# Tuberculosis

**Diagnosis**

- Diagnosis is very difficult in children due to non-specific features and the radiological features are not as easy to interpret as in the adult.
- How ever in children with risk factors who have suspicious clinical criteria (See below), more definitive diagnosis can be made if appropriate investigations are done

**Risk factors for Developing Childhood Tuberculosis**

- Close contact (household, close relatives, caregiver, neighbour and teacher with a newly diagnosed smear-positive case as well as smear negative-culture positive case
- Age <5 years of age
- HIV infection
- Severe malnutrition, measles and immunosuppressive drugs or illnesses
- Absence of BCG vaccination
- Failure to thrive or weight loss (documented)

**Criteria to Identify TB Suspect in Children**

The child can be considered as a TB-suspect if 2 out of 3 following features are present.

- Fever (38°C) for more than 2 weeks and/ or cough for more than 2 weeks
- Failure to gain weight (Weight loss if known/consult weight chart)

History of contact with suspected or diagnosed TB patient

| **Symptoms suggestive of childhood TB** |
| --- |
| • Cough for more than 2 weeks which is not improving with full course of antibiotics and /or bronchodilators<br>• Fever (>38°C) for >2 weeks after exclusion of common causes of fever (e.g. malaria)<br>• Failure to gain weight (Weight loss if known/see weight chart)<br>• Unexplained loss of appetite |

| **Signs suggestive of childhood TB** |
| --- |
| Pulmonary tuberculosis<br>Signs of persistent pneumonia after full course of appropriate antibiotics (ATB)<br>**Highly suggestive Extra-pulmonary tuberculosis (EPTB):**<br>• Pleural effusion<br>• Acute vertebral gibbus<br>• Non-painful glands with draining sinus<br>**Suggestive EPTB**<br>• Meningitis not responding to antibiotics<br>• Pericardial effusion<br>• Swollen non-painful joints<br>• Significant enlarged lymph glands more than 2 cm in diameter and more than 2 in number with no known local cause and not responding to usual antibiotics<br>• Distended abdomen with ascites<br>• Clinical features indicative of Tuberculin hypersensitivity (e.g. erythema nodosum. phlyctenular conjunctivitis) |

**Diagnostic Tests**

**Microbiological confirmation**

- Sputum examination
    - Indicated in children older than 8 years or in any younger children who isable to provide a good quality sputum
    - Sputum should be collected spot, early morning and spot strategy
- Gastric lavage (aspiration)-Indicated in children less than 8 years or in children who is unable to produce sputum
    - Should be carried out after 4 hours of not eating or drinking (starvation)

**Chest X ray**

- Unequivocal hilar lymph gland enlargement with or without parenchyma opacification
- Miliary mottling (especially in HIV non-infected host)
- Large pleural effusion (≥⅓% of pleural cavity) in children >5 years

- Apical opacification with cavitation (adult type disease; very rare in children, common in adolescents)

**Tuberculin skin tests (TST)**

Tuberculin skin tests are useful in the diagnosis of TB infection in young children for contact tracing. It is also useful as an adjunct test where the diagnosis of TB is uncertain. TB should never be ruled out in children based on a negative TST result.

- Induration >10 mm is considered positive irrespective of whether BCG has been administered
- Induration >5 mm is considered positive in HIV positive children
- Negative TST never rule out TB in children

**Interferon-gamma release assays (IGRAs)** should not replace the tuberculin skin test (TST) in low- and middle-income countries for the diagnosis of latent TB infection in children or for the diagnostic work-up of children (irrespective of HIV status) suspected of TB disease in these settings.

Commercial sero-diagnostics should not be used in children suspected of active pulmonary or extrapulmonary TB, irrespective of their HIV status.

**Recommendations for HIV testing**

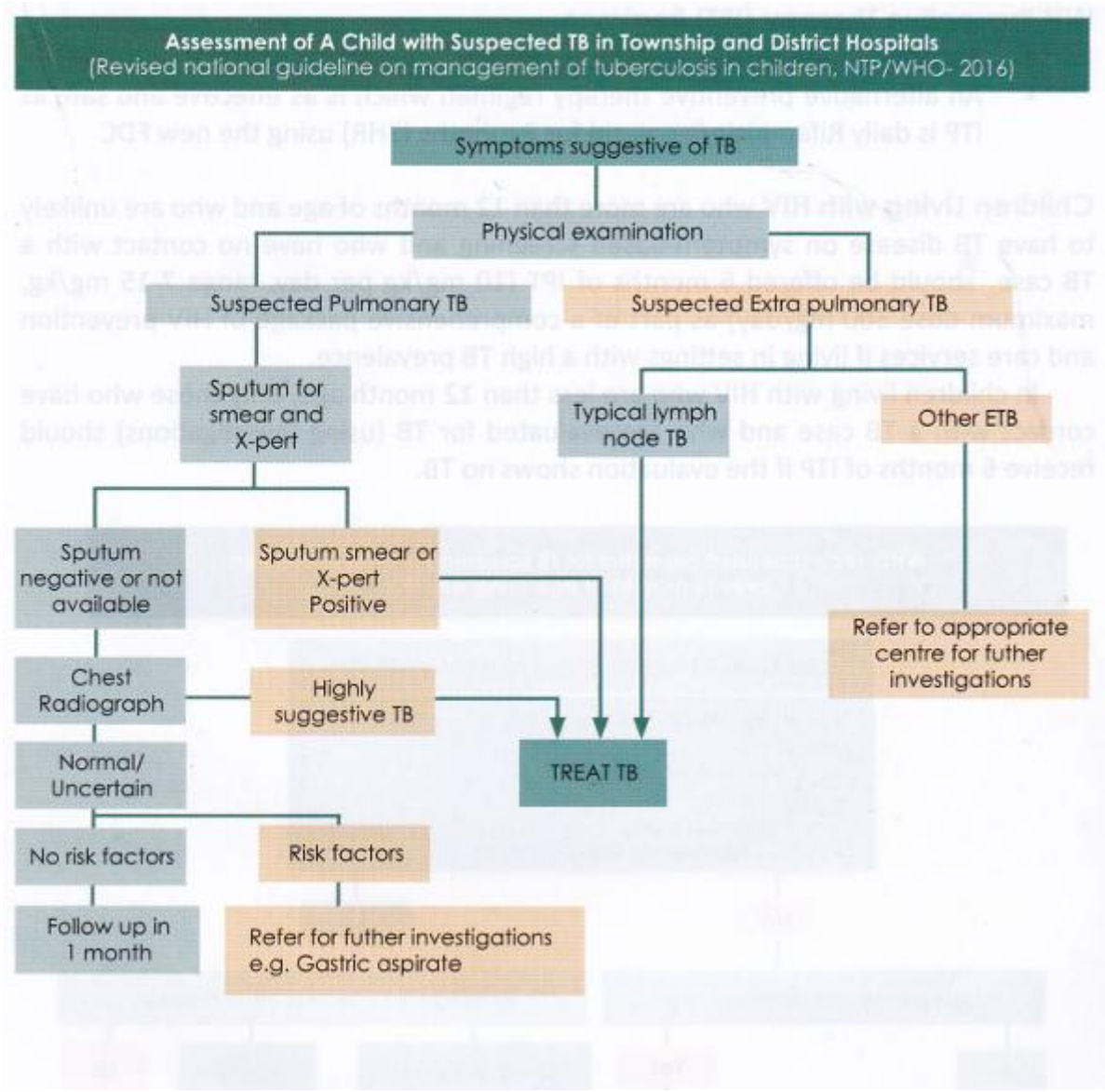
- Miliary TB
- Clinical signs suggestive of HIV disease
- Mother known to be HIV positive or either parent suspected of being HIV
- infected
- Relapse or treatment failure
- Severe acute malnutrition

| **Diagnosis Of EPTB** | |
|---|---|
| TB Site | Type of Test |
| Cervical/other lymph glands | Biopsy/FNAC |
| Meningitis | LP, CT brain scan |
| Arthritis | Aspiration, biopsy |
| Abdomen/Ascites | USG, aspiration |
| Vertebra | Vertebral X-ray |

**Diagnostic features for TB pleural effusion**

- Large pleural effusion (≥1/3 of pleural cavity) in children >5 years
- Pleural tap indicates a lymphocyte rich exudates

Clinical picture suggestive of TB

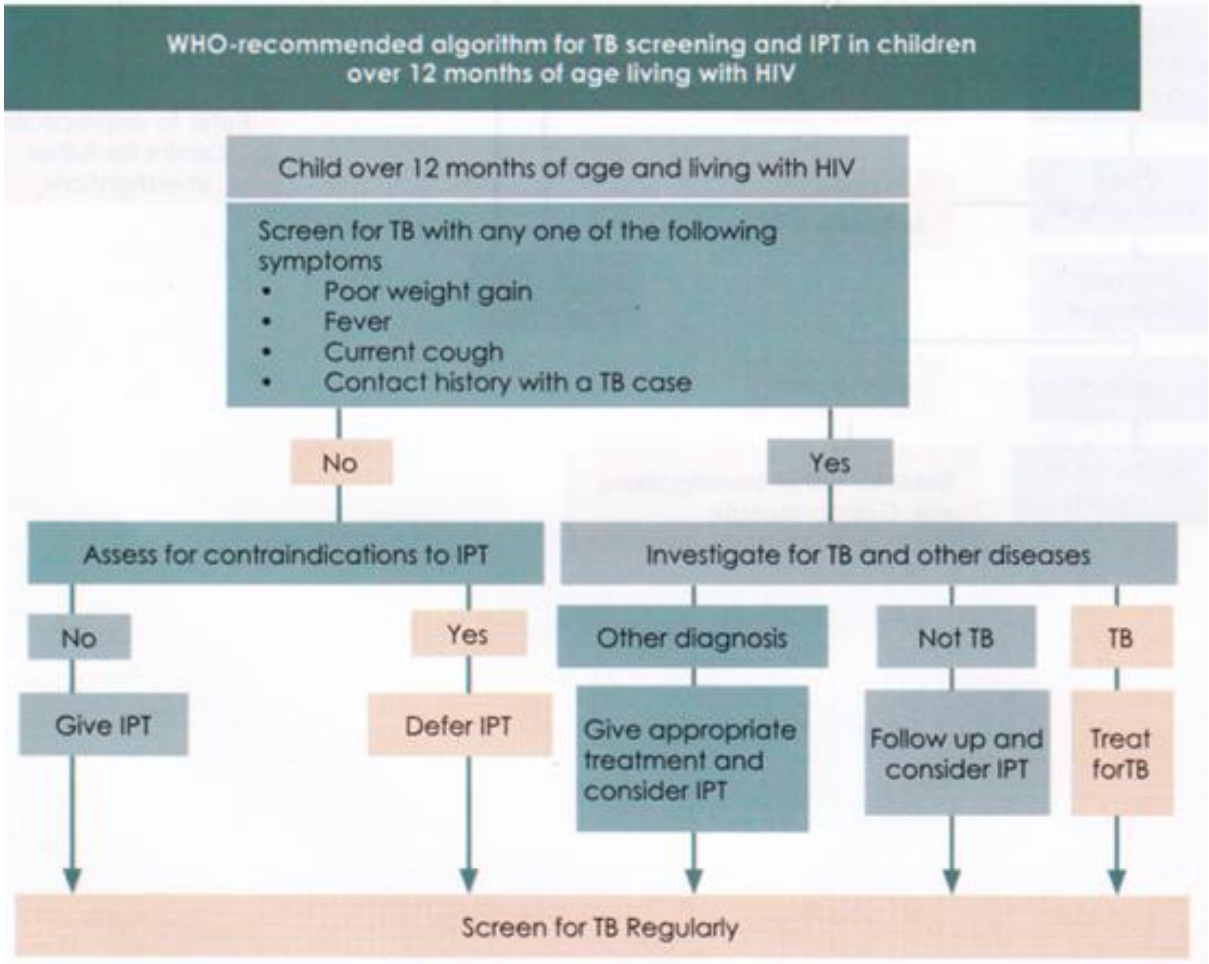


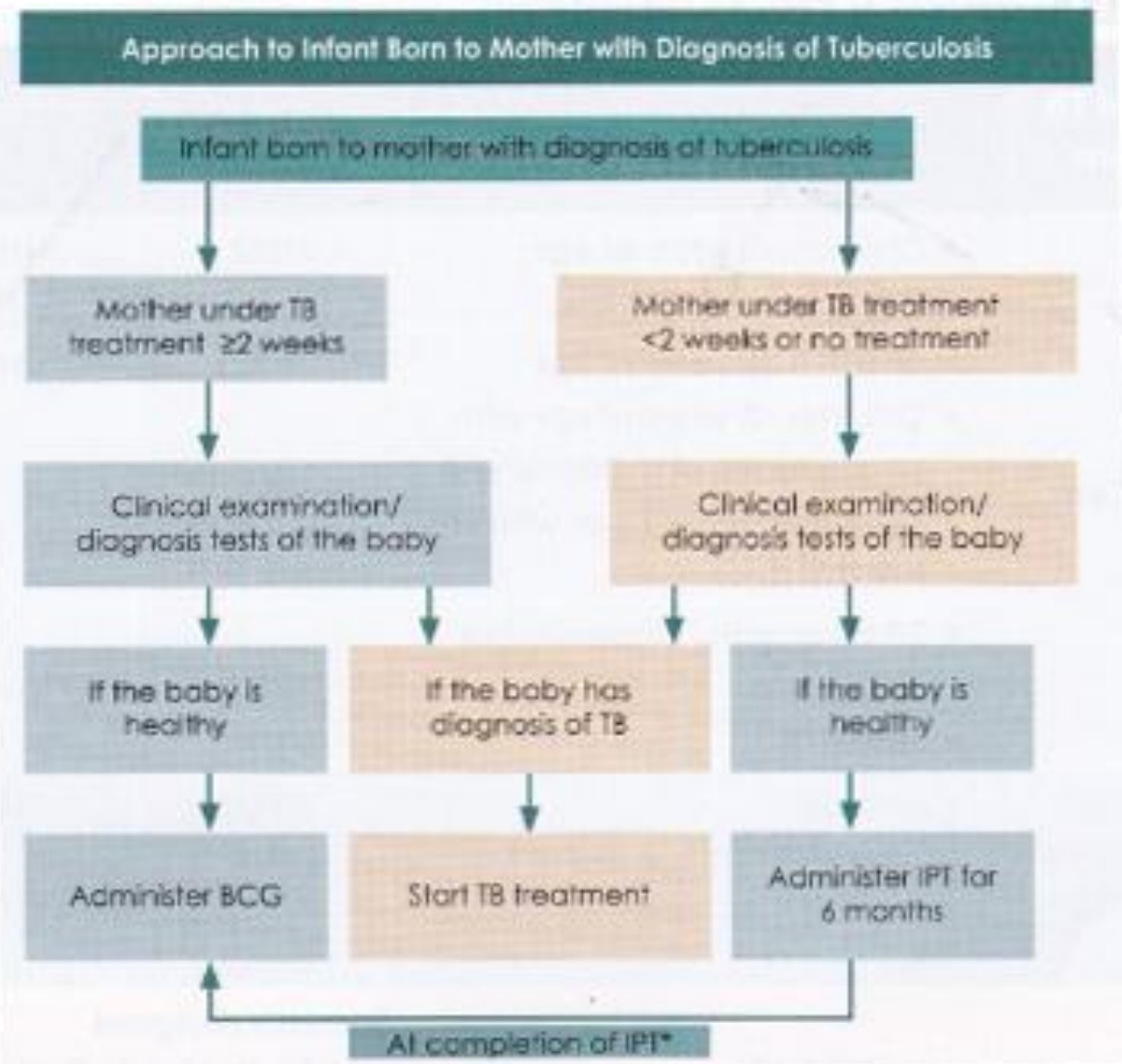
**INH Preventive Therapy (IPT) Regimen**

- Recommended dosage is 10 (7-15) mg/kg Isoniazid daily for 6 months (6H).
- An alternative preventive therapy regimen which is as effective and safe as ITP is daily Rifampicin/Isoniazid for 3 months (3HR) using the new FDC

**Children Living with HIV** who are more than 12 months of age and who are unlikely to have TB disease on symptom-based screening and who have no contact with a TB case should be offered 6 months of IPT (10 mg/kg per day, range 7-15 mg/kg maximum dose 300 mg/day) as part of a comprehensive package of HIV prevention and care services if living in settings with a high TB prevalence.

In children living with HIV who are less than 12 month age, only those who have contact with a TB case and who are evaluated for TB (using investigations) should receive 6 months of ITP if the evaluation shows no TB.






*PT-Isoniazid preventive therapy IIMH 10 mg/kg for ó months)

Breastfeeding can be safely given during this period and there is no need to separate baby from mother, children with active disease should be given full treatment and registered accordingly.

**Treatment of TB in children**

**Table 9.12 Recommended doses of first line anti TB drugs for children**

| Drug | Daily | |
|---|---|---|
| | Dose and range (mg/kg body weight) | Maximum (mg) |
| Isoniazid | 10 (10-15) | 300 |
| Rifampicin | 15 (10-20) | 600 |
| Pyrazinamide | 35 (30-40) | - |
| Ethambutol | 20 (15-25) | - |
| Streptomycin | 15 (12-18) | - |

Streptomycin should be avoided whenever possible in children because the injections are painful and irreversible auditory nerve damage may occur

New Fixed Dose Combination (FDC) - RHZ/R = 75/H = 50/2 = 150

Table 9.13 Recommended treatment regimens

| Type of TB Patient | TB cases | Regimen | |
|---|---|---|---|
| | | Intensive phase | Continuation phase |
| New Case | Children <8 years of age (Exceptions-see below) | 2HRZ | 4HR |
| | Children 28 years of age<br>Children <8 years of age with severe forms of pulmonary/extrapulmonary TB or who are HIV-infected | 2HRZE | 4HR |
| | TB meningitis/ Disseminated TB disease<br>Spinal TB | 2HRZE(S) | 10HR |
| Previously treated case | Relapse<br>Treat after failure<br>Treatment after lost to follow-up | 3HRZE<br>2HRZES/1HRZE* | 5HRE<br>5HRE |
| MDR TB | | Specially designed standardized or individualized regimens | |

E, ethambutol; H, isoniazid; R, rifampicin; S, streptomycin; Z, pyrazinamide

Direct observation of drug administration (DOT)is recommended during the initial phase of treatment.

**Note That Streptomycin is only used for retreatment of cases previously treated with HRZE that have relapsed and are not Rifampicin resistant On X-pert.*

**Corticosteroids**

- Indication
  - TB meningitis
  - TB glands causing airway obstruction
  - TB pericardial effusion

- Severe immune Reconstitution Inflammatory Syndrome (IRIS)

- Recommended drug
  - Prednisolone 2 mg/kg daily increased up to 4 mg/kg daily in the case of most seriously ill children
  - Maximum dosage of 60 mg/day for 4 weeks
  - The dose should then be gradually tapered over 2-4 weeks before stopping

**Adverse Events**

- Less common in children
- The most important adverse event is hepatotoxicity which can be caused by isoniazid, rifampicin or pyrazinamide.
- Serum liver enzyme levels are not to be monitored routinely, as asymptomatic mild elevation of serum liver enzymes (less than five times the normal values) is not indication to stop treatment.
- Occurrence of liver tenderness, hepatomegaly or jaundice should lead to investigation, measurement of serum liver enzyme levels and the immediate stopping of all potentially hepatotoxic drugs.
- Patients should be screened for other causes of hepatitis, and no attempt should be made to reintroduce these drugs until liver functions have normalized.
- An expert (experienced in managing drug- induced hepatotoxicity) should be involved in further management of such cases.
- If anti TB treatment needs to be continued for severe forms of TB, non hepatotoxic anti-TB drugs should be introduced (e.g. Ethambutol or an aminiglycoside or fluroquinolone).

**Indications for Hospitalization**

- TB meningitis
- Miliary TB
- Respiratory distress in any form of TB
- Spinal TB

- Severe adverse events (e.g. hepatoxicity)

**Follow Up**

- 2 weeks after treatment initiation, then at 2nd, 5th and 6th month
- At every follow up assess symptoms, treatment adherence, adverse events and body weight
- At 2nd, 5th and 6th month after treatment initiation-Collect sputum sample for smear microscopy only for the child smear positive at diagnosis
- Follow up chest radiographs
    - Not routinely required in children
    - Indications for follow up CXR
- Extensive pulmonary involvement
- Continued symptoms

Treatment failure regardless of smear positivity

**Management or Drug-Resistant TB in Children**

Any forms of drug resistance should be treated only in designate center, and in accordance with the National Guidelines on Management of (M) DR-TB. Basic principles described below are mentioned for information only. High expertise is required for management of DR-TB. Any fault in management will lead to amplification of resistance resulting in non-treatable DR-TB.

| | |
|---|---|
| Mono-resistance | Resistance to one first line anti-TB drug. |
| Poly-resistance | Resistance to more than one anti-TB drug, other than Isoniazid and Rifampicin |
| Multidrug-resistant TB (MDR-TB) | Resistance to at least Isoniazid and Rifampicin |
| Rifampicin-resistant TB (RR-TB) | Resistance to Rifampicin, with or without other anti TB drugs. It includes any resistance to Rifampicin, including mono-resistance, multi-drug resistance and polyresistance. |
| Extensively drug resistant TB (XDR-TB) | MDR-TB, plus resistance to at least one of the Fluoroquinolone, and at least one of the three injectable second-line drugs (Amikacin, Kanamycin and Capreomycin) |

***Multi-Drug Resistant Tuberculosis (MDR-TB)***

MDR-TB is defined as resistant to both isoniazid and rifampicin with or without resistance to other anti-TB drugs. MDR-TB in children is mainly the result of transmission of a strain of M. tuberculosis that is MDR from an adult source case and therefore often not suspected unless a history of contact with an adult pulmonary MDR-TB case is known, The clinical presentation of MDR-TB is similar to that of drug-susceptible TB

Treatment is challenging and prolonged and specialist referral is required.

MDR TB should be suspected in a child with TB-related symptoms who has:

- History of previous treatment for TB within the past 12 months
- Close contact with a person known to have MDR-TB
- Close contact with TB case that has died, failed TB treatment or is non-adherent to TB treatment
- Failure to improve clinically - persistence of symptoms, failure to gain weight after 2-3 months of first-line TB treatment, including persistence of positive smear or culture

All children with clinically suspected MDR TB should have appropriate specimens (sputum, gastric aspirate or lavage, lymph node aspirate) taken for Xpert, culture and DST. Therefore, any child with suspected MDR-TB require referral to a specialist center or at least a district hospital level.

Some basic principles treatments are as follows:

- Source case tracing
- Follow the same principles of treatment and regimen as for adults
- Use at least 4 drugs to which the organism is sensitive or the patient has previously not received
- Use daily treatment only and Directly observed therapy (DOT) is essential
- Counsel the child's caregiver at every visit, to provide support, advice about adverse events and the importance of compliance and completion of treatment
- Follow-up: clinical, radiological and bacteriological (culture for any child who had bacteriological confirmed disease at diagnosis)
- Treatment duration depends on the extent of the disease: at least 12 months after the last negative culture with minimal disease, or at least 18 months if extensive disease (lung cavities or widespread parenchymal involvement)

- Do not add a single new drug to a failing regimen
- Treat the child according to the drug susceptibility pattern (and using the treatment history) of the source case's M. tuberculosis strain if an isolated from the child is not available.
- Balance must be maintained between an effective regimen and the development of adverse events
- The commonest serious toxicity is permanent deafness due to injectable aminoglycoside. With correct dosing, few long term adverse events are otherwise seen with most of the second-line drugs in children, including Ethionamide and Fluoroquinolones.

First-line anti TB drugs may be used if their M. tuberculosis strain (or that of their source case) is found to be susceptible (e.g. Ethambutol and Pyrazinamide). Consider the use of Isoniazid and Rifampicin for 6 months if there is evidence that they may be effective, ie. No prior exposure to these medications. Ethambutol is bactericidal at higher doses, so that daily doses up to 25 mg/kg should be used in children being treated for MDR-TB.

***MDR-TB Contact Management***

**Prompt contact tracing should be conducted for all DR-TB patients-**

- If symptomatic-It is recommended that symptomatic children be referred to the specialist center or at least a district hospital level for evaluation as MDR.TB diagnosis is more difficult in children than adults.
- All asymptomatic close contact of MDR-TB patients should be followed up every three monthly intervals for first year and every six months for second years. HIV positive contacts should be followed up three monthly and if active MDR-TB develops, referred immediately for treatment. Asymptomatic patients should be educated about signs and symptoms of TB and to present at a health facility immediately if these develop.
- There are no evidence-based recommendations available on the prevention of MDR-TB in children after exposure.

**Standard MDR-TB regimens used in Myanmar (2017)**

**Standard MDR-T8 Regimen: 6-8 (Am+Z+Lfx+Eto+Cs)/12-14 (Lx=Eto+Cs=Z)**

**Total Duration -18-22 Months**

**Table 9.14 Medicines Recommended for the Treatment of RR-TB/ MDR-TB and Pediatric Doses**

| Group name | Anti-TB agent | | Abbr | Daily dose | Maximum daily dose |
|---|---|---|---|---|---|
| A. Fluoroquinolones | Levofloxacin | | Lfx | 5-10 mg/kg in 2 divided dose | 100 mg |
| | Moxifoxacin | | Mfx | 7.5-10 mg/kg od | 400 mg |
| | Gatifloxacin | | Gfx | 7.5-10 mg/kg od | |
| B. Second-line injectable agents | Amikacin | | Am | 15-22.5 mg/kg | 1000 mg |
| | Capreomycin | | Cm | od15-30 mg/kg | 1000 mg |
| | Kanamycin | | Km | od15-30 mg/kg od | 1000 mg |
| | Streptomycin | | S | 15-20 mg/kg od | 1000 mg |
| C. Other core second-line agents | Ethionamide | | Eto | 15-20 mg/kg od15- | 1000 mg |
| | Prothionamide | | Pto | 20 mg/kg od10-20 | 1000 mg |
| | Cycloserine | | Cs | mg/kg od | 1000 mg |
| | Terizidone | | Trd | 10-20 mg/kg od | 1000 mg |
| | Linezolid | | Lzd | 10 mg/kg tds | 600 mg |
| | Clofazimine | | Cfz | 1 mg/kg od | 200 mg |
| D. Add-on agents (Not part of the core MDR-TB regimen | D1 | Pyrazinamide | N | 0-40 mg/kg od | 2500 mg |
| | | Ethambutol | E | 15-25 mg/kg od | 2000 mg |
| | | High dose Isoniazid | H | 15-20 mg/kg od | 1500 mg |
| | D2 | Bedaquiline | Bdq | No | |
| | | Delamanid | Dlm | Recommendation for children | |
| | D3 | p-amino-salicylic | PAS | 300 mg bd or tds | 12 8 |
| | | acidImipenem-cilastatin | lpm | 60-100 mg/kg/day | 4000 mg |
| | | Meropenem | Mpm | divided 6 hourly20- | 6000 mg |
| | | Amoxicillin-clavulanate | AmX-Clv | 40 mg IV 8 hourly 80 mg/kg in | 4000 mg Amx/ |
| | | Thioacetazone | T | 2 divided dose | 500 mg Clv |