NATIONAL GUIDELINE
ON
PEDIATRIC TUBERCULOSIS MANAGEMENT IN BHUTAN

National Tuberculosis Control Programme
Department of Public Health
Ministry of Health

3rd Edition
March 2024

FOREWORD

According to the Global TB Report 2023, over 10 million people fell ill with TB, making it the world's second leading cause of death from a single infectious agent, after coronavirus disease (COVID-19). Of these total cases, about 10% were reported among children aged less than 14 years. However, pediatric TB received a less priority than adult TB despite the fact that children are at high risk of acquiring TB infection and die from TB disease due to difficulties in diagnosing TB in this age group. The success in ending TB by 2030 is not possible if children are ignored.

Therefore, the Ministry of Health continues to prioritize having a separate pediatric TB guideline as a crucial aspects of TB control efforts in the country. This National Guideline on Pediatric TB Management (3rd Edition) aims to create awareness about childhood TB and provide guidance to the health professionals at all the health centers in managing TB in children. I hope this guideline will not only enhance TB treatment services for children but also contribute significantly towards the goal of ending TB by 2030.

(Karma Jamtsho)
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ABBREVIATIONS

AFB	Acid Fast Bacilli
ATT	Anti-Tubercular Treatment
CSF	Cerebrospinal fluid
CXR	Chest X-ray
DOT	Directly Observed Treatment
DR-TB	Drug Resistant Tuberculosis
DS-TB	Drug Sensitive Tuberculosis
DST	Drug Susceptibility testing
EPTB	Extrapulmonary Tuberculosis
HAART	Highly active anti-retroviral therapy
HIV	Human Immunodeficiency Virus
MDR-TB	Multi drug resistant tuberculosis
MT	Mantoux test
NTRL	National Tuberculosis Reference Laboratory
PPD	Purified protein derivative
Pre-XDR-TB	Pre-extensively drug resistant tuberculosis
PT	Preventive therapy
PTB	Pulmonary tuberculosis
RCDC	Royal Centre of Disease Control
TB	Tuberculosis
TBI	Tuberculosis infection
TBM	Tuberculosis meningitis
TBST	Mtb antigen-based skin tests
TST	Tuberculin Sensitivity Test
ST	Supported Treatment
XDR-TB	Extensively drug resistant tuberculosis

Acronyms for first line and second line ATT drugs

Am	Amikacin
Bdq	Bedaquiline
Cfz	Clofazimine
Cm	Capreomycin
Cs	Cycloserine
Dlm	Delamanid
E	Ethambutol
Eto	Ethionamide
FQ	Fluoroquinolone
Gfx	Gatifloxacin
H	Isoniazid
Imp/Cln	Imipenem/Cilastatin
Km	Kanamycin
Lfx	Levofloxacin
Lzd	Linezolid
Mfx	Moxifloxacin
Mpm	Meropenem
PAS	Para- aminosalicylic Acid
Pto	Prothionamide
R	Rifampicin
RFB	Rifabutin
RPT	Rifapentine
S	Streptomycin
Trd	Terizidone
Z	Pyrazinamide

CHAPTER 1
INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis* and it is one of the top 10 infectious causes of death worldwide. TB is caused by the bacillus *Mycobacterium tuberculosis*, which is spread when people who are sick with TB expel bacteria into the air (e.g., by coughing). About a quarter of the global population is estimated to have been infected with TB bacillus. Although Bhutan is statistically considered relatively low TB burden country, TB still remains a major public health problem. For this reason, the Royal Government of Bhutan (RGoB) accords high priority to the National Tuberculosis Control Programme (NTCP).

As per the Global TB Report 2023, 10.6 million people fell ill with TB globally, and 1.3 million died due to TB. Children and young adolescents (aged below 15 years) represent about 11% of all people with tuberculosis (TB) globally. This means that 1.1 million children become ill with TB every year with almost half of them below five years of age. National TB programmes (NTPs) only notify less than half of these children, meaning that there is a large case detection gap.

The major reasons for this gap in diagnosis is on account of challenges with specimen collection and bacteriological confirmation of TB in young children, due to the paucibacillary nature of TB disease in this age group and the lack of highly sensitive point-of-care tests.
There is no actual data on TB burden among children in the country but it is estimated that if there is an accurate TB diagnosis and good reporting system in children in the country, it is likely to contribute much more of disease burden in the country.

A common misconception is, that children are not severely affected by the TB epidemic and rarely develop severe forms of the disease. This is not the case in developing countries where children unlike adults are often come with advanced and serious disease on the first presentation itself. If one case of TB infection is detected in a child, it will help to indicate the actual incidence of TB in the community by active contact tracing of the contacts. Children usually have smear negative and paucibacillary pulmonary disease, as cavitation is rare. In contrast, children develop extrapulmonary TB (EP-TB) more often than adults. Severe and disseminated TB (e.g., TB meningitis and miliary TB) occurs more commonly especially in young children aged less than 3 years. Diagnosis of TB in children is challenging as their symptoms are non-specific and they do not/cannot cough up sputum up for sputum examination making smear less positive, moreover because of paucibacillary nature of disease.

Therefore, the main reasons for low case detection on childhood TB are under diagnosis, misconception and underreporting in the country. This new guideline based on the World Health Organization (WHO) End TB Strategy targeting to achieve the United Nations Sustainable Development Goal (SDGs) on child TB, including targets to reduce TB incidence by 80% and TB deaths by 90% to be achieved by the year 2030, relative to baseline levels in 2015.It will enhance both diagnosis and treatment of childhood TB across the country and will contribute immensely to fulfill the dreams of country's End TB Strategy by 2030.

CHAPTER 2
TUBERCULOSIS IN CHILDREN

TB in children is a reflection of the extent of transmission of TB infection in the communities as the source of infection for children is usually an adult/adolescent with infectious pulmonary TB (smear /culture positive PTB).

Tuberculosis infection should be differentiated from disease:

- **TB infection**- A child becomes infected when the child inhales the TB organism. It is diagnosed when the child is asymptomatic and the Tuberculin Skin Test (TST) is positive. Not all children exposed to an infectious adult case of TB will become infected.
- **TB disease**- About 10% of children who have been infected with TB develop active disease. TB disease may manifest in many different ways but is indicated by the presence of well-defined symptoms.

2.1 Acquisition - How children get infected

Most of the children acquire TB infection from the adults with infectious TB through cough droplets. These infectious droplets containing *M. tuberculosis* bacilli can remain in the air and can be inhaled by the child causing infection. The proportion of children infected will depend on the duration of exposure (time), the closeness of the contact and the number of organisms in the sputum of the source case.

The risk of TB infection and disease is increased with:

- Age and HIV status: young children (< 5 years) and HIV positive children are at high risk of getting infected.
- Close exposure: where the mother or caregiver has active TB.
- Long duration of exposure to an infectious case.
- High intensity of exposure: smear positive cases are the most infectious, smear negative and culture positive cases are less

infectious while extra pulmonary TB Patients are normally not infectious.

- Children who are immunocompromised – like malnutrition, on prolonged immunosuppressive agents for more than a month, recent confirmed measles infection.

Infection can also occur before or during birth if the mother has disseminated tuberculosis. In this case the bacilli will pass through the placenta from the mother's circulation into the fetal circulation. Babies can also be infected through inhalation of infected material during birth or immediately after birth through exposure to an adult with infectious TB. Drug resistant TB is as infectious as drug susceptible TB. Children exposed to drug resistant TB therefore have the same risk of being infected as children exposed to drug susceptible TB.

2.2 Clinical Presentation

Children can present with TB at any age but it is commonest in the under 5-age group and during adolescence. In general TB is a slowly developing chronic disease, but it may present acutely in young and HIV-infected children. The time between initial infection and clinically apparent disease is variable. Pulmonary tuberculosis occurs within 2 years after exposure and most (90%) within the first year, is usually caused by endogenous regrowth of bacilli persisting in partially encapsulated lesions.

Disseminated and meningeal tuberculosis are early manifestations often occurring within 2-6 months of acquisition. Significant lymph node or endobronchial tuberculosis usually appears within 3-9 months. Lesions of the bones and joints take several years to develop, whereas renal lesions become evident after decades of infection.

2.2.1 Typical symptoms

WHO has developed well defined clinical features to suspect and diagnose TB clinically in children in the community.

These **4 cardinal symptoms** suggestive of childhood TB are:

1. **Persistent, non-remitting cough** for ≥2 weeks not responding to conventional antibiotics (amoxicillin, co-trimoxazole or cephalosporin) and/or bronchodilators
2. **Persistent documented fever (>38^{O}C/100.4^{O}F)** for ≥2 weeks after common causes such as pneumonia, scrub typhus, malaria or typhoid have been excluded
3. **Documented weight loss > 5% since last visit or weight for age < - 3 Z score or not gaining weight during the past 3 months** (especially if not responding to appropriate nutritional counseling with micronutrient supplementation and de-worming together) OR severe acute malnutrition
4. **Fatigue, reduced playfulness,** decreased activity.

2.3 Pulmonary Tuberculosis

TB disease in children is mostly pulmonary (60%), characterized by hilar and/or mediastinal lymph gland enlargement (**Figure 1**) and is usually smear negative or smear not done. Smear positive cases are found in older children and adolescents.

The hallmark of primary tuberculosis in the lung is the relatively large size of the regional lymphadenitis compared with the relatively small size of the initial lung focus. The usual sequence of events in pulmonary TB is *hilar lymphadenopathy, focal hyperinflation,* and then *atelectasis.* The resulting radiographic shadows have been called *collapse-consolidation* or *segmental* tuberculosis. The only factors that differentiate pulmonary TB

from other causes of chronic cough are history of contact with an infectious TB case and a positive tuberculin skin test (TST).

Pulmonary TB in children can manifest in various ways in different age groups:

- Infants (<1 year): primarily pneumonia-like features (**Figure 3**)
- Children (1-9 years): usually with a chronic cough
- Adolescents (10-19 years): as in adults with cough, expectoration and hemoptysis.

The pulmonary symptoms and signs are occasionally alleviated by antibiotics, suggesting bacterial super-infection. Hence a high degree of clinical suspicion is warranted to diagnose pulmonary TB in infants and young children.

Examples of Chest X Ray findings in pulmonary TB in children as below.

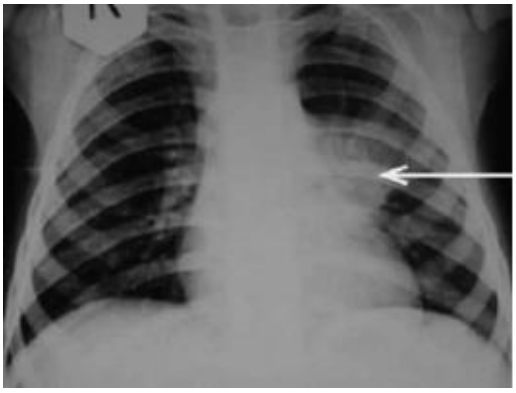


Fig.1 Left hilar lymphadenopathy

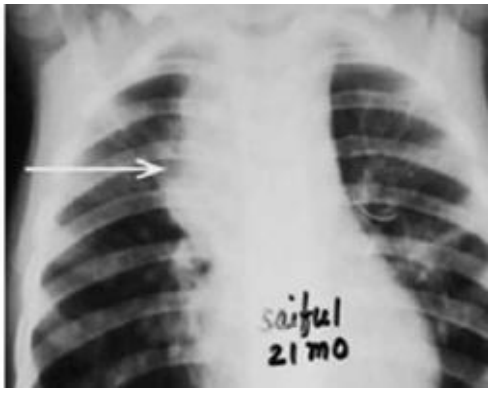


Fig.2 Right paratracheal lymphadenopathy

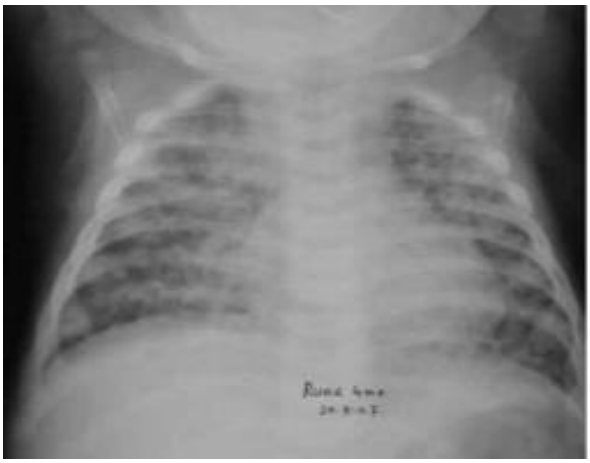


Fig 3: CXR: Bilateral Extensive opacities (Broncho pneumonic features in young children)

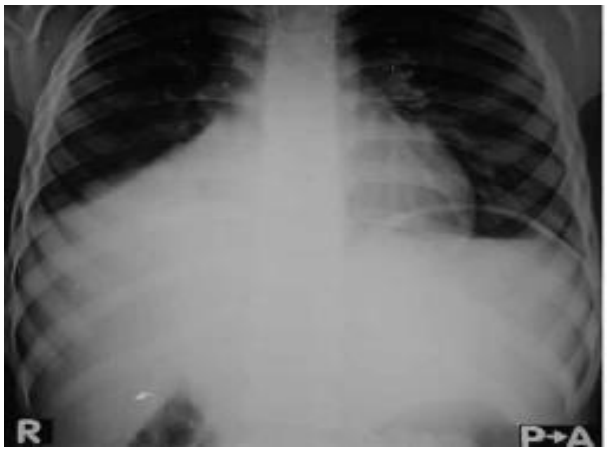


Fig 4: CXR: collapse-RML and RLL (complete obstruction of Rt airway by the infected lymph gland)

2.4 Extra pulmonary childhood TB (EPTB)

Extrapulmonary manifestations are more common in children than adults and develop in approximate 30 - 40% of children with tuberculosis, compared to approximately 10 % of immunocompetent adults. Some clinical signs in EPTB are highly suggestive as outlined in the table below.

Symptoms and Signs	Extra pulmonary TB
Painless enlarged mass of matted lymph nodes (> 2x2 cm), usually in the neck, often unilateral, not fixed to the underlying tissues, may present with sinus, does not respond to antibiotics	TB lymphadenitis (Commonly cervical)
Cough and shortness of breath	Pleural TB, Pericardial TB
Irritability, weight loss, headache, vomiting without diarrhea, drowsiness, lethargy, convulsions, unconsciousness; and meningitis of acute or sub-acute onset not responding to antibiotics	TB meningitis
Abdominal pain, altered bowel habit, mass or ascites	Abdominal TB
Gibbus (acute angulation) of spine	TB Spine
Chronic joint pain and swelling, mostly single joint and non-tender	Bone and joint TB

2.4.1 TB Lymphadenitis

- The most common extra pulmonary manifestation of TB in children is cervical lymphadenitis. Most cases occur within 6-9 months of initial infection by *M. tuberculosis,* although some cases appear years later.
- The usual age of presentation is 2-10 years of age.

- Clinically present as a painless visible neck mass, most often **unilateral** but bilateral involvement can occur because of the crossover drainage patterns of lymphatic vessels in the chest and lower neck. Usually composed of matted lymph nodes, not fixed to the underlying tissues. ***A size of > 2x2 cm is usually seen in tuberculosis.*** Suppuration and spontaneous drainage of the lymph nodes may occur with the development of sinus.
- The constitutional symptoms like fever, weight loss, fatigue, and malaise are usually absent or minimal.
- History of contact may be found in 50% cases of TB lymphadenitis.
- The tuberculin skin test (TST) is usually reactive, but the chest radiography is normal in 70-80% of individuals.
- FNAC or Lymph node biopsy should be performed to establish the diagnosis.

2.4.2 Tubercular pleural effusion

- Pleural effusions due to TB usually occur in children older than 5 years of age and rare before 2 years of age. The primary focus of infection in tuberculous pleural effusion is either a subpleural pulmonary focus or a caseated lymph node.
- Clinical onset of tuberculous pleurisy is often sudden with intermittent fever, chest pain that increases in intensity on deep inspiration, and shortness of breath are the typical presentation of tuberculous pleurisy. Chest pain is localized to one side of the chest associated with stony dull percussion note on the same side with diminished breath sounds. Restricted movement of the chest and intercostal fullness are highly suggestive of a tuberculous pleural effusion. Usually, a child with tubercular pleural effusion is not

sick looking in contrast to post-pneumonic pleural effusion or empyema. The TST is positive in only 70–80% of cases.

- The prognosis is excellent, but radiographic resolution often takes months.
- Acid-fast smears of the pleural fluid are rarely positive. Cultures of the fluid are positive in <30% of cases. Measurement of adenosine deaminase (ADA) levels may enhance the diagnosis of pleural tuberculosis, ADA levels over 40 units/L in the pleural fluid are observed in the majority of patients.
- Biopsy of the pleural membrane is more likely to yield a positive acid-fast stain or culture, and granuloma formation can be demonstrated.

2.4.3 Pericardial TB

- Cardiovascular involvement in tuberculosis is rare and occurs in older children (> 5years and older).
- It mainly affects the pericardium in the form of pericarditis or pericardial effusion (**Figure 5**). It occurs commonly due to rupture of mediastinal lymph node (sub-carinal) into pericardial space.
- The presenting symptoms are nonspecific, including low-grade fever, malaise, and weight loss. Chest pain is unusual in children. A pericardial friction rubs or distant heart sounds with pulsus paradoxus may be present.
- Acid-fast smear of the fluid rarely reveals the organism, but cultures are positive in 30–70% of cases. ADA levels are elevated in TB pericarditis. The culture yield from pericardial biopsy may

be higher, and the presence of granulomas often suggests the diagnosis.

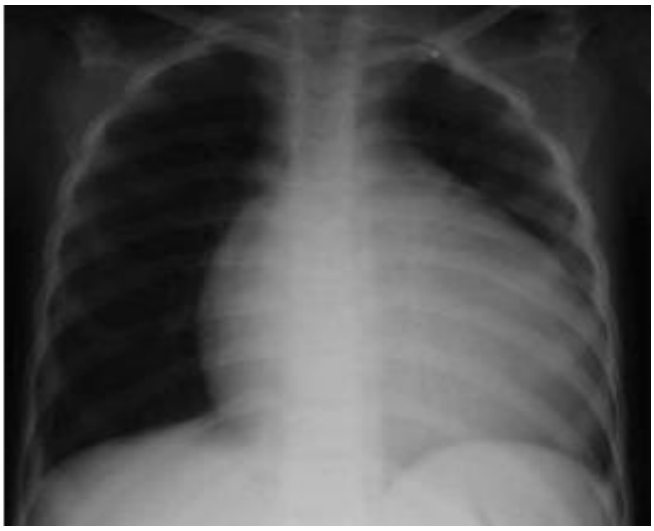


Fig 5: Large TB pericardial effusion, a small pleural effusion right side

2.4.4 TB meningitis

- Tuberculosis of the central nervous system (CNS) is the most serious complication in children and is fatal without prompt and appropriate treatment.
- The most severe manifestation is TB meningitis (TBM) and commonly occurs in children of 6 months to 4 years old.
- Presentation can be acute or chronic. *Rapid progression tends to occur in infants and young children*, where it is frequently fatal.
- Presenting clinical features in children with TBM progress slowly over weeks (1-2 weeks) and are divided into 3 stages.
    - The **1st stage** typically lasts 1-2 wk. and is characterized by nonspecific symptoms such as fever, headache, irritability, drowsiness, and malaise. Focal

neurologic signs are absent, but infants can experience a stagnation or loss of developmental milestones.

- The **2nd stage** usually begins more abruptly. The most common features are lethargy, nuchal rigidity, seizures, positive Kernig and Brudzinski signs, hypertonia, vomiting, cranial nerve palsies, and other focal neurologic signs.
- The **3rd stage** is marked by coma, hemi- or paraplegia, hypertension, decerebrate posturing, deterioration of vital signs, and eventually death.

- The prognosis of tuberculous meningitis correlates most closely with the clinical stage of illness at the time treatment is initiated. The majority of patients in the 1st stage have an excellent outcome, whereas most patients in the 3rd stage who survive have some form of sequelae. *It is imperative that anti tuberculosis treatment be considered for any child who develops basilar meningitis and hydrocephalus, cranial nerve palsy, or stroke with no other apparent etiology.*
- Most important diagnostic test in TBM is cerebrospinal fluid (CSF) analysis. The CSF glucose is typically < 40mg/dL but rarely 20mg/dL. The protein level is elevated, 400-5000mg/dL.
- Current recommendations include Xpert MTB/RIF or Ultra as an initial investigation for all presumptive TB Patients, for prompt recognition and treatment.

- TST is non-reactive in 50% of cases and 20-50% of children have a normal chest radiograph.
- Radiographic studies can aid in the diagnosis of TBM. CT or MRI of the brain of patients with TBM may be normal during early stages of the disease, but can manifest with basilar enhancement and communicating hydrocephalus with signs of cerebral edema or early focal ischemia as the disease progresses.

2.4.5 Miliary TB

- **Miliary tuberculosis** usually complicates the primary infection, occurring within 2-6 months of the initial infection. It affects young children, usually less than 5 years of children.
- It is the most clinically significant form of disseminated tuberculosis where massive numbers of tubercle bacilli are released into the bloodstream, causing disease in 2 or more organs.
- It manifests with a low-grade fever, malaise, weight loss and fatigue. Rapid onset of symptoms with rapid progression leading to death can be presented in infants and young children. Physical examination findings include enlarged lymph nodes, liver and spleen. Less common signs like papular, necrotic, or purpuric lesions on the skin or choroid tubercles in the retina of the eye should be carefully sought in the physical examination. Chest radiography showing diffuse miliary pattern can be helpful in the recognition of disseminated TB manifesting in

the lungs.

- Diagnosis of disseminated tuberculosis can be difficult, and a high index of suspicion by the clinician is required. Early sputum or gastric aspirate cultures have a low sensitivity. Biopsy of the liver or bone marrow with appropriate bacteriologic and histologic examinations more often yields an early diagnosis.

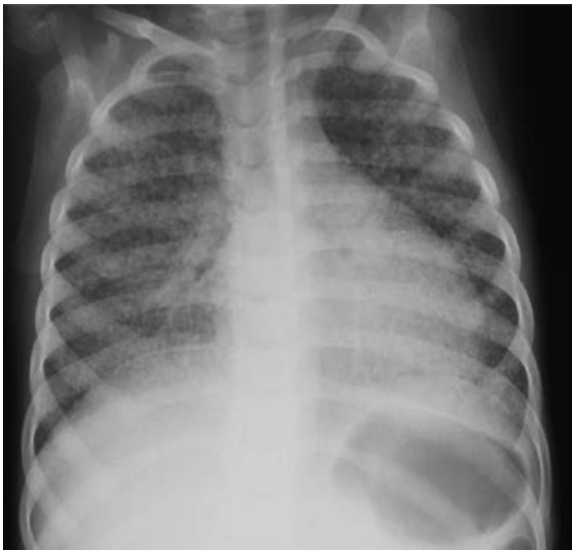


Fig.6 Miliary TB

2.4.6 Abdominal TB

The spectrum of abdominal TB disease in children is different from adults, poorly understood and often neglected by clinicians. The most common site of involvement is ileocecal region and adhesive peritoneal and lymph nodal involvement is more common than GI disease.

Most children have constitutional symptoms of fever, abdominal pain, constipation, alternating constipation and diarrhea, weight loss, anorexia and malaise. Abdominal distention due to ascites and palpable mass in ileocecal region is the common presenting feature of abdominal TB.

2.4.7 TB spine and TB arthritis: Osteoarticular TB

In osteoarticular TB, the spine is affected most commonly involving lower thoracic or lumbar vertebrae. The older children usually more than 5 years old are affected. In growing children, the disease can destroy areas responsible for their spinal growth (growth plates in vertebra). This may cause permanent deformity of spine or neurological complications in growing children if not treated properly.

The common clinical features are back pain for few weeks, more at night with tenderness in the affected area and angulation of the spine called "gibbus" deformity, a feature of Pott's disease (severe kyphosis with destruction of the vertebral bodies). It may also present acutely as cord compression, leading to paraplegia or quadripglegia causing difficulty in walking and voiding of urine/stool. Any child with local pain and tenderness over the spine must be suspected of having spinal tuberculosis.

A rapid onset of a gibbus ('hump back') is almost always due to tuberculosis.

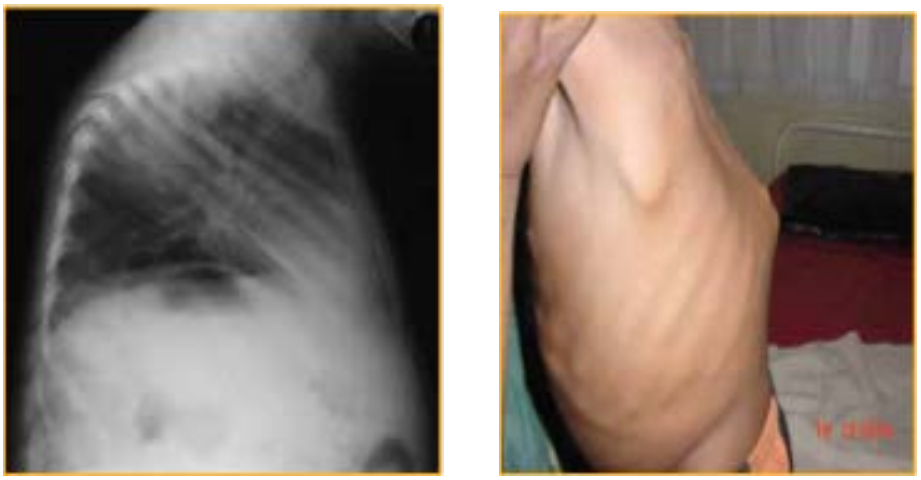


Fig.7 Gibbus deformity (Photo courtesy: from National TB Guideline, Bangladesh

Chapter 3
Diagnostic Investigations of Childhood Tuberculosis

The low case detection rate among (young) children is due to several factors including the fact that young children have paucibacillary TB and do not excrete enough bacilli to be detectable by available bacteriological tests; the lack of a sensitive point-of-care diagnostic test; difficulties in collecting suitable respiratory samples for bacteriological confirmation; and misdiagnosis due to the overlap of non-specific symptoms of TB with other common childhood diseases.

3.1 Investigations

1. Bacteriological confirmation

Despite challenges with bacteriological confirmation of paucibacillary TB in young children, every effort should be made to establish bacteriological confirmation.

In adolescents, who usually have adult-type disease, bacteriological confirmation is common.

Bacteriological confirmation is even more important for children and adolescents who:

- have presumed DR-TB;
- are living with HIV;
- have complicated (e.g., airway obstruction, pneumothorax, empyema) or severe TB disease;
- have an uncertain diagnosis
- have been treated previously.

WHO-recommends clinical samples for the diagnosis of PTB in children and adolescents using Xpert MTB/RIF or newer assay Xpert Ultra include sputum (expectorated or induced), gastric or nasopharyngeal aspirates, and

stool.

Stool is a newly recommended specimen for the diagnosis of PTB in children using Xpert MTB/RIF or Ultra. It can be used as an alternative specimen, especially in situations when it is challenging to obtain adequate respiratory specimens for the diagnosis of PTB, such as in younger children. Testing stool may be more acceptable and feasible in certain settings, as it is less invasive than gastric or nasopharyngeal aspiration (NPA).

Two stool samples provide a higher yield than one sample only.

Key points

- Recommendations for the use of stool as a non-invasive specimen for bacteriological confirmation of PTB and rifampicin resistance in children are an important new development.
- Two stool samples provide a higher yield than one sample only.

The following basic investigations should be done however if facilities are available at health center.

2. Chest Radiography

Chest radiography (CXR) should always be done in all forms of TB. It is useful in the diagnosis of TB in children along with other supporting signs/symptoms, history of exposure, tuberculin skin test.

CXR is an important tool to determine severity of disease in children. This is necessary to determine eligibility for the newer short course treatment regimen recommended for children and adolescents aged 3 months to 16 years with non-severe TB.

Good-quality CXRs are essential for proper evaluation. In the majority of cases, children with pulmonary TB have CXR changes suggestive of TB. The common radiological findings are:

a. Increased density in the hilar region due to enlarged hilar lymph nodes and/or a broad mediastinum due to enlarged mediastinal lymph nodes (**Figure 1 and 2**). **A lateral chest X-ray** is helpful to evaluate hilar lymphadenopathy (**Figure 3**).
b. Persistent opacity in the lung that does not improve after a course of antibiotics should be suspected for TB.
c. Segmental/lobar hyperinflation or collapses are seen less commonly due to compression of the airways (**Figure 4**).
d. Miliary pattern of opacification (highly suggestive in HIV-negative children).
e. Unilateral pleural effusions (usually in children > 5 years old).

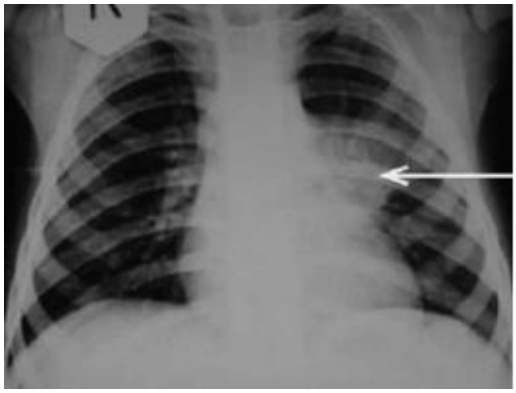


Fig.1 Left hilar lymphadenopathy

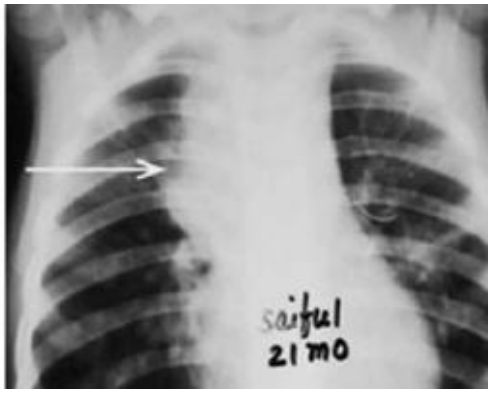
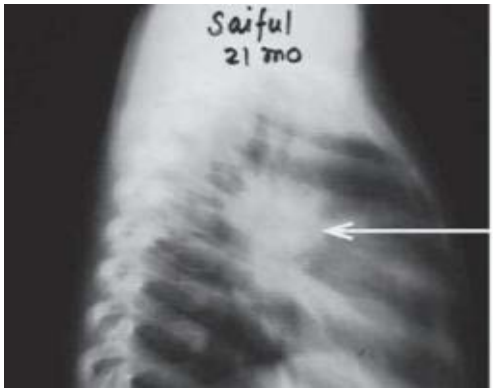


Fig.2 Right paratracheal lymphadenopathy



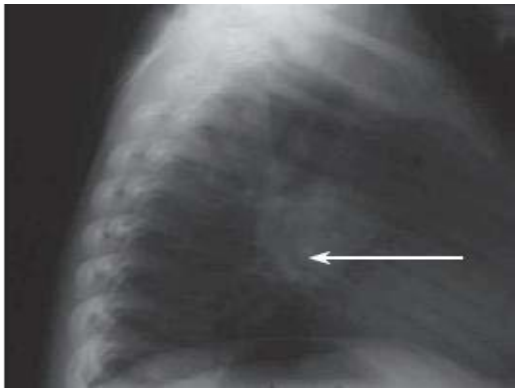


Fig.3 Massive hilar lymph gland enlargement on the lateral CXR (Arrow indicates hilar lymph glands)

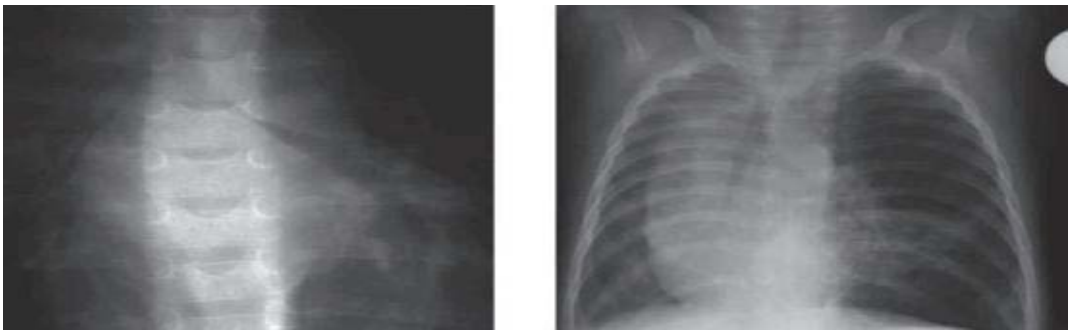


Fig.4 The left main bronchus partially obstructed, creating "check valve" leading to hyperinflation of the left lung

Key points on CXR

- CXR findings in children with PTB are often nonspecific.
- CXR is useful to support the clinical diagnosis of PTB when TB is suspected and bacteriological testing is negative.

CXR is an important tool to determine severity of disease in children.

3.Tuberculin skin test/Mantoux test

Tuberculin Skin Test (TST) or Mantoux test (MT) measures the delayed type of hypersensitivity response to tuberculin Purified Protein Derivative (PPD).

Health-care workers must be trained in performing and reading TST. It is performed by injecting 5 TU (0.1ml) of tuberculin PPD-S into the skin (intra-dermal) on the inner aspect of the left forearm. TST reading is best taken within 48-72 hours of the test. ***It is measured as the largest diameter of induration across the forearm (perpendicular to the long axis), not the diameter of redness.*** Interpretation of TST should be done irrespective of previous BCG vaccination.

A positive TST may be present in both TB infection (TBI) and in TB disease. Thus, although a positive TST may help support a diagnosis of disease, this finding alone is not diagnostic of disease; it must be considered together with other diagnostic criteria. The TST is helpful for diagnosis of TB in children only in circumstances when it is positive. A positive TST may be falsely positive due to prior vaccination with BCG, infection with nontuberculous mycobacteria, and improper administration or interpretation. The **TST** should be regarded as positive when the **induration is**:

≥5 mm	≥10 mm	≥15 mm

• Children suspected to have TB disease:
  ○ Clinical evidence of TB disease.
  ○ Radiological features suggestive of active or previous TB
  ○ Symptomatic children in close contact with infectious TB patients (known or suspected).
• Children receiving immunosuppressive therapy>1month duration or with immunosuppressive conditions, (including HIV infection and severe malnutrition).
	• Children at increased risk of disseminated tuberculosis disease:
	  ○ Children ≤ 4 years old
	  ○ Children with other medical conditions, including diabetes mellitus, chronic renal failure, hypertension or mild to moderate malnutrition
	• Children ≥ 5 years with close contact but asymptomatic, thriving well and normal chest Xray.
		• Children ≥ 4 years old without any risk factors.
		
		• BCG vaccinated children in the absence of risk factors.

Overall, up to 40% of immunocompetent children with culture-confirmed TB disease may have a negative TST. TST positivity rates vary by form of disease; in pulmonary and extrapulmonary TB, the TST is typically

positive (90% and 80% respectively), while in miliary and TBM, the TST is usually positive in only 50% of cases.

False negative TST may occur in:

- Severe malnutrition
- Immunosuppressive conditions:
    - Measles in last 3 months
    - Whooping cough, HIV infection, Drugs like steroids
    - Anti-cancer agents
- Disseminated and miliary TB and/or TB meningitis (TBM)
- Very recent TB exposure (within last 3 months)

It should be noted that, a ***negative TST does not exclude TB exposure, infection or disease.***

3.b Newer based Mycobacterium tuberculosis skin-based antigen test (TBST)

TBST is defined as in vivo skin tests for the detection of TB infection that uses *Mtb*- specific antigens (ESAT-6 and CFP-10). These tests combine the simpler skin-test platform with the specificity of IGRAs. It uses intradermal injection of antigen and like TST, are read after 48-72 hours as induration in millimetres, using the same method as TST (Mantoux).

This test may have similar specificity as IGRAs and provide more reliable results in children and adolescents than TST (Mantoux), as well as in people with HIV.

Currently, there are 3 tests available:

1.Cy-Tb (India)

2.Diaskintest (Russia)

3.C-TST (China)

Based on available evidences, TBSTs are likely to improve health equity through the provision of a more accurate, low cost test for resource limited settings where the TST is already in use. It was suggested that TBSTs were perceived to have greater accuracy than the TST and were considered desirable because they avoid the negative consequences of false positive results. Hence WHO recently recommend TBSTs to be used for detection of TB infection in all group of population, especially the following sub population:

1. Children and Adolescents aged under 18 years
2. People who have been vaccinated with BCG
3. People with HIV.

Therefore, once available in the country TBST (Cy-Tb) will be used instead of TST (Mantoux) in both contact testing and for TB diagnosis in children.

4. Culture

Demonstration of *M. tuberculosis* by culture is considered "gold standard" for diagnosis of TB. Culture for TB is of particular value in complicated cases or when there is a concern regarding drug resistance. Probability of obtaining a positive TB culture improves when more than one sample is taken with at least 2 samples.

Culture facilities are available only at National Tuberculosis Reference Laboratory (NTRL), Royal Center of Disease Control (RCDC), Thimphu. Two types of culture method are available in NTRL, Lowenstein-Jensen (solid) method which takes 8-12 weeks and liquid culture method using MGIT 960 which takes 7-14 days to get a positive culture.

Sl.No	Name of Health Center	Module/System
1	JDWNRH, Thimphu	16 Module, 6 Colour
2	Phuntsholing Hospital, Chukha	4 Module, 6 Colour
		4 Module 10 Colour
3	Central Regional Referral Hospital, Gelephu	4 Module, 6 Colour
		4 Module 10 Colour
4	Eastern Regional Referral Hospital, Mongar	4 Module, 6 Colour
		4 Module 10 Colour
5	SamdrupJongkhar Hospital, SamdrupJongkhar	4 Module, 6 Colour
6	Samtse Hospital, Samtse	4 Module, 6 Colour
7	Wangdue Hospital, Wangdue	4 Module, 6 Colour
8	Trashigang Hospital, Trashigang	4 Module, 6 Colour
9	Nganglam Hospital, Pemagatshel	4 Module, 6 Colour
10	Royal Centre for Disease Control, Thimphu	4 Module, 6 Colour
11	Gidakom Hospital, Thimphu	4 Module, 10 Colour
12	Tsirang Hospital*	4 Module, 10 Colour
13	Bumthang Hospital *	4 Module, 10 Colour
14	Paro*	4 Module, 10 Colour
15	Yebilaptsa*	4 Module, 10 Colour
16	Pemagatshel*	4 Module, 10 Colour
17	Lungtenphu Hospital, Thimphu	4 module, 6 Color

Table 1. GeneXpert Facilities available in the country

The availability of various diagnostic tools and technology in health facilities are based on existing referral system and tuberculosis caseload in the districts. Currently 17 GeneXpert machines are available including 6

machines with 10 coloured modules (Xpert MTB/XDR tests) placed at 13 sites. The program has plans to procure and install 3 more 10 colour machines at the Cluster Hospitals in the near future making GeneXpert services available at 16 strategic sites with 20 machines in the country.

NTP proposes to widely use available X-ray technologies as initial screening and diagnosis tool and will look to introduce new hand-held x ray devices with AI technology and other histopathological tests will be also performed based on the clinical manifestations and judgements of the physicians (Medical Specialist/Chest Physicians).

To enhance follow up of drug resistant-TB Patients, program is in the process of consultation to expand liquid culture facility in three referral hospitals (in future).

The procedures detail for all diagnostic tools and technology used in all level of health facilities can be referred in the Laboratory Manual developed by National Tuberculosis Reference Laboratory.

5. Other tests

HIV Testing - In areas with a high prevalence of HIV infection, where TB and HIV infection are likely to coexist, WHO advocates HIV counseling and testing for all TB patients as part of their routine management.

Complete blood count - may be indicated in a seriously ill patient but not for diagnosis of TB.

ESR - is a non-specific test for inflammation and has no role in confirming or excluding TB in children.

3.2 Approach to diagnosis of childhood TB

Clinical history taking is the most important part in the diagnosis of TB in children. This includes presenting symptoms and signs, history of contact with a known case of TB and medications taken. History should focus on the key risk factors for TB in children, which are:

- Age of the child (risk to develop TB Disease is highest in a children < 5 years)
- Close contact with a known case of TB (parents, siblings, close relatives, care givers, neighbors and teachers)
- Duration with close or household contact
- Severe malnutrition
- Other immune suppressive conditions like measles in previous 3 months, HIV infection, on prolonged immune suppressive medication.

Children acquire the TB disease mostly from a sputum-positive adult/adolescent (source/index case). They usually develop TB within 2 years after exposure and most of them (90%) within the first year. Therefore, history of close contact with a patient (adult or adolescent or even a child) with pulmonary TB within the recent past (last one year) is the most important clue. Especially young children less than 5 years of age living in close contact/household contact with an index case are at particular risk of TB infection and disease. The risk of infection is greatest if the contact is in close proximity, exposure is prolonged and a source case has sputum smear-positive PTB. Index cases that are sputum smear-negative but culture-positive are also infectious, but to a lesser extent. If no index case is identified, but someone else in household is found to have chronic cough upon further inquiry, assessment of that person for possible TB is warranted.

Conversely if a child is diagnosed with TB, active search should be made to find household contacts/cases with active TB (reverse contact tracing). If a child is infectious (sputum smear positive), other child contacts must be sought and screened. It is also important to document whether the suspected index case is responding to TB treatment or not (cured, not cured, dead). While taking history, if an index case is found not to be responding or poorly responding to treatment, it points that it may be a case of drug-resistant TB and the child contact (if diagnosed as TB) is most

likely to have drug-resistant TB. This is an important consideration in the diagnosis and treatment of the child.

In summary the approach to a diagnosis of TB in children includes:

i. Detailed clinical history (including contact history of TB and 4 typical symptoms suggestive of TB)
ii. Clinical Assessment (include weight monitoring)
iii. Diagnostic tests –
    a. Upfront GeneXpert test on stool (2 samples) and other EP samples
    b. Tuberculin Sensitivity Test (Mantoux test or newer skin antigen test)
    c. Chest X-ray
    d. Investigations relevant for suspected Extrapulmonary TB (EP-TB)
    e. HIV testing in high-risk patient.

A diagnosis of Tuberculosis (pulmonary or extrapulmonary) in a child should be strongly suspected on the presence of the **classic triad when bacteriologically is not confirmed by GeneXpert Ultra:**

1. Recent close contact with an infectious case,
2. A positive tuberculin skin test (TST), and
3. Suggestive symptoms and findings on chest radiograph or physical examination.

   The diagnosis can be made with confidence in majority of children with careful clinical history and examination. It is *usually not difficult to make a clinical diagnosis of TB* in a child though it is difficult to confirm diagnosis due to diagnostic challenges.

Key points:

- A trial of treatment with TB medicines is not recommended as a method of diagnosing TB in children.
- CXR and TST are useful to support the clinical diagnosis of PTB when TB is suspected and bacteriological test is negative.
- CXR findings in children with PTB are often non-specific. CXR alone cannot be used to determine the correct treatment for the child.

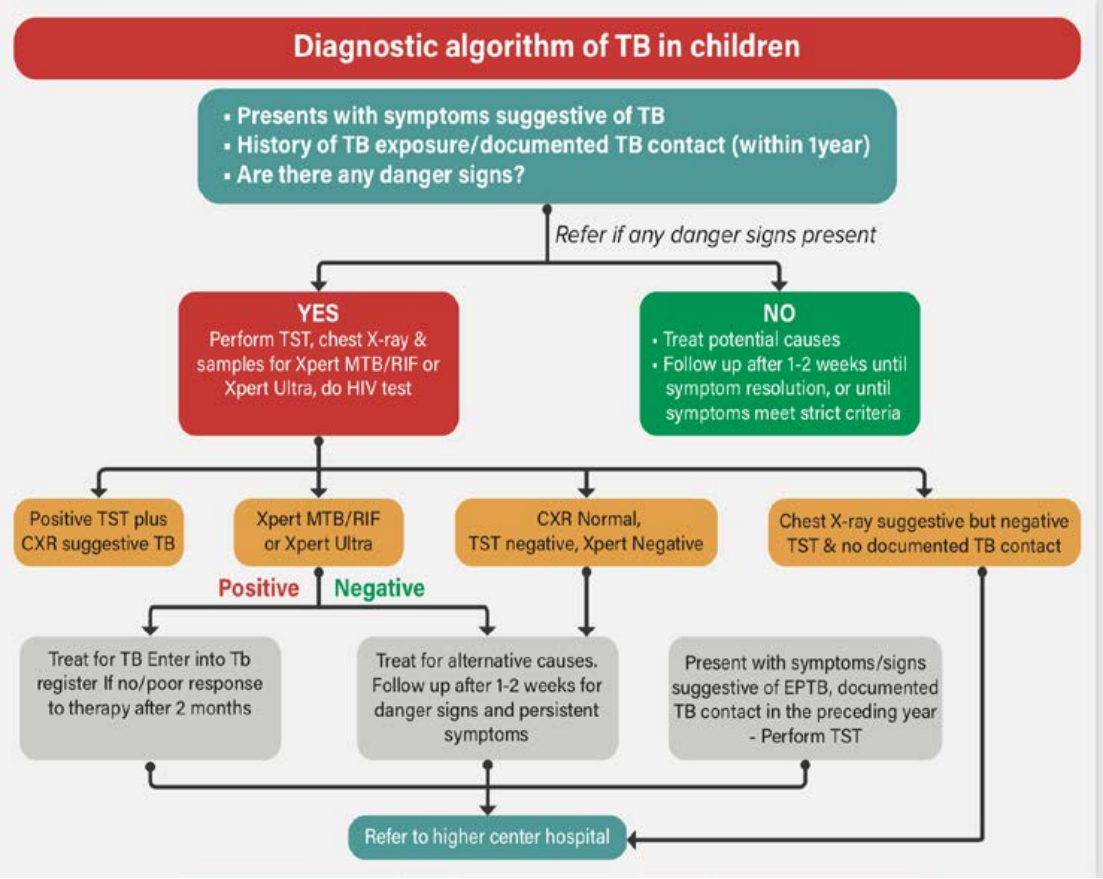


Figure 3.1 *Diagnostic algorithm of TB in children*

CHAPTER 4
TREATMENT OF TB IN CHILDREN

All children who have been diagnosed with TB disease must receive directly observed treatment (DOT) with the appropriate regimen and this must be **recorded in the TB treatment register**. Once TB treatment is started, it should be continued until completion, unless an alternative diagnosis has been confirmed. Treatment outcomes in children are generally good and tolerate anti-TB drugs well, even in young and immune compromised children who are at higher risk of disease progression and disseminated TB disease. Based on the recent WHO recommendation, assessing the severity of TB disease in children with clinical presentation and CXR, as non-severe and severe disease has become a cornerstone for the new recommended treatment regimen.

4.1 TB Disease severity:

a. Non severe TB is defined as:

i. Peripheral isolated lymph node TB
ii. Intrathoracic Lymph node TB without airway obstructions
iii. Uncomplicated TB pleural effusion (without empyema or pneumothorax)
iv. Non cavitary disease confined to one lobe of lungs and without a miliary pattern.

b. Severe TB disease is defined as:

i. Presence of cavities
ii. Bilateral lung disease on CXR
iii. Miliary pattern on CXR.

For non-severe TB (without suspicion or evidence of MDR/RR TB), a new 4-month treatment regimen (2HRZE/2HR) in children and adolescents between 3 months and 16 years of age are recommended.

Children and adolescents who do not meet the criteria for non-severe TB should receive the standard six-month treatment regimen (2HRZE/4HR).

Table 1: Pulmonary TB treatment regimens options by age group and disease severity for new patients with drug susceptible TB

Age and severity of TB	Duration and composition of treatment regimen	
	Intensive phase	**Continuation phase**
Infants aged <3 months or weighing <3 kg		
PTB of any severity	2HRZE	4HR
Children and adolescents aged 3 months to <16 years		
Non-severe PTB	2HRZE	2HR
Severe PTB	2HRZE	4HR

Table 2: Treatment regimens for Extra Pulmonary TB (EPTB) in children with drug susceptible

Age and severity of TB	Duration and composition of treatment regimen	
	Intensive phase	**Continuation phase**
Infants aged <3 months or weighing <3 kg		
Isolated Peripheral lymph node TB	2HRZE	4HR
Children and adolescents aged 3 months to < 16 years		

Isolated Peripheral lymph node TB	2HRZE	2HR
Osteoarticular TB	2HRZE	10HR
TB meningitis	2HRZE	10 HR (Standard regime)
	Intensive 6 HRZEto (Conditional recommendation)**	
All other forms of EPTB	2HRZE	4HR

**The short intensive regimen is composed of daily Isoniazid, Rifampicin, Pyrazinamide and Ethionamide for 6 months throughout (6HRZEto), with higher mg/kg doses of isoniazid and rifampicin compared with the 12-month regimen.

**This regime is optional for children with bacteriologically confirmed or clinically diagnosed DS-TBM.

- Children with TBM should preferably be hospitalized for initiation of treatment and close monitoring.
- Children aged under 2 years with miliary TB should be evaluated for TBM regardless of the presence of CNS symptoms.

Pyridoxine supplementation

- Pyridoxine (vitamin B6) supplementation is recommended in children and adolescents living with HIV and in malnourished children and adolescents who are treated for TB, at a dosage of 0.5–1 mg/kg/day.
- Children weighing up to 25 kg receive half a 25 mg tablet or quarter of a 50 mg tablet. Supplementation with pyridoxine aims to prevent symptomatic pyridoxine deficiency, which presents as peripheral

neuropathy, especially in children with severe malnutrition and children living with HIV.

- Pyridoxine dosages may be increased to 2–5 mg/kg/day if peripheral neuropathy develops, characterized by pain, burning or tingling in the hands or feet, numbness or loss of sensation in the arms and legs, or muscle cramps or muscle twitching.

Corticosteroid use in Tuberculosis:

Steroids may be used for the management of some complicated forms of TB:

i. TB meningitis
ii. Pericardial TB
iii. Complications of airway obstruction by TB lymph nodes
iv. Endobronchial TB
v. Severely ill children with disseminated TB disease.

WHO recommends the following dosage schedule:

Prednisolone - 2-4 mg /kg/day (max. 60mg) for 4 weeks, then tapered over 1-2 weeks.

Regular weight-based dose adjustment is especially important during intensive phase, particularly in young and/or malnourished children when weight gain may be accelerated as they respond to the treatment.

Table 4.1 Recommended daily dosages of first-line anti-TB drugs for children

Drug	**Daily dose**	**Range in mg/kg (maximum dosage)**
Isoniazid (H)	10	7-15 (300mg)
Rifampicin (R)	15	10-20mg (600mg)

Pyrazinamide (Z)	35	30-40 (2000mg)
Ethambutol (E)	20	15-25 (1200mg

4.2 Fixed Dose Combinations (FDCs) for children

Child-friendly formulations are ideal for use to ensure adequate therapeutic blood levels and compliance to treatment regimen. These are dispersible tablets and new available formulations contain 75 mg of Rifampicin, 50 mg of INH and 150 mg of Pyrazinamide per tablet.

Table 4.2.a Pediatric FDCs formulations available

Pediatric FDC Tablet	**Current FDC**
3-FDC	R 75, H50, Z150
2-FDC	R75, H50

Table 4.2.b Number of tablets by weight band for fixed dose combination (FDCs)

Weight bands (Kg)	**Number of tablets**		
	Intensive phase		**Continuation phase**
	RHZ (75/50/150 mg)	**E (100 mg)**	**RH (75/50 mg)**
4-7	1	1	1
8-11	2	2	2
12-15	3	3	3
16-24	4	4	4
>25	**Use adult FDCs**		
	HRZE (75/150/400/275)		HR (75/150)
25-29	2		2
30-34	3		3
35-64	4		4
>65	5		5

Key updates

Diagnostic tests- case finding

Xpert Ultra should be used as initial diagnostic test in children with suspected PTB and EPTB

Stool as the respiratory sample for Xpert Ultra testing in suspected PTB

AFB microscopy testing is no more recommended as initial diagnostic test

Role of CXR in diagnosis and disease severity

Treatment

Importance of disease severity assessment

4 months short course regimen (2HRZE/2HR) for non-severe disease in children and adolescent 3months to 15 years in DS-TB

Child-friendly dispersible FDC tablets should be used for children weighing less than 25 kg.

Children gain weight while receiving TB treatment, and dosages should be adjusted accordingly.

Caregiver should be identified as treatment supporters for children of all ages, including older children and adolescents.

Adherence to the full course of treatment should be emphasized and reinforced.

TB medicines are generally well tolerated in almost all children and adolescents. Side-effects are uncommon. The most important adverse event to look for is hepatotoxicity.

4.3 Management of drug related adverse events

Drug induced Hepatitis

Adverse events caused by TB drugs are much less common in children than in adults. **Most serious adverse event is hepatotoxicity**, which can be caused more in order by **pyrazinamide > Isoniazid > Rifampicin**.

Routinely monitoring of liver enzymes is not required as most of the children on TB medications are asymptomatic with mild elevation of serum liver enzymes (<5 times normal values) and this is not an indication to stop treatment. However, if symptomatic with vomiting, jaundice and tender hepatomegaly during the course of treatment should lead to immediate stopping of all the drug, do serum liver enzymes levels and urgent referral for further investigation.

Management of drug induced hepatitis

1. Stop all anti-TB therapy

2. Perform serum liver enzyme levels: severe involvement indicated by - ALT >3 times (with symptoms suggestive of liver disease)

3. Screen for viral hepatitis

4. Monitor the symptoms and repeat ALT level. When ALT < 2.5 times the upper limit and when symptoms resolve then gradually reintroduce medicines.

a) RMP- gradual reintroduce in 48-72 hours (5mg/kg on Day-1, 10mg/kg on Day-2, 15mg/kg on Day-3)

b) Repeat ALT, if no rebound elevation occurs; gradually add in INH reaching the maximum dose after 3 days of its addition

c) Repeat ALT, if no rebound elevation occurs, continue with RMP/INH

d) Add PZA from 8th day onwards, gradually increasing to its maximum dose after 3 days of its addition

e) Start Ethambutol from day 1 itself

5. If a child has an underlying liver disease, don't re-introduce Pyrazinamide. Give Rifampicin, INH and Ethambutol for 9 months instead.

6. If the child is unable to tolerate RMP, administer INH, Lfx, Ethambutol and Streptomycin instead.

INH induced peripheral neuropathy

INH may cause peripheral neuropathy particularly in severely malnourished, HIV-infected children on HAART, chronic liver disease and renal failure. Supplemental pyridoxine at 1mg/kg/day or (12.5-25 mg = 1⁄2 - 1 tablet/day) is recommended especially in the above-mentioned group of children.

4.4 Supported Treatment (ST)

During Supported Treatment or Directly Observed Treatment (DOT), an observer watches the patient swallowing their drugs, which is essential for completion of treatment and recovery from TB. This ensures that a patient takes right anti-TB drugs, in the right doses, at the right interval and for the right period of time.

Treatment of TB should always be directly observed and drugs are used as a fixed-dose combination or individual drugs. Ethambutol needs to be added additionally with the FDC when indicated. Drug dosages, depending on the body weight of the child, are given daily. **The dose should be adjusted as the weight changes during the course of treatment**. Children should therefore be weighed weekly for at least one month (or at a lesser interval when necessary) and monthly till completion of treatment,

their weight should be documented on the TB treatment card. If there is poor response to therapy (no weight gain, persistent symptoms after 2-3 months of treatment) they should be referred for urgent assessment.

4.5 Follow-up of children during treatment

All children and adolescents initiated on TB treatment should undergo a monitoring assessment at the following intervals as a minimum:

- HIV-negative children and adolescents: 2 weeks and 4 weeks after the start of treatment, at the end of the intensive phase (after 2 months), and then every 2 months until completion of treatment at 4 months or 6 months (depending on regimen used).
- Children and adolescents living with HIV: 2 weeks and 4 weeks after the start of treatment, and then every month until completion of treatment at 4 months or 6 months (depending on regimen used).

Monitoring should include the following as a minimum:

- Assess for resolution or persistence of TB-related symptoms, symptoms of side-effects of medicines, and other symptoms.
- Measure weight – dosages should be adjusted depending on weight gain.
- Assess adherence – review the treatment card and discuss with the patient, caregivers and other treatment supporters.
- Follow-up sputum samples for smear microscopy 2 months after the start of treatment and at treatment completion may be collected from any child who was Xpert MTB/RIF-positive, Xpert Ultra-positive, smear-positive or culture-positive at diagnosis if the treatment site has capacity to perform the test.
    - Symptomatic improvement and weight gain are, however, more valuable markers of treatment success or failure.
- If a follow-up smear is positive, the patient should complete

additional investigations to assess for drug resistance (Xpert MTB/RIF or Ultra, TB culture and DST or molecular tests for drug resistance) and other causes of poor treatment response.

- In children who cannot expectorate, a repeat specimen at the end of treatment is not necessary if the specimen collected at 2 months is negative.
- Repeat sample collection at 2 months in children with unconfirmed TB is not indicated unless there is an inadequate clinical response without symptomatic and nutritional improvement.
- Follow-up CXR is not needed if the child is responding well to TB treatment. Children commonly have a slow radiographic response to treatment and may have persistent radiographic abnormalities at treatment completion but this does not mean they are not responding to treatment.

DO NOT USE Xpert MTB/RIF and CXR TO MONITOR TREATMENT RESPONSE.

4.6 Referral to higher Center

The following children should be referred to higher center for expert opinion and management:

i. All children with severe forms of TB (TB meningitis, pericardial TB, tuberculoma, cavitary PTB, miliary TB, TB peritonitis, spinal or osteoarticular TB)
ii. If there is poor response to therapy (no weight gain, persistent symptoms after 2-3 months of treatment)
iii. Children with presumptive MDR-TB, XDR-TB (or in contact with MDR-TB, XDR-TB case and not responding to first-line therapy)
iv. Acute drug adverse events- symptomatic with acute hepatic toxicity/ injury.

CHAPTER 5
DRUG-RESISTANT TB DISEASE IN CHILDREN

Multi Drug Resistant/Rifampicin Resistant tuberculosis (MDR/RR-TB) is defined as TB that is resistant to at least RIF and usually to both RIF and INH. With increasing numbers of adults with MDR/RR-TB in a community determines how common it is in children in the same community.

Based on modelling estimates, between 25 000 and 32 000 children and young adolescents aged under 15 years develop MDR-TB disease annually across the world. When treated, outcomes of children with MDR/RR-TB are good, but relatively few children are diagnosed and treated for MDR/RR-TB each year. Most deaths among children with TB are in those who are not treated. It is critical, therefore, to ensure timely and appropriate identification, diagnosis and treatment of MDR/RR-TB in children and adolescents.

Most of the MDR-TB in children develops within 12 months of infection. Contact investigation and screening of child and adolescent contacts of infectious MDR/RR-TB source cases need to be prioritized and are essential for the rapid diagnosis of children with MDR/RR-TB disease and for prompt initiation of treatment.

Drug resistant TB in a symptomatic child should be suspected if any of the following features are present:

- Fails to improve clinically after 2-3 months of 1st line anti-TB drugs despite good compliance, including persistence of positive smears or cultures, persistence of symptoms and failure to gain weight.
- Contact with a known case of DR-TB patient, including household and school
- Contact with a person who died of TB or failed TB treatment or non-adherent to TB treatment
- Child with TB recurring after completing TB treatment in an adherent

patient

- H/o previous treatment with anti- TB drugs in last 6-12 months.

5.1 Diagnosis of MDR-TB

Bacteriologically confirmed MDR/RR-TB is based on identification of M. tuberculosis from a specimen from the child or adolescent by molecular or culture-based methods, along with demonstration of at least rifampicin resistance with a genotypic or phenotypic DST.

A diagnosis of MDR/RR-TB can be made clinically (TB disease without bacteriological confirmation) either exposure to a known case of MDR/RR-TB or presence of other risk factors for MDR/RR-TB (child treated previously for TB or exposed to a source case who died from TB or failed TB treatment).

As per data, Strain concordance between children and their adult source cases is around 83% for isoniazid and rifampicin susceptibility, meaning children are very likely to have TB with the same resistance pattern as their most likely source case. Therefore, children with clinically diagnosed MDR/RR-TB should initiate treatment for MDR/RR-TB without delay, while all efforts to confirm the diagnosis by bacteriological testing should be made.

Children with clinically diagnosed or bacteriologically confirmed MDR/RR-TB should be treated with a WHO-recommended regimen, guided by the DST results and history of exposure to TB medicines of most likely MDR/RR TB source case.

Children should not be denied of treatment solely on the basis of non-availability of sputum specimens, therefore a *high index of clinical suspicion is needed to initiate empiric therapy.*

Approach to diagnosis of MDR-TB in a child

1) Careful history
    - ***History of contact with MDR TB case is critical information***
    - Close contact with a patient who died from TB; failed TB

treatment or is a TB retreatment case.

2) Consider in child failing first line TB treatment despite adherence. Clinical examination
3) Investigations relevant for suspected PTB or EPTB- send samples for bacteriological confirmation through Xpert MTB/XDR and culture and DST if inconclusive on Xpert Ultra test.

4) HIV testing

- Failure to respond to TB treatment should consider HIV-related lung disease that is not TB as well as the possibility of MDR-TB.

Contact investigation and screening of child and adolescent contacts of infectious MDR/RR-TB source cases are essential for the rapid diagnosis of children with MDR/RR-TB disease and for prompt initiation of treatment.

Some Definitions in MDR TB in a child

Confirmed MDR TB- MDR-TB is isolated from a child with laboratory diagnosis (culture with DST or Xpert MTB/RIF)

Probable MDR TB – clinical features and/or radiology consistent with TB disease in a child who has been exposed to an adult with infectious MDR-TB

Possible MDR-TB – child is not improving after 2-3 months of first line treatment (with confirmation of treatment adherence and exclusion of likely diagnosis) OR Close contact with a patient who died from TB; failed TB treatment or is a TB retreatment case.

Disease severity in DR-TB in children (< 15 year)

Severe/advanced TB disease is usually defined by:

- The presence of cavities or bilateral disease on chest radiography. This highlights the importance of chest radiography as part of the

diagnostic work-up for patients, along with the usual patient–clinician interaction. Severe extra pulmonary TB is defined as the presence of miliary TB or TB meningitis.

Non severe TB disease:

- Peripheral nodes or isolated mediastinal mass without airway compression.
- Affects only one part of the lung without cavities.

5.2 Principles and regimen for MDR/RR-TB

(Sources: WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022 (3); WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2022)

- If a culture from the child or adolescent ultimately is positive for M. tuberculosis and demonstrates MDR/RR-TB, they should be treated according to the DST of their isolate.

- If a child or adolescent is started on treatment for clinically diagnosed MDR/RR-TB treatment and subsequently has a culture that shows drug-susceptible TB, their treatment can be switched to that for drug-susceptible TB; this is expected to be an uncommon occurrence.
- If a child or adolescent with clinically diagnosed MDR/RR-TB has a negative culture, the child should complete the originally prescribed course of second line treatment; they should not stop treatment or switch to drug-susceptible TB treatment.

- Diagnosing children with MDR-TB and designing an appropriate treatment regimen can be major challenge in the management of Pediatric MDR-TB.

- Current WHO guidelines recommend prioritizing the standardized shorter all-oral bedaquiline containing regimen for children with MDR/RR-TB.

- For people not eligible for this regimen, an individualized regimen composed of medicines in priority groupings A, B and C should be constructed.

5.3 Standardized shorter all-oral Bedaquiline-containing regimen for MDR/RR-TB

- May now be used in children of all ages under programmatic conditions. 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.
- The eligibility criteria for this regimen for children with confirmed MDR/RR-TB are the same as for adolescents and adults:
    i. no resistance to fluoroquinolones
    ii. no previous exposure for more than 1 month to second-line medicines used in this regimen (unless susceptibility to these second-line medicines has been confirmed);
    iii. no severe forms of EPTB (other than peripheral lymphadenopathy);
    iv. no extensive TB disease (presence of cavities or bilateral disease on CXR);
    v. Presence of mutations in both the inhA promoter region and the kat G gene, as determined by Xpert MTB/XDR in the child or adolescent or their most likely source case, as this suggests that isoniazid at high dose and thioamides are not effective.

- The standardized shorter all-oral bedaquiline-containing regimen is summarized as follows:

4–6 Bdq (6) – Lfx – Cfz – Z – E – Hh – Eto/5 Lfx – Cfz – Z – E

- In children on the standardized all-oral bedaquiline-containing regimen who can produce a specimen, if smear or culture is negative at 4 months the treatment can be changed to the continuation phase. If smear or culture is positive at 4 months, the initial phase should be extended until smear or culture converts (maximum duration 6 months).
- For children without bacteriological confirmation and those who cannot produce a specimen and who are clinically well, with improvement of clinical symptoms and weight gain, treatment can be changed to the continuation phase after 4 months (Bedaquiline to be continued to 6 months).
- Children who need an extension of the initial phase, who remain smear- or culture-positive, or who deteriorate further at 6 months should be switched to an individualized regimen. It is important to obtain follow-up specimens for culture and DST before changing treatment, but without waiting for these results. Results should be reviewed and treatment adjusted further as needed.
- The pill burden of this regimen is relatively high, especially in the first 4–6 months, which may be challenging for young children, even if dispersible formulations are used. Treatment support is important to support administration.
- Children with a diagnosis of rifampicin resistance only, without further DST (such as a child diagnosed with Xpert Ultra testing on a stool sample but no further DST on respiratory samples), can be treated with available Bedaquiline-containing regimens as suggested by the specialist treating clinician.

5.4. Individualized regimens for children with RR/MDR TB

(Who are not eligible for the standardized all-oral bedaquiline-containing regimen)

Children who are not eligible for the standardized all-oral Bedaquiline-containing regimen include:

i. Without bacteriological confirmation (e.g., with a clinical diagnosis)
ii. Without fluoroquinolone resistance ruled out (in their own specimens) or with drug-resistant EPTB other than peripheral lymphadenopathy
iii. With extensive pulmonary disease; or with prior exposure for more than 1 month to the medicines in the shorter regimen.

Individualized regimens should consist of at least four medicines to which the organism is likely to be susceptible. Most medicines will be used for the duration of treatment, but some may be used for shorter periods, such as bedaquiline (recommended for 6 months) or linezolid (for 2 months) often used for shorter durations because of its potential for severe adverse effects).

Children and adolescents with extensive forms of MDR/RR-TB may benefit from an additional fifth medicine at least at the beginning of treatment, with the duration depending on the extent of disease, response to treatment, number and efficacy of companion medicines in the regimen, and potential for adverse effects.

Key Points

The new recommendations expand the age indications for both Bedaquiline (as part of shorter and longer regimens) and Delamanid (as part of longer regimens) to children of all ages.

Group A and Group B medicines should be prioritized in the construction of the treatment regimen, as well as delamanid and other Group C medicines (Table below mentions all the group medicines, Group C ranks the relative balance of benefit and harm).

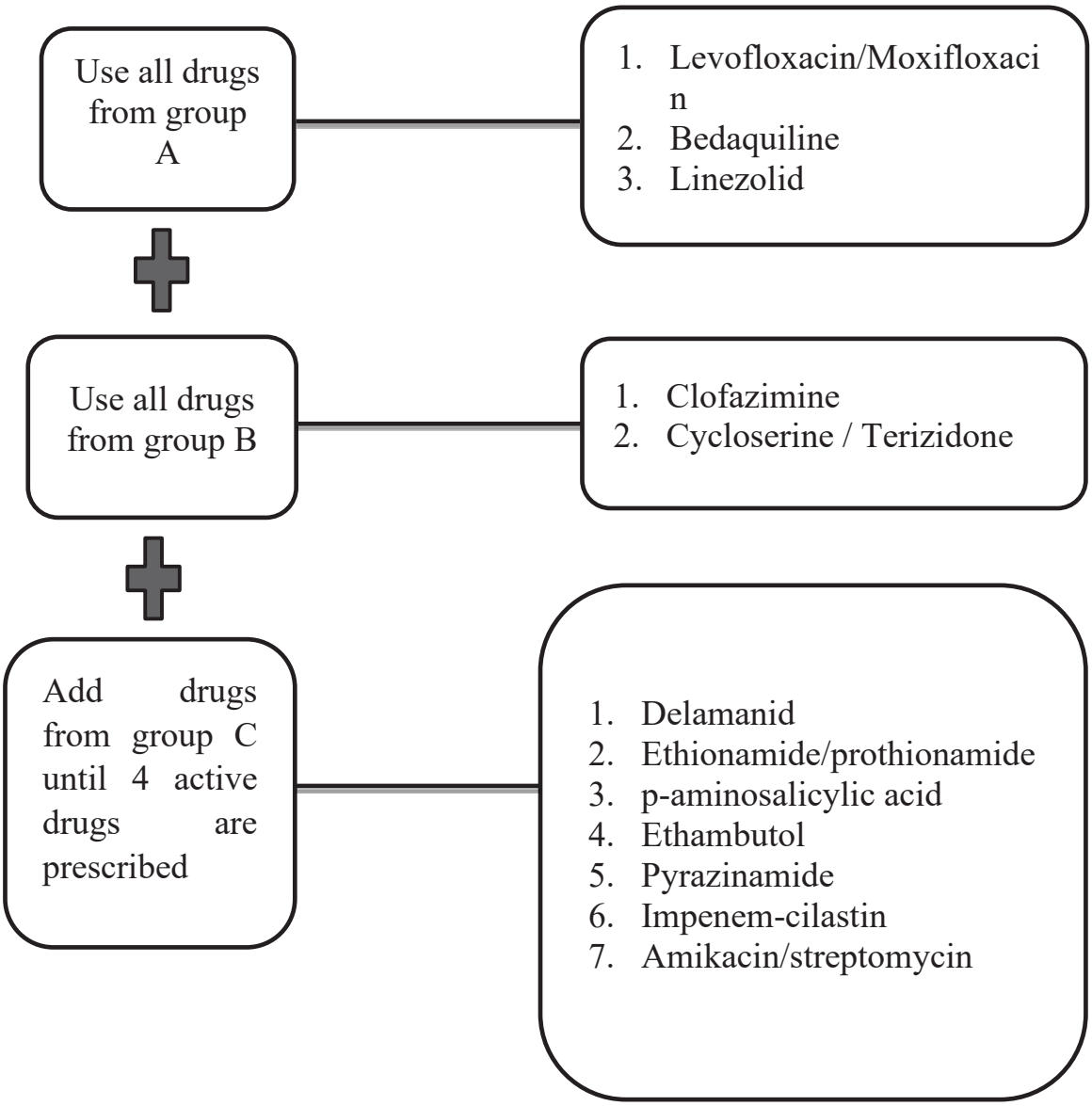


Figure 5.1 *Principles in the construction of an MDR-TB regimen for children*

*(**Lfx-** levofloxacin, **Lzd** – linezolid, **Cfz**-Clofazimine, **Cs**- Cycloserine, **Dlm** –Delamanid, **Bdq-** Bedaquiline, **PAS-** p-aminosalicylic acid, **Eto-** Ethionamide)*

5.5 The recommended duration for Individualized MDR/RR – TB regime in children

i. For non-severe MDR-TB - total duration is for 6- 9 months

ii. For Severe MDR-TB- total duration is for 9-12 months

Clinicians may also extend treatment in individuals with slow or inadequate clinical, radiological and/or microbiological treatment response or immunological compromise.

Table 1: Possible Individualized MDR/RR-TB treatment regimens for children of all ages and adolescents, by fluoroquinolone resistance and disease severity

Fluoroquinolone susceptibility	**Regimen**	**Additional medicines**
Fluoroquinolone-susceptible	Bdq–Lfx–Lzd–Cfz-(Cs)	Cs, Dlm, PAS, Eto b,c (E, Z) d
Fluoroquinolone-resistant	Bdq–Lzd–Cfz–Cs–(Dlm) e	Dlm e, PAS, Eto b,c (E, Z) e
Both Fluoroquinolone and bedaquiline (±clofazimine)-resistant	Lzd–Cs–Dlm e –E–Z d	Mpm/Clav, Eto b c, PAS c

a Medicines in parentheses in this column are suggestions for a fifth medicine when there is severe disease.

b Use ethionamide only if the child or source case does not have a known or suspected inhA mutation.

c P-aminosalicylic acid and ethionamide showed effectiveness only in regimens without bedaquiline, linezolid, clofazimine or delamanid, and are proposed only when other options to compose a regimen are not possible.

d Ethambutol and pyrazinamide should be considered if there is evidence of susceptibility and a regimen with sufficient medicines cannot be composed.

e When administering delamanid and cycloserine concurrently, monitoring for neuropsychiatric side-effects is important.

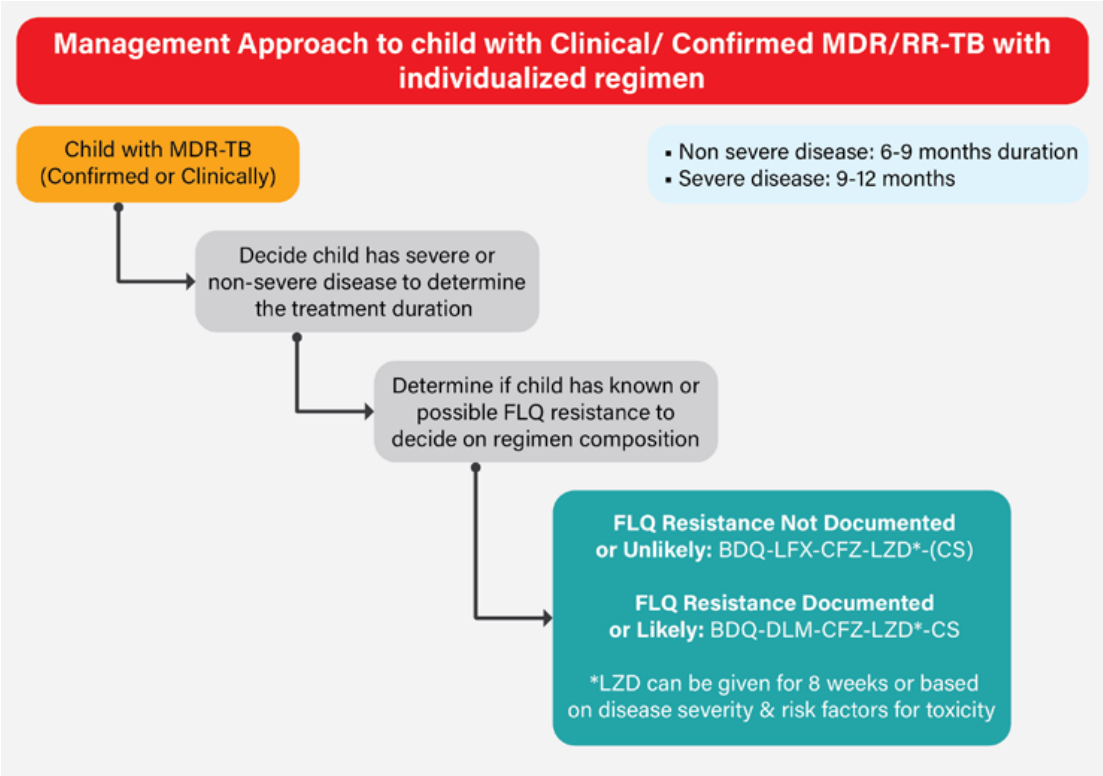


Figure 5.2. Management Approach to child with Clinical/ Confirmed MDR/RR-TB with individualized regimen

Table 5.1 Weight band dosing of 2nd line ATT drugs in children (<15 years old)

Drugs	Formulation	Weight bands							
		3-<5kg	**5-6kg**	**7-9kg**	**10-15kg**	**16-23kg**	**24-30kg**	**31-34kg**	**>34Kg**
Levofloxacin	100mg dt (100 mg in 10 mL = 10 mg/mL)	5 mL (0.5 dt)	1	1.5	2 or 3	3 or 4	-	-	-
	250mg tab	2 mL	0.5	0.5	1 or 1.5	1.5 or 2	2	3	Adult doses
Moxifloxacin	100mg dt	0.4	0.8	1.5	2	3	4	4	Adult dose (max 400mg)
	400mg tab							Adult dose (max 400mg)	
	100mg tab	-	-	-	-	2 tabs OD for 2 weeks then 1 tab OD M/W/F for 22 weeks.		4 tabs OD for 2 weeks then 2 tabs OD M/W/F for 22 weeks.	

	Bedaquiline	20mg dt	0 to <3 months: 1.5 od for 2 weeks; then 0.5 od M/W/F for 22 weeks ≥ 3 months: 3 od for 2 weeks; then 1 od M/W/F for 22 weeks		0 to <3 months: 1.5 od for 2 weeks; then 0.5 od M/W/F for 22 weeks 3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F for 22 weeks ≥ 6 months: 4 od for 2 weeks; then 2 od M/W/F for 22 weeks	3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F for 22 weeks ≥ 6 months: 6 od for 2 weeks; then 3 od M/W/F for 22 weeks	10 dts OD for 2 weeks then 5 dts OD M/W/F for 22 weeks.		20 dts OD for 2 weeks then 10 dts OD M/W/F for 22 weeks.	
	Linezolid	20mg/ml susp	2ml	4ml	6ml	8ml	11ml	14ml	15ml	20ml
		600mg tab (dissolve in 10ml water)		0.25ml	0.25ml	0.25ml	0.5ml	0.5ml	0.5ml	0.75ml
	Drugs	**Formulation**	**3-<5kg**	**5-6kg**	**7-9kg**	**10-15kg**	**16-23kg**	**24-30kg**	**31-34kg**	**>34kg**
		50mg cap/tab			1 alt days	1 alt days	1	2	2	

		1 twice wkly	1 alt days						Adult dose (max 100mg)
Clofazimine	100mg cap/tab		M/W/F	M/W/F	1 alt days	1 alt days	1	1	Adult dose (max 100mg)
Cylcoserine	125mg minicapsule	2ml	1	1	2	3	4	4	Adult dose (max 1g)
	250mg cap (dissolve in 10ml water)	1ml	4ml	5-6ml	7-10ml	2 caps	2 caps	2 caps	Adult dose (max 1g)
Ethambutol	100mg dt (dissolve in 10ml water)	5 mL (0.5 dt)	1	2	3	4	-	-	
	400mg tab (dissolve in 10ml water)		3ml	4ml	6ml	1 tab	1 or 1.5 tab	2	Adult dose
Delamanid	25mg (pediatric formulation)	<3 months: 1 od	<3 months: 1 od ≥ 3 months: 1 bd		1 bd	2 morning 1 evening	2 bd	2 bd	2 bd
	50mg tablet (50 mg in 10		<3 months: 5 mL (0.5 tab)			10 mL (1 tab)	1 bd	1 bd	1 bd

	mL = 5 mg/mL	5 mL (0.5 tab) od	od c ≥ 3 months: 5 mL (0.5 tab) bd		5 mL (0.5 tab) bd	morning 5 mL (0.5 tab) evening			
Pyrazinamide	150mg dt (150 mg in 10 mL = 15 mg/mL)	5 mL (0.5 dt)	1	2	3	4 or 5	-	-	
	400mg tab (400 mg in 10 mL = 40 mg/mL)	2.5 mL	5 mL (0.5 tab)	7.5 mL (0.75 tab)	1	2	2.5	3	4
	500mg tab (500 mg in 10 mL = 50 mg/mL)	2 mL	5 mL (0.5 tab)	6 mL (0.5 tab)	1	1.5	2	2.5	3
	Formulation	**3-<5kg**	**5-6kg**	**7-9kg**	**10-15kg**	**16-23kg**	**24-30kg**	**31-34kg**	**>34kg**
Ethionamide or Prothionamide	125mg dt (125 mg in 10 mL = 12.5 mg/mL)	3 mL	7 mL	1	2	3	4	4	1g
	250mg tab (250 mg in 10 mL = 25 mg/mL)	-	3 mL	5 mL (0.5 tab)	1	2	2	2	1g

P-aminosalicylic acid	PAS sodium salt 60% w/w (9.2 g equivalent to 4 g PAS acid) sachet	0.3 g bd	0.75g BD	1 gm BD	2g BD	3g BD	3.5g BD	4g BD	4g BD
Isoniazid	100mg (100 mg in 10 mL = 10 mg/mL)	5 mL (0.5 dt)	1	1.5	2	3	4	4	4.5
Clavulanic acid Only to be used with carbapenems	62.5mg clavulanic acid as amoxicillin/Clavulanate, 250mg/62.5mg Powder for solution, 5 ml	1.5 ml tid	2ml tid	3ml tid	5ml tid	8ml BD	10ml BD	(For children and adolescents weighing ≥30 kg, the 500 mg/125 mg amoxicillin/clavulanate tablet can be used)	

Table 5.2 Weight based daily dosing of 2nd line ATT drugs in children

Drugs	Dosing
Levofloxacin	15-20mg/kg/day
Moxifloxacin	10-15mg/kg/day
Linezolid	<16kg: 15mg/kg once daily >16kg: 10-12mg/kg/day
Bedaquiline	First 14 days, 6mg/kg/day then 3-4mg/kg thrice weekly
Clofazimine (gelcap)	2-5mg/kg/day
Cycloserine (cap)	15-20mg/kg/day
Delamanid	3-4mg/kg/day
Ethambutol	15-25mg/kg/day
Pyrazinamide	30-40mg/kg/day
Ethionamide	15-20mg/kg/day
PAS (Para-aminosalicylic acid)	200mg/kg/day
Meropenem	20-40mg/kg IV every 8 hourly
Amikacin	15-20mg/kg once daily
Isoniazid	15-20mg/kg

Regimen for Rifampicin Susceptible and Isoniazid Resistant TB

In patients with confirmed rifampicin-susceptible, isoniazid resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months and it is not recommended to add streptomycin or other injectable agents to the treatment regimen.

The recommendations apply to both adults and children, including people living with HIV (PLHIV).

The basic regimen can be summarized as:

Hr-TB regimen: 6(H)REZ-Lfx

5.6 Monitoring and Follow-up

Monitoring is needed to evaluate therapeutic efficacy, adherence as well as to anticipate the development of adverse events. Routine safety monitoring of treatment should generally follow the recommended approach in adults and should be guided by the known adverse effect profile of the medicines included in the regimen.
Another challenge is maintaining the patient on therapy for 9-18 months and making sure that heath workers closely follow up him or her. Children have been successfully treated for MDR-TB but only with appropriate monitoring and follow up. Counselling tools and a family-centred approach to the treatment and prevention of DR-TB in children and adolescents needs to be looked into.

In children, smear and culture monitoring of the response to treatment may be challenging, for the same reasons it is difficult to obtain a bacteriological confirmation of the diagnosis. In children with a bacteriologically confirmed diagnosis, all reasonable efforts should be taken to demonstrate bacteriological conversion. Once cultures have become negative or in children who never had a confirmed diagnosis, repeated respiratory sampling may not be useful if the child is otherwise responding well clinically. Resolution of clinical symptoms and weight gain can be used as indicators of improvement. All children should have regular clinical follow-up, including weight and height monitoring. Drug dosages should be adjusted with weight gain, as needed.

Table 5.3 Suggested monitoring test of second line medications

Medication	Monitoring test	Comments
Amikacin	Electrolytes, Renal function test, Hearing	Formal hearing tests like pure tone audiometry and otoacoustic emissions

Bedaquiline	Electrolytes, liver function, QTc interval	
Clofazimine	Electrolytes, liver function, QTc interval	Patients and families should be counseled about skin color changes, since it can be distressing and/or lead to inadvertent disclosure.
Delamanid	Electrolytes, liver function, QTc interval	
Ethambutol	Color vision, visual acuity	
Ethionamide/ prothionamide	Liver function, TFT	
Isoniazid	Liver function, peripheral neuropathy	Should be administered with vitamin B6
Levofloxacin	Electrolytes, QTc interval	Less likely to cause QTc prolongation than moxifloxacin
Linezolid	Color vision, visual acuity, complete blood count, peripheral neuropathy	
PAS	Electrolytes, Liver function, Thyroid function	
Pyrazinamide	Liver function	
Pretomanid	Peripheral neuropathy Acne Anaemia Nausea and vomiting Headache Liver dysfunction Rash Pruritus	

	Gastrointestinal intolerance	

Table 5.4 Treatment monitoring schedule

All children	Baseline	Month										Ongoing
		1	2	3	4	5	6	9	12	15	18	
HIV status	✓											
Toxicity (*symptoms/signs*)	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Growth assessment (*Wt. &Ht.*)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hearing assessment (*Audiology*)	✓	✓	✓	✓	✓	✓	✓					
Vision assessment (*acuity and color vision if on ethambutol*)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CBC (*if on linezolid or HIV infected*)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
LFT (*AST, ALT and total bilirubin*)	✓			✓			✓	✓	✓	✓	✓	
TSH, T4, T3 (*if on ethionamide, prothionamide or PAS*)	✓			✓			✓	✓	✓	✓	✓	✓
CXR (*if any pulmonary involvement*)	✓			✓			✓					

* TB culture and DST (*if initial sputum/gastric aspirate smear or culture positive*)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
ECG (*assess QTc interval if on bedaquiline, delamanid, clofazimine or moxifloxacin*)	✓	✓	✓	✓	✓	✓	✓					
If HIV infected children:												
1. Cholesterol	✓						✓					
2. CD4 count and viral load	✓						✓					
Psychosocial counseling and adherence support	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

* Monthly stool or sputum if old enough to expectorate; if unable to expectorate and initially smear or culture positive, monthly until culture converted then every 3 monthly. If initially smear and culture negative perform if clinically indicated. DST should only be done on specimens that are positive after a negative culture has been documented.

Key messages for DR TB

- Actively screen all children and adolescents exposed to MDR/RR-TB for TB symptoms (including siblings of children diagnosed with MDR/RR-TB).
- Obtain specimens for molecular testing, mycobacterial culture and first- and second-line DST for all children and adolescents with presumed MDR/RR-TB whenever feasible.
- Offer (empirical) second-line treatment to all children with clinically diagnosed MDR/RR-TB while awaiting bacteriological confirmation, with the regimen based on DST and risk factors of the most likely source case. If cultures are eventually negative, continue on the MDR/ RR-TB regimen based on the DST results of the source case.
- Offer the standardized shorter all-oral bedaquiline-containing regimen or an individualized regimen following the principles described in this section.
- Use child-friendly formulations of second-line medicines whenever possible.
- Do not use injectable agents in children and adolescents unless an effective regimen cannot be constructed with sufficient oral medicines as a last resort.
- Obtain baseline weight and height in all children with MDR/RR-TB and measure weight regularly throughout treatment. This will form the basis for dose adjustments of the TB medicines for weight, and allow following of weight gain, an important indicator of clinical response.
- Regularly assess the clinical, radiological and microbiological (if relevant) response to treatment.
- Avoid unnecessary hospitalization of children and adolescents with MDR/RR-TB and implement evidence-based infection prevention and control measures when needed.
- Minimize disruption of education by allowing children and adolescents with MDR/RR-TB to go back to school as soon as possible if clinically feasible and no longer infectious.
- Carefully monitor for adverse events and adherence at every visit.
- Offer additional age-appropriate social support for children and adolescents and their families throughout screening, diagnosis, treatment initiation and follow-up.

CHAPTER 6
TB-HIV CO-INFECTION IN CHILDREN

Tuberculosis is the most common opportunistic infection and leading cause of mortality in people living with the human immunodeficiency virus (PLHIV) contributing to at least one in four of these deaths. Children in particular, living with HIV infection have increased risk of TB exposure, infection, progression to disease, and TB related morbidity and mortality. The risk is influenced by the degree of immune maturity and immunosuppression.

HIV-infected children may develop multiple episodes of TB and a previous TB episode disease does not exclude future TB.

6.1 Diagnosing TB in HIV-infected Children

There is a dual risk that TB may either be over-diagnosed, resulting in unnecessary TB treatment or under diagnosed resulting in increased morbidity and mortality because of complexity and more challenging in the diagnosis of TB disease in HIV-infected children. This is due to the following reasons:

- The clinical presentations and radiological findings of TB and other HIV related lung diseases in children living with HIV are often similar and confusing, hence lacks specificity for diagnosis of TB, e.g., Lymphocytic interstitial pneumonia may look similar to miliary TB.

- TST is frequently negative even though child may be infected with TB or has TB disease. **Hence induration of > 5mm is considered positive in HIV infected child.**

The pulmonary diseases in the HIV infected condition are much broader which includes, bacterial or viral pneumonia, fungal infections, Pneumocystis jiroveci pneumonia, pulmonary lymphoma and Kaposi's sarcoma. Therefore, smear microscopy and culture for AFB in sputum or in gastric aspirate and Xpert MTB/RIF testing should be done in any TB suspect in children living with HIV.

6.2 Treatment of TB in HIV Infected Children

In a TB/HIV co infection, the priority is to treat TB first to prevent immune reconstitution syndrome (IRIS), there for TB treatment should be commenced first. WHO recommendations (2021) suggest that ART should be initiated in all adolescents and children living with HIV, regardless of WHO clinical stage and CD4 cell count. Rapid initiation of ART (within 7 days from the day of HIV diagnosis) should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment. Children and adolescents with advanced HIV disease should be given priority for assessment and initiation. Initiation of ART should be offered on the same day to people living with HIV who are ready to start.

Antiretroviral therapy should be started as soon as possible within 2 weeks of initiating TB treatment, regardless of CD4 count, among adolescents and children living with HIV (except when signs and symptoms of meningitis are present)

- Antiretroviral therapy should be delayed at least 4 weeks (and initiated within 8 weeks) after treatment for TB meningitis is initiated.
- Corticosteroids therapy with dexamethasone or prednisolone (tapered over 6–8 weeks) should be considered adjuvant treatment for TB meningitis.

2weeks later. If patients with HIV who are already on ART get TB,

continue ART and start anti-TB treatment at the earliest.

Clinicians to consider treating children and adolescents living with HIV with non-severe TB for 4 months, depending on the degree of immunosuppression, ART status and presence of other opportunistic infections. These children and adolescents will need to be monitored closely, especially at 4 months of treatment, and treatment extended to 6 months if there is insufficient progress.

Choice of antiretroviral therapy regimen

WHO consolidated guidelines (2021) on HIV prevention, testing, treatment, service delivery and monitoring provide recommendations based on rapidly evolving evidence of safety and efficacy and programmatic experience using DTG and low-dose EFV in pregnant women and people (including children and adolescents) with TB/HIV co-infection. Dispersible 10 mg formulation of DTG is approved for use among children aged over 4 weeks and weighing more than 3 kg. If DTG is not available, the preferred first-line ART regimen is a LPV/r-based regimen. RAL should be used only under special circumstances, such as in neonates. RAL is considered an effective option and is approved for use from birth (with dose adjustments during TB treatment). RAL should be substituted with DTG as soon as it is available from 4 weeks of life.

DTG in combination with a NRTI backbone is recommended as the preferred first-line regimen for adolescents living with HIV and for infants and children with approved DTG dosing who are starting ART. EFV at low dose (400 mg) in combination with a NRTI backbone is recommended as the alternative first-line regimen for adolescents living with HIV starting ART. EFV 400 mg can be co-administered with rifampicin-containing TB treatment, with co-administration well tolerated and plasma concentrations maintained above the levels considered to be effective.

Additional therapy recommended for HIV-infected children with TB, which may help to improve TB treatment outcome is **co-trimoxazole preventative therapy (CPT)** and **pyridoxine supplementation** along with nutritional support and the early start of HAART.

CPT is started at 6 weeks of age in HIV exposed uninfected infants until the risk of HIV infection is excluded. In children with HIV infection CPT is continued till 5 years of age and thereafter may be discontinued who are clinically stable with evidence of viral load suppression on ART.

Recommended Cotrimoxazole prophylaxis

Age	**Recommended daily Co-trimoxazole prophylaxis once daily**
< 6 months of age	20 mg Trimethoprim (TMP) + 100 mg Sulfamethoxazole (SMX)/ 2.5 ml
6 months- 5 years of age	40 mg TMP + 200 mg SMX/ 5 ml
≥ 5 years of age	80 mg TMP + 400 mg SMX/ 1 tab or 10 ml

The approach to designing MDR/RR-TB treatment regimens is largely the same for all children and adolescents, regardless of HIV status, although potential drug–drug interactions should be avoided through the careful selection of TB medicines in the regimen.

The most important clinically significant drug–drug interaction with ART that must be considered is for bedaquiline. ART regimens

including integrase inhibitors such as DTG are the best option for children living with HIV receiving bedaquiline, as clinically significant drug–drug interactions are not expected. ART regimens that contain EFV should be avoided in children and adolescents while they are on bedaquiline, as EFV substantially lowers the concentrations of bedaquiline. Other options for children living with HIV on ART receiving bedaquiline are:

- LPV/r – co-treatment with LPV/r may result in elevated bedaquiline exposures, but experience has not shown this to result in an increase in adverse effects, so this may be considered with careful monitoring.
- NVP – the reduced efficacy of NVP-containing regimens means this is not an ideal choice when other options are available and as, indicated above, substitution with EFV is not an option.

6.3 Neonatal TB

A neonate born to a mother who is diagnosed as TB in the last two months of pregnancy or who has no documented sputum smear conversion needs to be carefully managed. About 50% of children born to mothers with active pulmonary tuberculosis develop the disease during the first year of life if chemoprophylaxis or BCG vaccine is not given.

Newborns may acquire tuberculosis by the following means:

i. Trans-placental spread through the umbilical vein to the fetal liver
ii. Aspiration or ingestion of infected amniotic fluid
iii. Airborne inoculation from the close contacts in the household

Definitions:

Congenital TB – Tuberculosis acquired in utero through hematogenous spread via umbilical vessels or at the time of delivery through aspiration or ingestion of infected amniotic fluid or cervico-

vaginal secretions. It usually presents in the first 3 weeks of life and the mortality and morbidity is high approaching more than 50%.

Neonatal TB – Tuberculosis acquired after birth through exposure to an infectious case of TB-usually the mother but sometimes another close contact in the household. Exposed neonate may or may not be symptomatic. It is often difficult to differentiate between congenital and neonatal TB but the management in both the types of TB in neonate is same.

Therefore, all newborns that were exposed to tuberculosis during the last two months of pregnancy should be screened for active TB. Pulmonary and particularly extrapulmonary tuberculosis other than lymphadenitis in pregnant women is associated with vertical transmission of TB in the fetus. The clinical features in newborn exposed to TB may be present at birth but more commonly begin by 2nd or 3rd week of life.

6.3.1 Risk factors for neonatal TB

The following factors possess high risk of transmission of TB bacilli from mother/ close contact to the newborns:

- Mother with pulmonary (irrespective of sputum smear positivity) or extrapulmonary TB (except TB lymphadenitis or Pleural TB) during pregnancy
- Mother has received ATT < 2 weeks before delivery
- No documented sputum conversion in last 2 months of pregnancy or at delivery
- Close post-natal contact apart from mother, with sputum positive.

6.3.2 Clinical presentation of TB in neonate

Neonates infected with TB presents with **nonspecific symptoms** like feeding problems or poor weight gain fever, breathing difficulty,

jaundice, and abdominal distension either due to ascites or organomegaly. They may present at birth **but commonly presents in first 3 weeks of life.**

6.3.3 Recommended screening tests for TB in newborn born to mother with TB

The following investigations are recommended for screening of TB in newborn if baby has any above risk factors (*as described above in Chapter 3).*

6.3.4 Treatment of neonatal TB

The treatment regime with anti-tubercular agents of neonatal TB, either congenitally or post-natally acquired is the same.

If TB is confirmed with above investigations or neonate is clinically suspicious (symptomatic with confirmed TB in mother or close contact), a complete course of TB treatment with ATT must be given. TB meningitis should be ruled out by doing CSF analysis, if one of the above investigations is positive.

- **Standard treatment regimen**: 2HRZE/ 4HR
- **TB meningitis treatment regimen**: 2HRZE followed by 7 to 10 months of HR. Along with steroid at 2mg/kg/day for 4 weeks and taper over 2 weeks.
- **Neonatal MDR-TB**: same as in children MDR regime (< 3years age) depending on the disease severity

6.3.5 Breast Feeding

Breast milk is not contraindicated in all circumstances of TB exposure in newborns. **WHO recommends to breast milk feeding to all the neonates irrespective of tuberculosis status in mother.** However, TB infection control practices must be adhered to all the times, by letting mother use facemask with normal surgical mask, cough etiquette and

hand hygiene. 3HR therapy for newborns has shown effective in other SAARC countries that separation of the mother and infant is no longer considered mandatory. Separation should occur only if the mother is ill enough to require hospitalization, has been or is expected to become non-adherent to treatment, or has suspected drug-resistant tuberculosis. Once the mother and child are taking adequate therapy, it is usually safe for the mother to breastfeed, because the medications, although found in milk, are present in low concentrations.

Infant formula feeding is kept as an alternative to breastfeeding if mother is too sick enough to breastfeed directly/expressed or there is not enough breast milk production. The infant formula should be available free of charge for the patient, especially in resource-poor settings. Since the formula milk is already available through the HIV Programme, however concerned hospital administration should provide formula milk from the regular patient diet budget. In Bhutan, the number of such mothers is expected to be few and hence there appears to be no problem in following this recommendation.

6.3.6 Tuberculosis Preventive Treatment (TPT) for newborn.

- If a newborn is asymptomatic and screening tests are negative for active TB disease but with history of close contact with TB, we should start on **3HR* preventive therapy along with pyridoxine for 3 months** and *delay BCG vaccination until TPT is complete*.

  Dose of Isoniazid: 10mg/kg/day

  Dose of Rifampicin: 15mg/kg/day

  Pyridoxine: 1mg/kg/day

- **If baby is HIV exposed (mother is HIV infected) and on Nevirapine, start on INH prophylaxis for 6 months instead of 3HR*.**

- **If mother/contact has drug resistant TB,** Start on Levofloxacin (15-20mg/kg/day OD) for 6 months.
    - Ensure close monthly clinical follow up.

Key point: preferred TB preventive treatment options

3HR* is a preferred TPT option among HIV-negative children since child-friendly dispersible FDCs are widely available and already used for TB treatment, while awaiting data on dosages across all age groups and child-friendly formulations for rifapentine-based regimens.

For children living with HIV, 6H remains the preferred option until further data are available.

* - 3HR: 3 months of daily isoniazid and rifampicin

6.3.7 BCG vaccination

BCG vaccine should not give to neonates exposed to tuberculosis at birth while screening for active TB diseases since it is a live attenuated vaccine, which is affected by the use of TB drugs including INH.

WHO recommends BCG vaccination **only after 2 weeks of completion of TB- disease treatment or 3 or 6 months of TPT**

6.3.8 Follow-up

Clinical follow up of a neonate on TPT is mandatory at 2 weeks, 6 weeks and then monthly till completion of treatment or prophylaxis to assess for development of any symptoms of active TB disease and also for treatment compliance.

CHAPTER 7
PREVENTION OF TUBERCULOSIS

The following methods will help to interrupt the chain of transmission of childhood TB disease:

i. BCG vaccination
ii. Identification of infectious cases
iii. Successfully complete treatment of TB Patients
iv. Infection control
v. Contact tracing
vi. Prophylaxis therapy for latent TB infection
vii. Community participation and ownership
viii. Socio-economic findings

In this section, we will discuss on BCG vaccination, contact tracing, prophylactic therapy for latent TB infection and infection control.

7.1 BCG Vaccination

Bacilli calmette –Guerin (BCG) is a live attenuated vaccine derived from Mycobacterium bovis that was originally isolated in 1902 from a tuberculous cow. BCG has demonstrated significant effectiveness, but protection has not been consistent against all forms of TB in all age groups. BCG has also shown effectiveness in preventing leprosy (caused by Mycobacterium leprae) and Buruli ulcer (caused by Mycobacterium ulcerans). BCG provides good (up to 90%) protection against severe forms of TB, including TBM and miliary TB, if given during the neonatal period. Although neonatal vaccination also provides protection against PTB in children, it mainly prevents progression to disseminated forms of TB.

Neonatal BCG immunization is used widely in developing countries where TB is endemic. It is used as a part of national immunization

program. The main proven benefit of neonatal BCG is protection against severe disseminated forms of TB rather than pulmonary TB in children. However, its efficacy is variable against and its protection wanes to zero after 20 years.

7.2 Contact Tracing

Contact investigation helps to identify people with undiagnosed TB, thus reducing treatment delays and onward transmission. It is also key to preventing TB by improving access to TPT for child, adolescent and adult contacts.

This strategy is to trace all individuals in contact with a case of suspected or confirmed pulmonary TB and screened them for TB infection or disease. Through contact screening, a TB case could be identified early and treated, thereby reducing not only the risk of developing serious disease but also preventing transmission. Young children (< 5 years) are immune-immature and if they are in close/household contact with a sputum-positive case, the chance of getting the disease is very high (5-50%)

Key steps in contact investigation

The following steps in contact investigation are important:

- Review available information on the index patient & assess the duration and degree of infectiousness to identify contacts.
- Counsel the index patient and enumerate household and close contacts & develop a plan.
- Conduct home visits for screening for contacts.
- Conduct a clinical assessment of contacts and refer for testing for TB infection or TB disease, and for HIV testing as appropriate.
- Provide treatment for TB disease or TPT as per eligibility, and provide ongoing support until treatment completion.
- Review the completeness of the contact investigation and attempt to follow up on missing contacts and complete missing information.
- Ensure systematic recording and reporting of the whole contact investigation process.

Reverse Contact Tracing

This is adopted when a child is the index case with active TB disease. The potential source case usually adults in the household is sought by symptom screening and/or chest radiograph. Chest radiographs of adults particularly close contacts may highlight the presence of previously undiagnosed TB disease.

7.3 TB infection

TB infection (previously called latent TB infection) is defined as a "state of persistent immune response to stimulation by M. tuberculosis

antigens without evidence of TB disease TB infection (TBI) is defined as the infection with *M. tuberculosis* without evidence of active TB disease. **A person with TBI has a positive TST without signs/symptoms and without evidence of active TB on chest radiograph.** Such cases should be treated with isoniazid monotherapy or combination of isoniazid and rifampicin (refer below in the treatment option).

Investigations for TBI

TST and IGRA provide a marker of TB infection but may be influenced by mechanisms unrelated to TB infection and give false-negative or false-positive results. Newer Mtb antigen-based skin tests (TBST) have been developed to measure the cell-mediated immunological response to Mtb specific antigens. Evidence suggests that these tests may offer similar specificity to IGRA, and when compared with TST they may provide more reliable results in children and in people living with HIV. The TBST class is defined as skin tests for the detection of TB infection that use Mtb specific antigens.

TST has been recommended in resource constraints settings like our country. The interpretation of TST result is given in page no. 20.

WHO recommends that testing for TB infection should not be a requirement for initiating TPT among people living with HIV and child contacts aged under 5 years, particularly in countries with a high TB incidence, given that the benefits of TPT (even without testing) clearly outweigh the risks.

7.4 TB Preventive Treatment (TPT) & Treatment for TBI

The preventive therapy is only given to the most vulnerable children (those at highest risk to develop TB disease in the near future) following documented TB exposure and/or infection, after active disease has been ruled out.

The following target groups should be considered for TPT among

children and adolescents:

- Infants, children and adolescents living with HIV: Infants aged under 12 months living with HIV who are in contact with a person with TB and who are unlikely to have TB disease on an appropriate clinical evaluation or according to national guidelines should receive TPT
- Children aged 12 months and over living with HIV who are considered unlikely to have TB disease on an appropriate clinical evaluation or according to national guidelines should be offered TPT as part of a comprehensive package of HIV prevention and care.
- Children aged under 5 years, over 5 years and adolescents who are household contacts of people with bacteriologically confirmed PTB and who are found not to have TB disease on an appropriate clinical evaluation or according to national guidelines should be given TPT, even if TB infection testing is unavailable
- In selected high-risk household contacts of people with MDR-TB, TPT may be considered based on individualized risk assessment and a sound clinical justification (conditional recommendation, very low certainty in the estimates of effect).

7.5 Recommended drug regime options for TPT in different situations in children

The following options for TPT are recommended by WHO for use in children and adolescents:

- 6 months of isoniazid daily (6H) (all ages); or
- 3 months of isoniazid plus rifampicin daily (3HR) (all ages); or
- 3 months of isoniazid plus rifapentine weekly (3HP**) (age 2 years and over); or
- 1 month of daily isoniazid plus rifapentine (1HP) (aged 13 years and over) may be offered as alternative regimen.

***3HP (Isoniazid and Rifapentin) is the preferred option when data on safety, tolerability and dosage are available across all age group and child friendly FDC formulations become available. Children weighing > 30kg or >14 years old, may receive 3HP as for adults using adult FDC (HP-300mg/300mg).*

Currently in the country, children contact with DS-TB, the recommended drug regime for TB preventive therapy and TBI are 3 months of dispersible FDC formulation isoniazid and rifampicin (3HR) or 6 months of isoniazid monotherapy (6H) depending on the following situation as below:

Table 7.1 Children <25 kg – 3HR (Pediatric 2-FDC) *(doses as below)*

Weight (Kg)	H50 R75 (3HR)
4-7	1
8-11	2
12-15	3
16-24	4

Table 7.2 Older Children (>25kg) – 3HR (adult 2-FDCs) (*doses as below)*

Weight (Kg)	H75 R150 (3HR)
≥ 25kg	1
26-34 kg	2
35-54 kg	3
> 55kg	4

All HIV infected children

- **3RH** is recommended for children and adolescents *not on NVP/PI based ART.*

- **6H** for children *on (NVP/PI) based ART regimen* (at 7-15mg/kg/day OD monotherapy).

1. **If children contact with DR-TB**: close follow up and consider starting on Levofloxacin (15-20mg/kg/day OD) for 6 months. If levofloxacin 100mg dispersible tablet is not available, the 250mg tablet can be used as given below.

Table 7.3 Children Contact with DR-TB (*doses as below)*

Weight bands in children	**Levofloxacin 250 mg (tab)**	**Levofloxacin 100mg (Dispersible, dt)**
5-6 kg	0.5 tablet/ day	1tablet/day
7-9 kg	0.5 tablet/ day	1.5 tablets/day
10-15 kg	1-1.5 tablet/ day	2 or 3 tablets/day
16-23 kg	1.5-2 tablets/ day	3 or 4 tablets/day
24-30 kg	2 tablets/day	Follow >14 years schedule
31-34 kg	3 tablets/day	
>34 kg	Follow adult schedule (up to 1.5 g/day)	

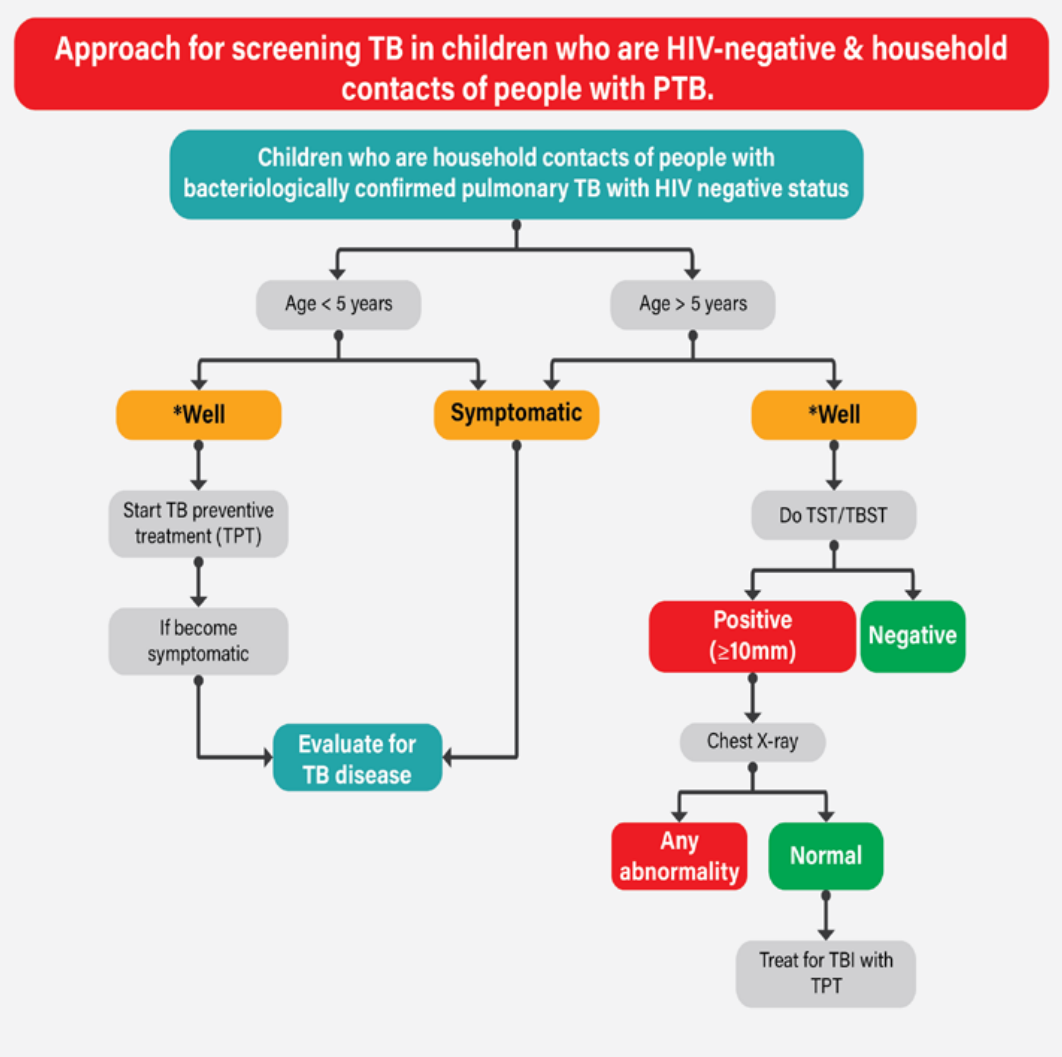


Figure 7.1 *Approach for screening TB in children who are HIV-negative & household contacts of people with PTB.*

* Child who are free from **any 4 cardinal symptoms** (below)are considered well:

1) Unremitting fever ≥2weeks
2) Persistent cough ≥ 2weeks
3) Documented weight loss (>5% from last weight) or weight for age > -3SD or flattering weight curve for last 3 months
4) Fatigue /Reduced activities/ loss of appetite

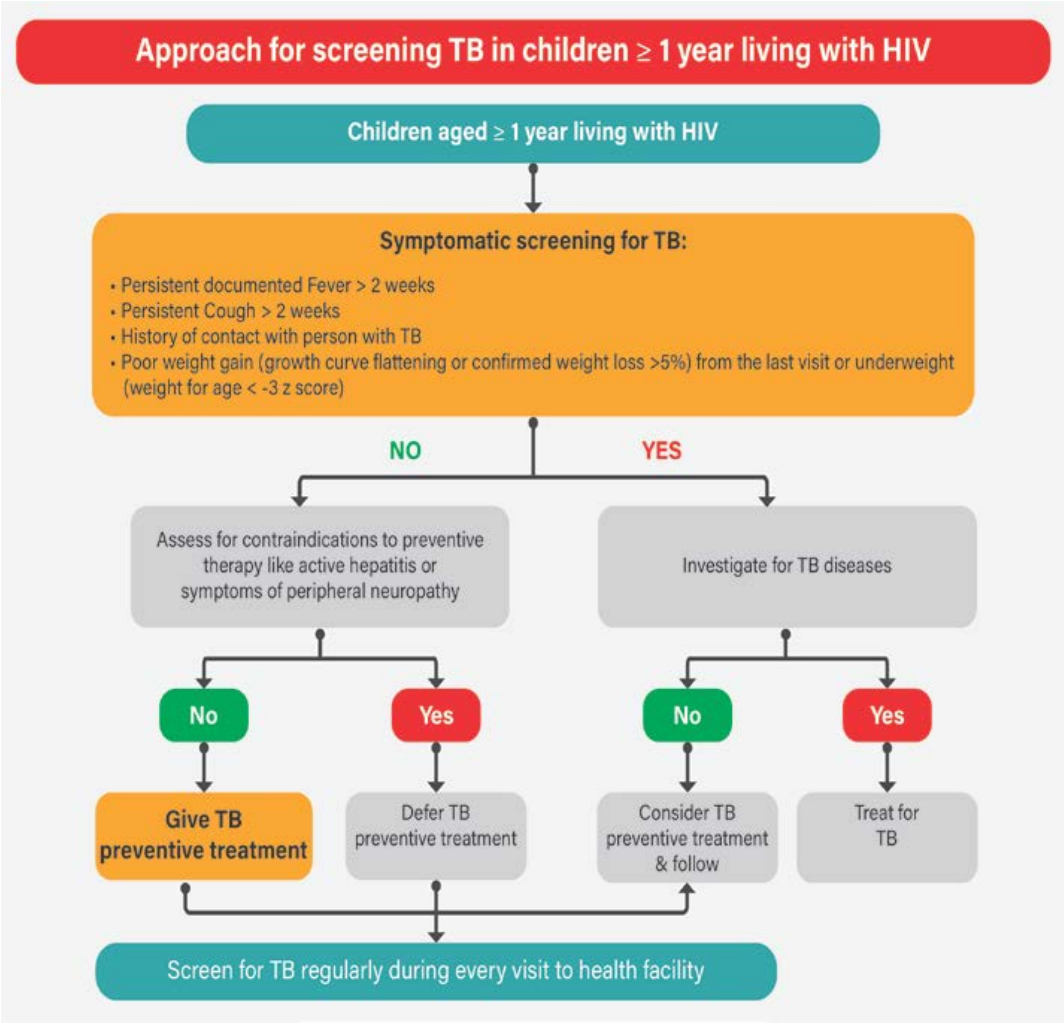


Figure 7.2 *Approach for screening TB in children ≥ 1 year living with HIV*

**All infants <1 year of age born to HIV infected mother should be given TPT only if they have a history of contact with TB case and active TB has been excluded in investigations (CXR and Xpert Ultra)*

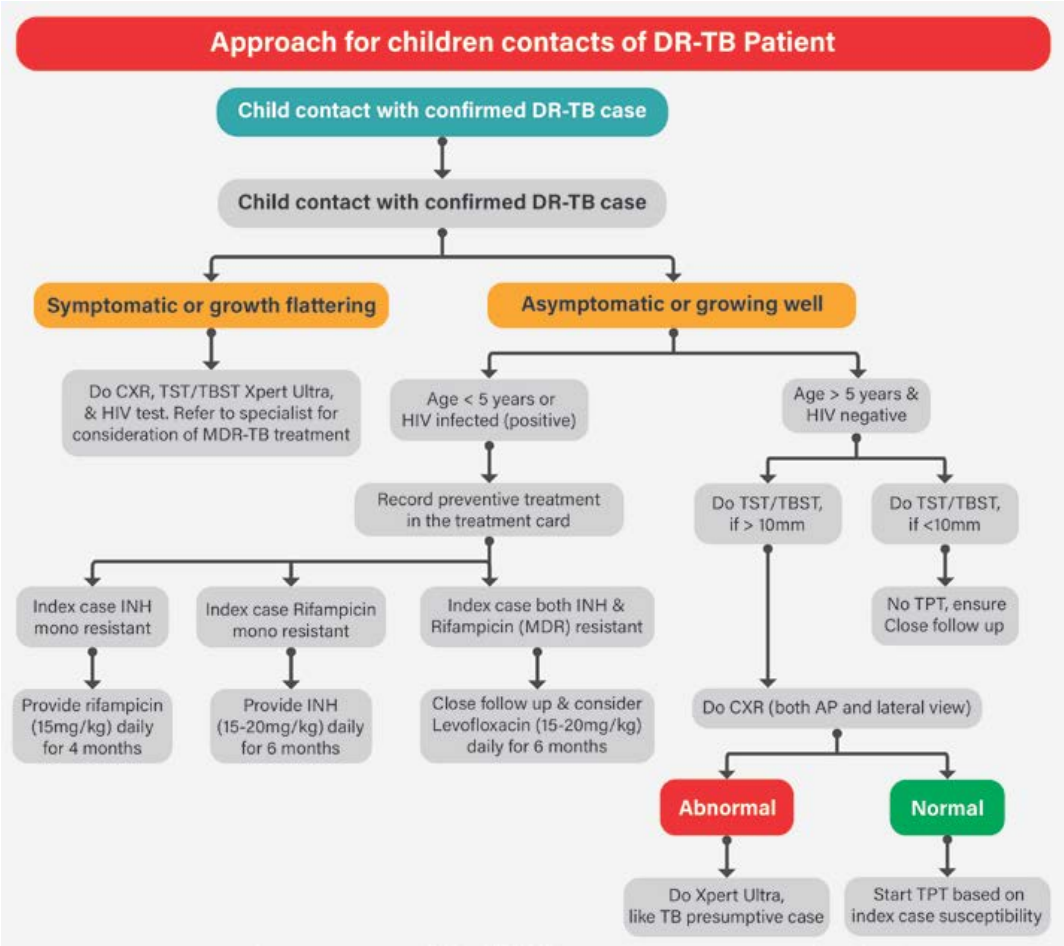


Figure 7.3 Approach for children contacts of DR-TB Patient

Chapter 8
Infection Control

Prevention of TB transmission and infection in the household and health facilities are important components of control and management of TB in children. Prompt recognition and treatment of TB patients at community settings will act as the most effective measure of decreasing nosocomial transmission of TB.

The following simple procedures are effective in TB infection control at home and clinics:

i. Place posters containing TB (Infection and Environment Control) IEC messages in clinic and as well as in the community.
ii. Provide health education about TB transmission without stigmatizing TB patients.
iii. At the clinic promptly identify potential and known infectious cases of TB; separate and treat them with minimal delay by conducting triage and screening.
iv. Early diagnosis and treatment of adult TB Patients in the household
v. Encourage proper cough hygiene, hand hygiene and appropriate spitting in a cloth or container with lid, both at home and at health facilities.
vi. Ensure natural ventilation and sunlight: Keep doors and windows open on opposite sides of the TB clinic and even at home for effective ventilation- air circulation and exchanges. HCWs/ caregivers should be screened out if symptomatic.

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