB case detection, treatment success, and eligible children initiated on TPT.

14. ANNEXURES

Annexure 1
Tuberculin Skin test (TST)

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.** 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

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

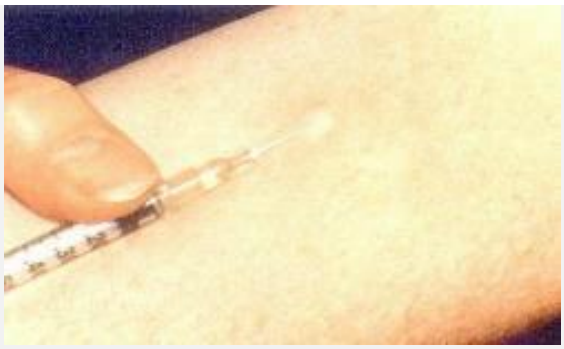
- Expiry date and Tuberculin strength (2 TU of PPD RT23) checked
- A single-dose syringe with a short (1/4 to 1/2 inches) 27-gauge needle with a short bevel loaded with 0.1 ml tuberculin

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
- PPD injected gently raising an Intra-dermal wheal of at least 6 mm diameter
- If not, repeated 2 inches away from the original site
- Discard the used syringe in the sharp container (as per BMW guidelines)



Box 13. Key Points The technique of administration of tuberculin and reading of the test

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 colour.

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

Test reading: Induration should be measured and not 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 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. The width of reaction (induration) in the horizontal plane is noted for interpretation.

Mantoux's test or PPD skin test is considered positive if the induration is 10 mm or more, In HIV coinfected, 5mm may be taken as the cut off.

The cut-off 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 Fallacy

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

- 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

Causes of false positive

- Incorrect ***technique*** of Interpretation
- ***BCG*** vaccination
- Infection with ***mycobacterium other than TB***

Box 14. Interpretation Fallacy

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 2
Method to collect Gastric Aspirate (GA)

Steps for GA sample collection procedure:

1. Explain the procedure and take consent from the parent or guardian
2. Patient should be fasting overnight or at least for 4-6 hours prior to collection procedure. In an admitted child it may be done early in the morning, while the child is still asleep and in bed.
3. Place the patient in a supine position and restrain using the long-folded sheets.
4. The Feeding / Ryle's tube needs to be placed in the body of stomach through the nose. The required length of the tube to be inserted can be ascertained by measuring the distance from tip of the nose to the tragus and then from the tragus to the midpoint between xiphisternum and umbilicus. One could make this measurement directly using the tube or else using a measuring tape.
5. Apply lubricant jelly to the tube
6. Gently insert the tube through the nose in the direction perpendicular to the face up to the measured length. This can often be assisted by asking the patient to swallow.
7. Fix it to the nose with an adhesive tape.
8. It is important to confirm that the tube is correctly positioned in the stomach. This can be ascertained by pushing some air with a syringe into the tube and simultaneously auscultating for the gush of air over the epigastrium with a stethoscope. In case, the patient starts choking or coughing while inserting the tube then the tube should be withdrawn and re-inserted after the patient has settled.
9. Once the Ryle tube has been inserted into the stomach, its position can be checked by hearing a gush of air over the epigastrium. One can also aspirate the stomach contents to confirm the position.
10. Gently aspirate from the tube keeping the patient in the supine position.
11. If there is no aspirate or the quantity is inadequate, try re-aspiration after shifting the patient in the left and right lateral positions.
12. If one still does not get adequate specimen in both supine as well as lateral positions, further aspiration can be retried by shifting the tube a little in or out, in an effort to hit the stomach contents. The repeat aspiration should be done while rotating the patient through supine and lateral positions.
13. In case, direct aspiration fails to provide adequate specimen, one should instil about 10 ml normal saline through the tube slowly. Align it to gravitate on its own.
14. After instilling, re-aspirate rotating the patient through supine as well as in left and right lateral positions.
15. Repeat these steps till gastric aspirate is obtained

16. Collect the aspirate in a sterile container. A specimen is considered adequate if contains about 10-15 ml of stomach contents.
17. After collection of gastric aspirate, gently remove the tube by closing its cap or pinching the tube

Video for the steps for GA sample collection procedure can be downloaded and viewed at the TBC India website resources; the link to the video is: https://tbcindia.gov.in/index1.php?lang=1&level=2&sublinkid=5305&lid=3415

Annexure 3
Method to collect Induced Sputum (IS)

Steps for induced sputum sample collection procedure:

1. Patient should be fasting for 2-3 hours prior to collection procedure.
2. Explain the procedure and take consent from the parent or guardian.
3. Procedure should be performed in a well-ventilated room having an exhaust fan while wearing a N95 facemask
4. Baseline values of respiratory rate, pulse rate, chest retractions, wheeze and oxygen saturation should be taken prior to the procedure
5. Priming with Salbutamol can either be done through Metered Dose Inhaler (i.e. MDI) or nebulization using either respiratory solution or respule. MDI has an advantage that it takes less time and is as effective as nebulization. However, nebulization facility is essential to give 3% hypertonic saline.
    a. MDI: Salbutamol is administered by sequentially giving 2 puffs, i.e. 100 micrograms through MDI with a spacer. This prevents bronchospasm from 3% hypertonic saline nebulization in children predisposed to it.
    b. Nebulization using respiratory solution or respule: The Neb respirator solution contains 5 mg of Salbutamol per ml. The dosage for administration is 0.15 mg/kg. Taking age in to consideration, the administered dosage varies. For neb respule, use equivalent doses as respirator solution. Fill up the required amount of salbutamol from respiratory solution or respule. Load the drug formulation to the nebulization chamber. Add saline if required to ensure that volume of formulation in the chamber is above its minimal fill volume.
6. Nebulize with 5 ml of 3% sterile hypertonic saline. Use a sterile commercially available preparation. Nebulization can be done through a jet nebulizer attached to pressurized oxygen or air supply, at the lowest flow rate needed to produce adequate mist which usually is 5 to 7 L per min.
7. While the child is being nebulized, give a container to the child to collect any expectorated sputum.
8. Child may start expectorating while being nebulized with 3% saline. If the sample is adequate, then the procedure may be wrapped here, and expectoration may be sent to lab for further processing.
9. Few children will only produce or bring up saliva or no expectoration on their own after 3% hypertonic saline nebulization. In such situations, one can loosen up secretions and assist child in secreting sputum by chest percussion. The purpose of chest percussion is to bring the secretions from the peripheral to central airways, from where the child can cough out the secretions.
10. Palm of the hands while doing percussion should be made into a cup shape formed by the fingers and the thumb, instead of flat open hand. This avoids hurting the child. For younger

children, it is ideal to percuss with fingers. Movement while doing percussion should be at wrist and not elbow or shoulder. For percussion, we must cover all areas of chest in sitting, supine and prone positions.

11. If there is sputum production and child can expectorate, collect this sputum in sterile container
12. If still a child is unable to expectorate or if it is a young child who needs assistance to collect secretions, then sputum can be collected by suction through nasopharynx or oropharynx.
13. Use sterile mucus extractor or suction trap with the other end of the extractor connected to gentle suction of around 100 cm of water. The catheter is inserted through the nose.
14. The length of tube to be inserted is measured from side of the nose to the angle of the mandible.
15. Apply lubricant jelly or wet the tube.
16. The catheter is gently inserted into the nose in a direction perpendicular to the face.
17. Release suction. As the catheter touches the posterior pharyngeal wall, it can provoke cough. The loosened secretions are brought up with the cough and suction will facilitate its collection in mucus extractor or suction trap.
18. In this child, as you can see respiratory secretions have been collected. This should be immediately transported to GeneXpert lab
19. Monitor for 30 minutes after the procedure for respiratory complaints like respiratory rate, pulse rate, chest retractions, wheeze etc.
20. Fresh sterile disposable tubing and chamber for nebulization should be used for each patient.

Video for the steps for IS sample collection procedure can be downloaded and viewed at the TBC India website resources; the link to the video is: https://tbcindia.gov.in/index1.php?lang=1&level=2&sublinkid=5305&lid=3415

Annexure 4
Steps for Needle Aspiration of the Lymph Node and Other Superficial Swellings

1. Explain the procedure and take consent from the parent or guardian
2. Place the patient in a supine position and restrain using the long-folded sheets.
3. Disinfect the skin at the planned needle puncture site
4. Firstly, with alcohol (70%) followed by povidone-iodine and again with alcohol (70%).
5. Between each application, let the area dry.
6. The swelling or lymph node should be immobilized in between the fingers of one hand.
7. Pass the needle through the skin, avoiding any superficial veins
8. Direct the needle towards the centre of the target.
9. Precautions must be taken to ensure that the needle tip is not pointing towards the operator's fingers immobilizing the lymph node or deep structures below the node.
10. Once in the target, the needle tip is moved within the target, while applying suction using 10 or 20 ml syringe.
11. Prior to withdrawal of the needle from the swelling, negative pressure must be released.
12. Remove the needle from the swelling by pulling straight out so as not to lacerate the skin.
13. Remove as much aspirate as possible from the swelling. Aspirate may be taken from multiple swellings and pooled before sending to laboratory for bacteriological confirmation.
14. At the end of the procedure, dress the site after applying antiseptic
15. Send the aspirated collection to laboratory for further processing.
16. If the aspirate is too small for transferring to container, then one may collect the material after aspirating and rinsing the syringe using minimal sterile normal saline. Avoid excess dilution with saline as it can lead to false negative result.

Annexure- 5

Sequence of using replacement drugs to modify the longer oral M/XDR-TB regimen

Sr. No	Drugs to be replaced	No. of drugs to include from			Final Regimen after replacement
		Group A (3 drugs)	Group B (2 drugs)	Group C (7 drugs)	
1	**None#**	3	2	-	6-8 Lfx, Bdq, Lzd, Cfz, Cs / 12 Lfx, Lzd, Cfz, Cs
2	**1 group A drug@**	2	2	1	**No FQ,** then 6-8 Bdq, Lzd, Cfz, Cs, Dlm / 12 Lzd, Cfz, Cs **No Bdq,** then 6-8 Lfx*, Lzd, Cfz, Cs, Dlm / 12 Lfx*, Lzd, Cfz **No Lzd,** then 6-8 Lfx*, Bdq, Cfz, Cs, Dlm / 12 Lfx* Cfz, Cs
3	**1 group B drug**	3	1	1	**No Cfz,** then 6-8 Lfx* BdqLzd Cs Dlm / 12 Lfx* Lzd, Cs **No Cs,** then 6-8 Lfx* BdqLzdCfzDlm / 12 Lfx* Lzd, Cfz
4	**1 group A drug@& 1 group B drug**	2	1	2	**No FQ & Cfz** then 6-8 Bdq, Lzd, Cs, Dlm, Am# / 12 Lzd, Cs, Z#, Eto# **No FQ & Cs** then 6-8 Bdq, Lzd, Cfz, Dlm, Am# / 12 Lzd, Cfz, Z#, Eto# **No Bdq & Cfz** then 6-8 Lfx* Lzd, Cs, Dlm, Am# / 12 Lfx* Lzd, Cs **No Bdq & Cs** then 6-8 Lfx* Lzd, Cfz, Dlm, Am# / 12 Lfx* Lzd, Cfz **No Lzd & Cfz** then 6-8 Lfx* Bdq, Cs, Dlm, Am# / 12 Lfx*, Cs, Z#, Eto# **No Lzd & Cs** then 6-8 Lfx* Bdq, Cfz, Dlm, Am# / 12 Lfx*, Cfz, Z#, Eto#

5	**2 group A drugs@**	1	2	2	**No FQ & Bdq** then 6-8 Lzd, Cfz, Cs, Dlm, Am# / 12 Lzd, Cfz, Cs, Z# **No FQ & Lzd** then 6-8 Bdq, Cfz, Cs, Dlm, Am# / 12 Cfz, Cs, Z#, Eto# **No Bdq & Lzd** then 6-8 Lfx*, Cfz, Cs, Dlm, Am# / 12 Lfx*, Cfz, Cs, Z#
6	**2 group B drugs**	3	0	2	**No Cfz & Cs** then 6-8 Lfx* Bdq, Lzd, Dlm, Am# / 12 Lfx*, Lzd, Z#, Eto#
7	**3 or more from group A drugs@& group B drugs**	Use the remaining drugs		3 or more	Remaining drugs from Group A and B plus 3-5 drugs from Group C using the conditions/sequence# below to make a regime with at least 5-6 drugs known to be effective. If Bdq and Dlm can be used, their combined use in the regimen with at least 4 -5 drugs or its extended use beyond 6 months till clinical and bacteriological conversion is achieved. If Bdq and Lzd can be used, explore the possibility of using BPaL regimen under prevailing ethical conditions.

Table 22. Replacement drugs to modify the longer oral M/XDR-TB regimen

No replacement required if any one drug is dropped in the last 12 months of treatment.

@ FQs would be counted together as one drug of group A if neither Lfx nor Mfx(h) can be used.

* if Lfx can't be used, use Mfx(h) if SL LPA pattern suggests and continue if Mfx(1.0) sensitive on LC-DST.# if sensitive on LPA or LC-DST. inhA mutation would indicate Eto resistance. If resistance detected, then the drugs to be used in the order of Dlm, Am#, Z#, Eto#, PAS, E and as a final resort Imp/Cls or Mpm in combination with Amoxiclav. Dlm & Am may not be introduced after initial 8 months of treatment and during this later phase the replacement sequence would be Z#, Eto#, PAS, E.

Annexure- 6
Shorter Injectable Containing Regimen

(4-6) Mfx^{h}, Km/Am, Eto, Cfz, Z, H^{h}, E	(5) Mfx^{h}, Cfz, Z, E

A. Exclusion Criteria:

I. DST based Exclusion Criteria:

- MDR/RR-TB patients with H resistance detected with both KatG and InhA mutation or
- MDR/RR-TB patients with FQ or SLI resistance detected

II. Other Exclusion Criteria:

- History of exposure for > one month to Km/Am, Mfxh, Eto or Cfz.
- Intolerance or risk of toxicity from a drug in the shorter regimen (e.g. drug-drug interactions)
- Extensive TB disease – the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography.
- In children aged under 15 years, presence of cavities or bilateral disease on chest radiography.
- Severe EP-TB disease - the presence of miliary TB or TB meningitis or central nervous system (CNS) TB.
- In children aged under 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression)

B. Pre-treatment Evaluation and Follow up Investigation:

In addition to the test listed above in Table 10 (except serum electrolytes) till injectables are continued:

- Audiometry – baseline and then every two months till SLI course is completed and then as and when clinically indicated.
- Serum Creatinine – baseline and then monthly till SLI course is completed.

C. Regimen Composition and Duration:

- The injectable is only given three times a week in the extended intensive phase.
- Neither replacement of drug (except the use of Am instead of Km) nor extension of treatment duration (beyond 11 months) is permitted.
- Pyridoxine is to be given as per weight band.
- Duration and extension of regimen is similar to Shorter oral Bedaquiline-containing MDR/RR-TB regimen.

Annexure -7
Newer Drugs

Bedaquiline (Bdq) is a diarylquinoline that specifically targets mycobacterial ATP synthase, an enzyme essential for the supply of energy to Mycobacterium TB. Strong bactericidal and sterilizing activities against M.tb have been shown in pre-clinical, laboratory and animal experiments. The drug has a high volume of distribution, with extensive tissue distribution, highly bound to plasma proteins and is hepatically metabolized. The drug has an extended half-life, which means that it is still present in the plasma up to 5.5 months post stopping Bdq. Bdq has shown significant benefits in improving the time to culture conversion in MDR-TB patients (Bdq is now well incorporated within NTEP as a part of standard longer oral M/XDR-TB regimen for eligible patients.)

Bedaquiline(Bdq) for children

It will be given to children >5 years of age weighing 15kg or more.

Child-friendly (i.e. dispersible and palatable) formulations of the medications should be used whenever available. Bedaquiline tablets suspended in water have been shown to have the same bioavailability as tablets swallowed whole, and can be used to treat DR TB in children until a child-friendly formulation are available under NTEP.

Delamanid (Dlm) is the first approved drug in the class of nitro-dihydro-imidazo-oxazoles for the treatment of MDR-TB. It is bactericidal drug with 36 hours of half-life and act with two different mechanisms of action. It blocks the synthesis of mycolic acids (i.e., stopping the bacteria from creating building blocks important for their cell walls) as well as poison the bacilli with nitric oxide, which the drugs release when metabolized.

Delaminid (Dlm) for children

It will be given to children 6 years onwards. Although the use of Dlm in the age group of 3-5 years has been approved by WHO, the regulatory approval in India is awaited.

Appropriate dose in children aged 3–5 years will be easier when dispersible 25 mg tablet are available under NTEP

Key Considerations for newer drugs:

- Take a light meal with Bdq and other anti-TB drugs,
- Patients should not consume milk containing products at the time of taking drugs, as the calcium in these can decrease the absorption of FQs.
- Large fatty meals should be avoided, as these can impair absorption of some of the other anti-TB drugs (Cs, H etc.).
- The following medications are not allowed during the 24-week administration of Bdq and up to one month after the last dose of Bdq because of potential drug–drug interactions:

- Systemic use of moderate and strong CYP3A4 inhibitors, e.g. azole antifungals: ketoconazole, voriconazole, itraconazole, fluconazole; ketolides such as telithromycin and macrolide antibiotics other than azithromycin for more than 2 consecutive weeks.
- Systemic use of strong CYP3A4 inducers, e.g. phenytoin, carbamazepine, phenobarbital.
- St. John's Wort and Rifamycins (rifampin, rifabutin, rifapentine); and
- Cholesterol lowering medications of the "statin" class.
- Bdq use in PLHIV infection should be with caution with ARVs that exhibit drug-drug interactions with Bdq (efavirenz) or prolong the QT interval (lopinavir/ ritonavir).
- Other second-line drugs that are likely to be administered with Bdq/ Dlm, notably FQs and Cfz may potentially increase the risk of cardiotoxicity. Therefore, monitoring of patients for cardiac dysrhythmias or QT interval prolongation (i.e. using ECG), and for electrolyte imbalances (especially serum potassium) that can predispose to cardiotoxicity is imperative.

Additional considerations for the use of Delaminid

- Dlm can be provided to adults and children aged 6 years to less than 18 years, given their special needs in consultation with pediatrician.
- Dlm will be considered only for longer oral M/XDR-TB regimen.
- Take light meal with Dlm and other anti-TB drugs, do not consume milk containing products simultaneously as the calcium in these can decrease the absorption of FQs.
- Dlm be taken daily preferably after a standard meal to improve bioavailability.
- Drug-drug interaction studies of Dlm with tenofovir, efavirenz and lopinavir/ritonavir, respectively, suggested that no dose adjustments were needed. No new or significant drug-drug interactions between Dlm and ARV drugs were observed in Trial 213, although the number of participants receiving dual treatment was low and results should be interpreted with caution.

Annexure -8
Drug Interruptions

Bedaquiline:

Patients who interrupt Bdq during the first two weeks of Bdq course

- if interruption is up to 7 days, Bdq will be continued to complete the doses and the duration of treatment will be extended to complete full course of Bdq. Follow-up cultures will be done as per the revised schedule
- if interruption is more than 7 consecutive days, Bdq course will be reloaded (started afresh with a new bottle and old bottle sent for reconstitution). Follow-up cultures will be done as per the revised schedule.

Patients who interrupt Bdq during 3-24 weeks of Bdq course and return to resume treatment:

- *If interruption is up to two months* - Bdq containing regimen will be continued to complete the doses and duration of treatment will be extended to complete full course of Bdq. Follow-up cultures will be done as per revised schedule.
- *if interruption is more than two months* - the regimen will be permanently discontinued. Such patients will be given an outcome of "Lost to follow-up" (LTFU), registered afresh and initiate longer oral M/XDR-TB regimen with appropriate modification if needed after a re-evaluation with FL-SL LPA, LC-DST as per algorithm and PTE.
- Patient who are required to be shifted from shorter oral Bedaquiline-containing MDR/RR-TB regimen to longer oral M/XDR-TB regimen due to reasons of resistance, tolerability, availability and emergence of exclusion criteria, re-evaluated for necessary modification of longer oral M/XDR-TB regimen as required and initiated on a full course of longer oral M/XDR-TB regimen. Bedaquiline should be given for the entire 6 months' duration without the loading dose.
- Patients who are placed on a longer oral M/XDR-TB regimen based on history of exposure to second line drugs for > 1 month awaiting LPA results and later found to be eligible for the shorter oral Bedaquiline containing MDR/RR-TB regimen (and in whom resistance is not detected on baseline specimen to H i.e. both inhA and katG or to FQ or Z, Cfz*, Bdq*) can be switched, provided that treatment has not lasted for more than 1 month. If patients are switched in this way, the shorter oral Bedaquiline-containing MDR/RR-TB regimen is given for the full duration, without any changes to its composition or duration. Bedaquiline should be given for the entire 6-month duration without the loading dose.
- Bdq can be reinitiated with the loading dose, if the interruption, if any, is up to two months.

Delaminid

- If the patient misses one or more doses of Dlm during treatment up to a maximum of one month, one should continue the treatment and complete the Dlm for rest of the period which may prolong the Dlm containing phase beyond 24 weeks from initiation of treatment to make the adjustment of missed dosage.
- Patients who have consumed more than one month of any regimen with Bdq or/and Dlm and return after treatment interruption of two month or more will be declared as "lost to follow up". Such patients would not be considered eligible for administration of same drug (Bdq/ Dlm) anymore, unless they are found to be susceptible on DST whenever available under NTEP.
- Where further treatment is concerned, if the patient has any indication of a treatment failed or recurrence, the NDR-TBC Committee will be contacted to discuss the appropriate regimen design. The decision will be made on an individual patient-to-patient basis, using all available bacteriological, clinical, radiological, biochemical, ECG, h/o exposure to drugs and most recent resistance pattern data to all drugs in group A, B and C from which a reliable DST method is available

Stock Management of New Drugs

Dispensation of child friendly formulation of Bedaquiline 20 mg DT

- Paediatric BDQ is available as 20 mg dispersible tablets and the recommended dose is 200 mg daily for 2 weeks followed by 100 mg thrice a week for 22 weeks.
- Paediatric BDQ is supplied in a Jar which contains 60 tablets
- the whole course is of 470 tablets (8 bottles)
- When family member is a treatment supporter, entire course can be handed over to family member with instruction to monitor treatment adherence.

➢ *Note: when allocating entire course to the patients, SDS/DDS shall remove 10 tablets from any of 8 bottle course .10 tablets shall be utilized for reconstitution.*

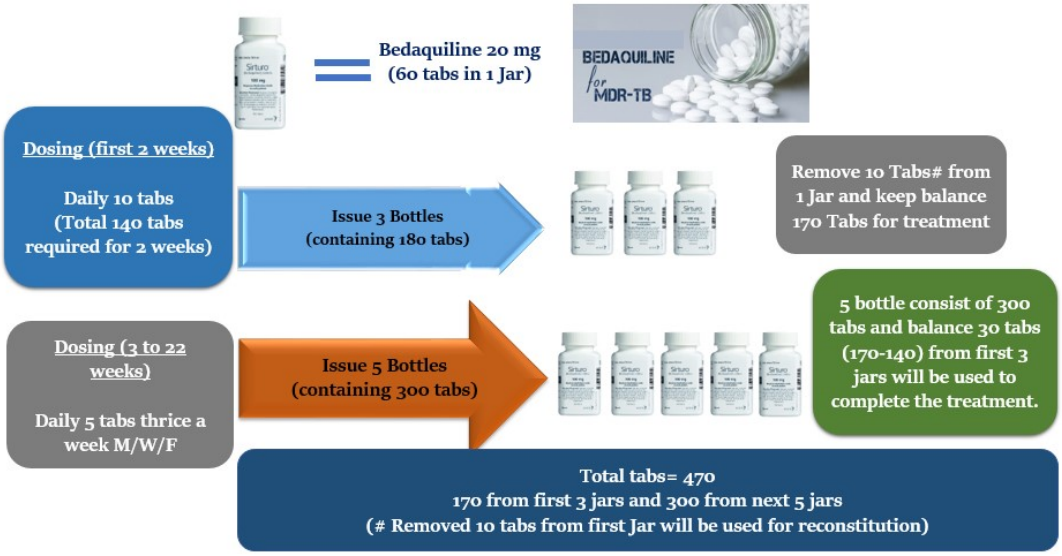


Figure 16. Bedaquiline 20mg dosing for children (5 years to less than 18 years of age and body weight greater than or equal to 15kg to less than 30kg)

Dispensation of Delaminid to Children

- Ensure entire course of treatment for the patient.
- Dlm provided on monthly basis along with other SL drugs for a period of 24 weeks.
- Dlm is available as 50mg tablets and the recommended dose is 50 mg twice a day for (6-11yrs) and 100 mg twice a day for 12 – 17 yrs for 24 weeks.

6 years to 11 years of age: 2 tablets a day (monthly requirement 60 tablets except in 6th month where drugs are given only for 18 days))

- 7 boxes required for full duration of treatment.
- Each box contains 48 tablets i.e. 6 strips of 8 tablets per strip.
- Patient is provided with 8 strips (64 tablets) every month for 5 months.
- The four extra tablets issued every month are carried over and in the sixth month only 2 strips are issued, thereby ensuring that the patient consumes only 36 tabs over 18 days.

12 years and above: 4 tablets a day (monthly requirement 120 tablets except in 6th month where drugs are given only for 18 days)

- 14 boxes required for full duration of treatment.
- Patient is provided with 15 strips (120 tablets) every month for 5 months.
- 9 strips are issued in the sixth month thereby ensuring that the patient consumes only 72 tablets over 18 days.
- In the event of loss to follow up or death or discontinuation of DLM for any reason, the leftover tablets will be returned back and taken back in stock.

Annexure -9
List of the drugs can be used safely or to be avoided along with Bdq

Group	Safe to Use	Drugs to be Avoided
Antiemetics	Metoclopramide	Domperidone, Ondansetron
Analgesics	NSAIDs, Paracetamol	Tramadol
Antacids	Ranitidine, Milk of Magnesia	Pantoprazole, Omeprazole
Antihistaminics	Pheniramine, Fexofenadine, Cetirizine	Diphenhydramine, Loratadine
Antimalarials	Artesunate	Chloroquine
Antibiotics	Penicillins, Cephalosporins, Tinidazole	Ciprofloxacin, Norfloxacin, Cotrimoxazole, Metronidazole
Antifungals	Terbinafine	Fluconazole, Ketoconazole, Itraconazole
Antiepileptics	Sodium Valproate	Phenytoin, Carbamazepine, Phenobarbital
Antidiabetics	Mostly safe	
Antihypertensives	Safe (except Diuretics)	Diuretics
Lipid Lowering Agents		Statins Best to avoid
Antiarrhythmics	Diltiazem, Lignocaine	Amiodarone, Procainamide, Digoxin
Other Cardiac Drugs	Nitroglycerine, Sorbitrate	Sotalol
Antiretrovirals	Tenofovir, Zidovudine, Nevirapine, Dolutegravir	Efavirenz, Lopinavir, Ritonavir
Anxiolytics	Benzodiazepines (Alprazolam)	Avoid other sedatives
Antipsychotics	Risperidone	Haloperidol, Clozapine, Quetiapine, Olanzapine
Antidepressants	Best to be avoided, give only if essential with ECG monitoring	Citalopram, Fluoxetine, Sertraline

Table 23. List of the drugs can be used safely or to be avoided along with Bdq