The SAARC Regional Programme Guidelines of Diagnosis & Management of Pediatric Tuberculosis (TB) 2017

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Foreword

The burden of TB in children is an important indicator of ongoing transmission within the community.

But the true global burden of TB in children is unknown because of the lack of child-friendly diagnostic tools and inadequate surveillance and reporting of childhood TB cases.
World Health Organization estimates that worldwide, at least 1 million TB cases occur each year in children less than 15 years of age.

Children are more likely to develop more serious forms of TB such as milliary TB and TB meningitis resulting in high morbidity and mortality. On the other hand most public health programs have limited capacity to meet the demand for care and high-quality services for childhood TB especially in resources limited settings.

Due to inadequate case detection it is estimated that a large number of children suffering from TB are not appropriately treated. This is further compounded by drug stock outs , different regimen used by child specialists and the lack of child-friendly formulations of drugs for TB treatment and prevention.

Studies have revealed that MDR-TB was positively associated with being aged <15 years. While adults represented the contamination source in most cases, in resource-limited settings with a high-burden of TB, the results of DST from adult index cases were not systematically used to investigate drug resistance in children.

The diagnosis of TB disease in HIV-positive children is particularly difficult because of HIV-related co-morbidities and chronic lung disease. HIV-positive children must, therefore, be screened routinely for TB and HIV testing should be offered to all TB suspects.

The goal of reaching zero TB deaths among children worldwide is within our grasp. Achieving this requires sustained advocacy, greater commitment, mobilization of increased resources and a joint effort by all stakeholders involved in providing health care for children and in TB control.
This document is designed to complement existing WHO guidelines for managing TB in children and to provide standard recommendations and evidence-based best practices appropriate for SAARC countries. The guideline is specifically designed for general health care workers' readership and is therefore expected to stimulate interest in pediatric TB treatment and how to protect the children from getting infected. This guideline will also act as a reference material for medical students, researchers and the community.

I gratefully acknowledge the guidance rendered by Members of the Governing Board of STAC.

Dr. R. P Bichha
Director

List of Abbreviations

AFB	Acid Fast Bacilli
ABC	Abacavir
AIDS	Acquired immunodeficiency syndrome
AZT	Zidovudine
ART	Antiretroviral therapy
BCG	Bacille Calmette Guerin
CXR	Chest X-ray
CPT	Co-trimoxazole preventive therapy
DOTS	Directly observed treatment short course
DST	Drug Susceptibility Testing
DR-TB	Drug resistant Tuberculosis
E	Ethambutol
EFV	Efavirenz
EPTB	Extra-pulmonary tuberculosis
FDC	Fixed-dose combination
FTC	Emtricitabine
H	Isoniazid
HIV	Human Immunodeficiency Virus
IGRA	Interferon-gamma release assay
IRIS	Immune reconstitution inflammatory syndrome
IPT	Isoniazid Preventive Therapy
LPV	Lopinavir
LPV/r	Lopinavir/ritonavir
MDR-TB	Multidrug-resistant tuberculosis
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NTP	National Tuberculosis Programme
NVP	Nevirapine
PAS	p-aminosalicylic acid
PI	Protease inhibitor
PLHIV	People living with HIV
PMTCT	Prevention of mother-to-child transmission (of HIV)
PPD	Purified protein derivative
PTB	Pulmonary Tuberculosis
R	Rifampicin
RTV	Ritonavir
SAARC	South Asia Association for Regional Cooperation
TB	Tuberculosis
TST	Tuberculin Skin Test
TDF	Tenofovir disoproxil fumarate
3TC	Lamivudine
TSH	Thyroid-stimulating hormone
WHO	World Health Organization
XDR-TB	Extensively Resistant Tuberculosis
Z	Pyrazinamide

Table of Contents of pediatric TB guideline

The guideline focuses on being able to provide guidance in child TB to health workers working at the primary or secondary level. It is important that the guideline will achieve a high level of understanding and knowledge of just a few simple messages. The guideline consists of the following topics:

1 Introduction

The Sustainable Development Goals, when they are adopted in September 2015, are likely to incorporate the goals of the End TB Strategy, although the TB targets may need to be adapted to a 2030 timeframe. The End TB Strategy assumes acceleration in the decline of new TB cases (incidence) to a rate of 10% per year by 2025, and a further acceleration to 17% decline per year from 2025 onwards. The average annual decline in new cases between 2000 and 2013 has been only 1.5%, a rate that is actually slowing rather than accelerating (0.6% reduction between 2012 and 2013).

The End TB Strategy:

INDICATORS	MILESTONES		TARGETS	
	2020	2025	SDG 2030	END TB 2035
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	**90%**	**95%**
Reduction in TB incidence rate compared with 2015 (%)	20% (<85/100 000)	50% (<55/100 000)	**80% (<20/100 000)**	**90% (<10/100 000)**
TB-affected families facing catastrophic costs due to TB (%)	Zero	Zero	**Zero**	**Zero**

1.1 Epidemiology of TB in Children:

Global: The World Health Organization (WHO) estimates that childhood TB accounts for 6% to 10% of all TB cases worldwide each year. In countries with a high rate of TB disease, children account for as much as 40% of all new TB cases. In 2014, there were an estimated 9.6 million new TB cases: 5.4 million among men, 3.2 million among women and 1.0 million among children. There were also 1.5 million TB deaths (1.1 million among HIV-negative people and 0.4 million among HIV-positive people), of which approximately 890 000 were men, 480 000 were women and 140 000 were children.

As a consequence, TB is an important cause of morbidity and mortality in children in TB endemic countries. Unfortunately, these figures underestimate the burden of childhood TB worldwide. TB in children has been a "hidden epidemic" for many years because of a number of challenges (CDC 2014).

- Childhood TB is particularly difficult to diagnose in resource-poor settings and is often not reported to health authorities in many countries.
- Many children cannot cough up sputum for TB testing. Even when sputum from a child is available, sputum smear microscopy test, which is the most available diagnostic measure in the community, can diagnose only about 30% of case
- A common misperception is that children are not severely affected by the global TB epidemic, and that they rarely develop severe forms of disease. However, this is not the case in TB endemic areas where children often present with advanced disease and TB is a major contributor to under-5 morbidity and mortality.

Childhood tuberculosis (TB) is common in the developing world, where over 90% of global TB cases occur, and has increased in human immunodeficiency virus (HIV) endemic regions. Most children with TB are not infectious, and so, from a public health perspective, are not afforded the same priority by TB control programmes as older age groups in settings of limited resources. In addition, the diagnosis of pulmonary TB is particularly difficult in young children. This has resulted in TB being a neglected disease in children, although it causes substantial morbidity and mortality.

SAARC Region: In 2014, there were an estimated 3.1 million incident cases of TB, equivalent to 185 cases per 100000 populations and estimated deaths due to TB was 0.37 million. This carries 32% of the global burden of TB incidence. Four of the eight Member Countries in the Region are among the 22 high burden countries, with India accounting for 23 % of the world's TB cases. Among 3.1 million incident TB cases, 2.1 million are notified new and relapse cases. Published data about the epidemiology of TB in children is scarce in SAARC Region, though it is considered one of the most common causes of childhood morbidity.

In Afghanistan, WHO estimated approximately 60,000 all types of TB cases occurred in year 2014 with incidence of (189/ 100,000) population. The prevalence of TB is around 110,000 cases (340/ 100,000 pop per year) and mortality is 14,000 (44/ 100,000). The incidence of Multi-Drug Resistant (MDR) TB is derived from a sub national drug resistance survey conducted in six provinces of Afghanistan during 2010. As per WHO estimates around 750 new MDR-TB cases among notified pulmonary TB cases are present in the country by end of 2014. 1,283 cases of pulmonary TB among children aged five years and younger were diagnosed, and there are 4,475 cases among children aged 15 years and younger as of 2013. These numbers dramatically increased after NTP started training on the standard operating procedures for pediatric TB control and utilizing tuberculin skin testing as the diagnostic tool.

In Bangladesh, Child TB (CTB) activities are progressing steadily in Bangladesh. National guidelines on CTB management have been published in 2012. In 2013, TB cases among children of 0–14 years old represented 2.8% of all new TB cases detected, of which 13% were in the age group 0–4 years. Providing IPT to eligible children living in the families of active TB patients is part of NTP policy. About 2996 children were evaluated and 321 children registered for IPT; among the registered children, 78 completed the full course of prophylaxis in 2014.

In Bhutan, Tuberculosis (TB) is a major public health problem in Bhutan. The National TB Control Programme (NTCP) was established in 1986 and adopted the World Health Organization (WHO) recommended DOTS strategy in 1997. Estimated TB prevalence and incidence rate of all forms of TB respectively of 190 and 164 per 100 000 population. Total 1066 notified new and relapse cases were detected, among the notified new and relapse cases 56 (5%) cases aged under 15 years. The first tuberculin survey in Bhutan in 1991 gave an infection rate of 1.5%, while a repeat survey in 2009 showed it to be 0.4–0.5%. Although there are no representative data on the situation and burden of childhood TB in Bhutan, a 6-year retrospective study conducted in Phuentsholing General Hospital, a TB centre in Bhutan, found that children accounted for 12.4% of the total number of cases.

In India, in 2014, out of the estimated global annual incidence of 9.6 million TB cases, 2.2 million were estimated to have occurred in India. Tuberculosis incidence per lakh population has reduced from 216 in year 1990 to 167 in 2014. Tuberculosis prevalence per lakh population has reduced from 465 in year 1990 to 195 in 2014. Almost 40% of India's population is under 15 years of age. Although child tuberculosis (TB) in India is estimated to be approximately 10% of total adult incidence, only 6% of the total cases reported to the Revised National Tuberculosis Control Programme (RNTCP) are children, and this proportion has remained constant for the last 9 years. The maximum risk of a child getting TB is between 1-4 years when there is an increased risk of progression from infection to disease. A large proportion of children with TB are probably diagnosed and managed by India's vast private sector. Data from Sitamarhi District, Bihar State, show that the proportion of children diagnosed with TB is higher in the private sector (17% vs. 8% in RNTCP). However, as most private practitioners do not notify cases to the RNTCP, the overall burden of childhood TB in the country is unknown due to diagnostic difficulties.

In Maldives, Maldives had estimated TB prevalence and incidence rate of all forms of TB respectively of 56 and 41 per 100 000 population. Total 131 notified new and relapse cases were detected, among the notified new and relapse cases 14 (11%) cases aged less than 15 years. However male female ratio is 1.2 in 2014. Treatment success rate among new smear-positive cases was 84% for the cohort of patients registered in 2013.

In Nepal, the annual risk of getting TB infection in children is 2-5%, but 8-20% of the deaths are children. The childhood TB is low at 2% (might not be a true reflection of actual number, as age distribution is only available for new smear positive cases and as production of sputum and positivity rate for childhood TB is relatively lower than adults).

In Pakistan, though the exact prevalence of TB in children is not known, according to National Tuberculosis Control Programme data (2001-2004), 4% registered cases of TB are seen in children. 25,000 (2.5%) children are at risk of acquiring TB infection. Among those infected 5-10% develops progressive Tuberculosis whereas the remaining 80-90% has latent tuberculosis. Tuberculosis is responsible for 8-20% of all deaths in children. However, findings from an inventory study indicated that TB was as high as 27% in children.

In Sri-Lanka, Sri Lanka is among the low TB prevalence countries in the Region. The estimated prevalence and incidence rates of all forms of tuberculosis were 103 and 66 respectively per 100 000 population, in 2014. The notification rate of all new and relapse TB cases (all types) and new bacteriologically confirmed cases were 44 and 21 respectively per 100 000 population; while the notification of laboratory confirmed cases is fairly stable over time, the notification of clinically diagnosed cases in 2012–2013 was lower than in the period 2006–2011.

1.2 The Roadmap for Childhood TB: Toward Zero Deaths

- Prioritize childhood TB at all levels and develop child-specific TB guidance.
- Empower healthcare workers to think about TB when they see cases of chest symptomatics or with other signs of TB, through training and access to childhood TB screening tools.
- Integrate TB screening into existing family, community, and health services.
- For every adult TB case, look for exposed children through contact tracing.
- Provide therapy to prevent TB for children at high-risk of developing disease.
- Collect and report more accurate data about TB in children to enable improved approaches.
- Invest in development of new tools, including child-friendly diagnostics and medicines.

1.3 Rational of developing the guidelines on Diagnosis and Management of Childhood TB:

TB in a child represents recent and ongoing transmission of TB bacteria. Young children are most likely to become exposed and infected with TB by close contacts, such as family members. Children can develop TB disease at any age, but the severe forms of TB are most common among children between 1 and 4 years of age. Children can get sick with TB disease very soon after being infected with TB bacteria, or they can get sick at any time later in life. They can even infect their own children, decades later, if not treated.

TB in adults and children is curable if identified and treated appropriately. Children at risk of developing TB disease can be identified using simple methods and screening tools. Many children with TB disease can be diagnosed with a clinical evaluation by a trained health care worker.

Although, there are many tools available that can help to prevent, find, and treat TB among children. However, SAARC Tuberculosis and HIV/AIDS Centre (STAC) is trying to develop pediatric TB guideline for all member state to ensure the right tools are in the hands of families, communities, and health care

workers to identify children at-risk for TB and link them to appropriate care. Therefore, **main objective of this guideline** is to bridge the gap between policy and practice in order to ensure all children have access to TB diagnosis and care, and to finally develop diagnostics and drugs that are suited for children's needs.

1.4 Methodology:

- Required materials, data and information through published reports, documents, website etc. of SAARC, STAC, NTP and NACP in collaboration with STAC were collected and reviewed for the reference and situation analysis.
- In depth discussion (e-mail/correspondences/telephone/meetings) with STAC.
- The consultation meeting with stakeholders and experts on diagnosis and treatment of pediatric TB were conducted to review the evidence base and advances in pediatric TB diagnosis and treatment.
- Used the best, current, evidence-based technical practices and approaches for prevention, control, diagnosis, treatment and care;
- Involved private sector through Pediatrician Association.
- Develop draft Guideline- shared and discussed with STAC and revised according to feedback.

1.5 Target users of child TB guideline:

- NTP staff that are not necessarily clinically trained in child health but need to manage or address child TB activities as part of their NTP duties, for example registration of cases, training, data management, drug procurement and distribution, monitoring and evaluation;
- Health workers at district hospital (secondary level of health care system) involved in the diagnosis and management of sick children;
- Health workers at community-based clinic (primary level of health care system) involved in the diagnosis and management of sick children;
- Health workers (clinical staff and volunteers) that are involved in the diagnosis and management of TB cases in the community;
- Health workers that are involved in the management of mothers and children with HIV.

1.6 Expected outcomes:

The guideline will focus on building the capacity of health care workers at the primary and secondary level to address and manage TB in children:

- Increase detection of children with TB in the community.
- Improve the clinical and overall management of children with TB.
- Increase implementation of child contact screening and preventive therapy.
- Prioritize childhood TB at all levels and for every adult TB case; look for exposed children through contact tracing.
- Provide therapy to prevent TB for children at high-risk of developing disease.
- Provide accurate data on childhood TB for better monitoring and evaluation.

1.7 Definition:

Tuberculosis (TB) is caused by bacteria (Mycobacterium tuberculosis) that most often affect the lungs. Tuberculosis is curable and preventable.

TB is spread from person to person through the air. When people with pulmonary TB cough, sneeze or

spit, they propel the TB germs into the air. A person needs to inhale only a few of these germs to become infected.

TB infection is when a person carries the Mycobacterium tuberculosis bacteria inside the body. Many people have TB infection and are well. A positive tuberculin skin test indicates infection but a negative tuberculin skin test does not exclude the possibility of infection.

About one-third of the world's population has latent TB infection, which means people have been infected by TB bacteria but are not (yet) ill with disease and cannot transmit the disease.

TB disease occurs in someone with TB infection when the bacteria inside the body start to multiply and become numerous enough to damage one or more organs of the body. This damage causes clinical symptoms and signs and is referred to as "tuberculosis" or active disease.

Index Case: Usually an adult with smear positive pulmonary TB.

Close contact is defined as living in the same household as, or in frequent contact with (e.g. child minder, school staff), an index case with PTB.

Pulmonary tuberculosis (PTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree.

Pulmonary TB sputum positive

A child is defined as smear positive if any of the following is true:

1. AFB is detected via microscopy on either a sputum or gastric lavage sample.
2. MTB is isolated by culture on either a sputum or gastric lavage sample.
3. MTB is detected by MTB/RIF Gene X-pert on either a sputum or gastric lavage sample.

Extra-pulmonary tuberculosis (EPTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, abdomen, genitourinary tract, skin, joints and bones, meninges.

Drug Resistant TB

This is a laboratory diagnosis. Drug resistant TB should be suspected if:

1. Child has contact with a known case of DRTB
2. Child has contact with an adult who has suspected DRTB as follows:
    - The adult remains sputum smear positive after 2 months of treatment,
    - An adult who has a history of previously treated TB,
    - An adult with a history of treatment interruption or died of TB.
3. Child is not responding to the anti- TB treatment regimen considering clinically and by duration.
4. Child has a recurrence of TB after successful TB treatment.

Children refers to 0 to 14 year age group

Infant is a child of less than 1 year of age (0-12 month age group)

2 Diagnosis of TB in Children

2.1 Purpose

This covers recent novel techniques for diagnosing and confirming TB and their application to children. It also describes the recommended approach to diagnosis of TB in children. Diagnosis of TB refers to the recognition of an active case of TB disease, i.e. a patient with current disease due to M. *tuberculosis*.

2.2 Introduction to diagnosis of TB in children

The diagnosis of TB in children relies on thorough assessment of all the evidence derived from a careful history of exposure, clinical examination and relevant investigations e.g. *Tuberculin Skin Test (TST*), chest X-ray (CXR) and/or sputum smear microscopy. Pulmonary TB is the common form of TB in children, although bacteriological confirmation through sputum microscopy is not always possible for young children who cannot cough up sputum for microscopic examination. Sputum microscopy should always be tried for the older children who can produce a sputum sample.

Any child with pneumonia, pleural effusion, or a cavitary or mass lesion in the lung that does not improve with standard antibacterial therapy should be evaluated for TB. Patients with fever of unknown origin, failure to thrive, significant weight loss (>5% of weight loss from last visit), severe malnutrition and/or other immunosuppressive conditions such as measles in the previous 3 months, whooping cough, HIV, being on medication like steroids, or unexplained lymphadenopathy, should also be evaluated for TB.

Any child with symptoms suggestive of TB, with history of exposure to an adult or adolescent pulmonary TB patient, or with evidence of documented TB infection (TST positive) should be investigated.

2.3 Difficulties in the diagnosis of TB in children

Diagnosis of TB in children is often difficult for several reasons:

- Symptoms are often non-specific, particularly in young children.
- Diseases are paucibacillary and microbiological diagnosis is often not possible.
- Difficult to obtain sputum for bacteriological confirmation.
- Mantoux or Tuberculin test is often negative in malnourished children or overwhelming TB cases. These tests also fail to differentiate TB disease from infection.
- X-rays are often non-specific.

Despite the difficulties, an accurate diagnosis can still be made in the majority of children from careful history taking, clinical examinations and relevant investigations, even in an outpatient setting.

2.4 Recent improvements in diagnostics

Now, new diagnostic tools are available to confirmation of TB. These include more rapid culture techniques and genotypic and phenotypic (molecular) techniques that improve detection of M. tuberculosis.

For example, commercially available liquid culture systems, molecular line probe assays and gene X-pert for rapid detection of MDR-TB have been endorsed by WHO although their uptake is constrained in resource-limited settings by their cost and complexity.

X-pert TSTB/RIF

Most attention recently is that of the X-pert assay. This is a fully automated real-time DNA based test which can detect both TB and resistance to rifampicin in less than 2 hours. Data shows an improved yield and sensitivity compared with smear microscopy. However, sensitivity of X-pert TSTB/RIF is still lower than culture confirmation or clinical diagnosis. The recommendations are grouped in two categories: (i) X-pert TSTB/RIF for the diagnosis of pulmonary TB and rifampicin resistance in children; and (ii) X-pert TSTB/RIF for the diagnosis of extra-pulmonary TB in children. The technology is recommended, especially in severely ill children when rapid diagnosis is crucial. It is important to note that a negative X-pert TSTB/RIF result does not exclude TB in children and a clinical decision should be made in all such cases.

Recommendation: X-pert TSTB/RIF for the diagnosis of pulmonary TB and rifampicin resistance in children

1. X-pert TSTB/RIF should be used rather than conventional microscopy and culture as the initial diagnostic test in children suspected of having MDR TB or HIV-associated TB.
2. X-pert TSTB/RIF may be used rather than conventional microscopy and culture as the initial test in all children suspected of having TB.

Remarks for above recommendations:

1. These recommendations apply to the use of X-pert TSTB/RIF in processed and unprocessed sputum specimens.
2. These recommendations also apply to gastric lavage and aspirates.
3. Children suspected of having pulmonary TB but with single X-pert TSTB/RIF negative result should undergo further diagnostic testing, and a child with high clinical suspicion for TB should be treated even if an X-pert TSTB/RIF result is negative or if the test is not available.

Recommendation: X-pert TSTB/RIF for the diagnosis of extra-pulmonary TB in children

1. X-pert may be used as an adjunct test for usual practice (including conventional microscopy, culture, and/or histopathology) for testing of specific non-respiratory specimens (lymph nodes and other tissues) from children suspected of having extra-pulmonary TB.
2. X-pert TSTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test in testing cerebrospinal fluid specimens from children suspected of having TB meningitis.

Remarks for above recommendations:

a. Children suspected of having extra-pulmonary TB but with a single X-pert TSTB/RIF-negative result should undergo further diagnostic testing, and those with high clinical suspicion for TB should be treated even if an X-pert TSTB/RIF result is negative or if the test is not available.

b. For CSF specimens, X-pert TSTB/RIF should be preferentially used over culture if the sample volume is low or additional specimens cannot be obtained, in order to reach quick diagnosis. If sufficient volume of material is available, concentration methods should be used to increase yield.

c. Pleural fluid analysis is a suboptimal sample for the bacterial confirmation of pleural TB, using any method. A pleural biopsy is the preferred sample. The sensitivity of X-pert TSTB/RIF in pleural fluid is very low (43.6%). Nevertheless, any positive X-pert TSTB/RIF result based on pleural fluid should be treated for pleural TB, while those with a negative X-pert TSTB/RIF result should be followed by other tests (Culture and DST).

d. These recommendations do not apply to stool, urine or blood, given the lack of data on the utility of X-pert TSTB/RIF on theses specimens.

Blood tests

A number of blood tests have been developed that aim to measure the immune response to infection with M. tuberculosis. Interferon-gamma release assays (IGRAs) measure the in vitro response to specific M. tuberculosis antigens. While these assays are more specific than TST (BCG does not cause a false-positive result), they have not been found to perform better than TST. IGRAs should not be used for the diagnosis of TB disease. A positive IGRA, like a positive TST, only indicates infection and so does not confirm a diagnosis of TB disease. Equally, a negative IGRA, like a negative TST, does not rule out a diagnosis of TB. Moreover, IGRAs are expensive and technically difficult to implement in resource-limited settings, and indeterminate results are common, especially in young children.

Recommendation:

1. IGRAs should not replace the tuberculin skin test (TST) in our settings 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. In some settings, commercial sero-diagnostics are marketed as diagnostic tests for TB. In children as in adults, these should not be used to diagnose TB.
2. Commercial sero-diagnostics should not be used in children suspected of active pulmonary or extrapulmonary TB, irrespective of their HIV status.

HIV testing

An HIV test is a very important "point-of-care" test that is already widely available. Making a diagnosis of HIV infection has obvious implications for the management of TB as well as HIV. Exclusion of co-infection with HIV also has important implications because it often makes the clinical diagnosis of TB more straightforward.

Recommendation:

Routine HIV testing should be offered to all patients, including children, with presumptive and diagnosed TB. HIV testing is routinely recommended for all children who are to be evaluated for TB or are TB patients in HIV-endemic settings and in populations at risk for HIV infection.

2.5 Recommended approach for diagnosing of TB in children

2.5.1 Careful history (including history of TB contact and symptoms suggestive of TB)

History of a child diagnosed as a first case and history of the close contact with a known case of TB should be carefully documented. Children usually acquire the disease from an adult source case. It is also important to document whether the suspected index case is responding to TB treatment or not. If an index is not responding to treatment, this indicates that the case may be drug-resistant TB. This should be taken into consideration when treating the child.

Trace Contact:

The main purposes of screening of child contacts are to identify symptomatic children (i.e. children of any age with undiagnosed TB disease) and provide preventive therapy for susceptible individuals (i.e. asymptomatic children under 5 years of age in close contact with a smear-positive pulmonary TB case).

Close exposure to a source case with TB involves sharing a living or working space with them. A source case with sputum smear-positive TB is much more likely to infect contacts than cases with sputum smear-negative TB. A household contact is often found to be the source of infection in children under 5 years of age with TB; infants and young children are especially likely to have contracted TB at home. Contact with

the source case is usually recent because children who develop TB usually do so within 1 year following exposure and infection.

The following points concerning contacts are of importance for diagnosing TB in children:

- All children aged 0–4 years (regardless of symptoms) and children aged 5 years and above who are symptomatic, who have been in close contact with a TB case, must be evaluated for TB.
- Children of all ages living with HIV who have been in close contact with a TB case must be evaluated for TB.
- When any child is diagnosed with TB, efforts should be made to detect the source case (if not already identified) and any other undiagnosed cases in the household.
- If a child presents with infectious TB, other child contacts must be sought and screened, as for any smear-positive source case. Children should be regarded as infectious if they have sputum smear-positive pulmonary TB or cavitary TB on chest X-ray (not uncommon in older children and adolescents).

Symptoms:

In most cases, children with symptomatic TB develop chronic unremitting symptoms, i.e. symptoms that persist for more than 2 weeks without sustained improvement or resolution following appropriate treatment for other potential diagnoses (e.g. antibiotics for pneumonia; antimalarials for fever; nutritional support for failure to thrive). The commonest symptoms include –cough- fever

- not eating well/anorexia

- weight loss or failure to thrive

- fatigue, reduced playfulness, decreased activity.

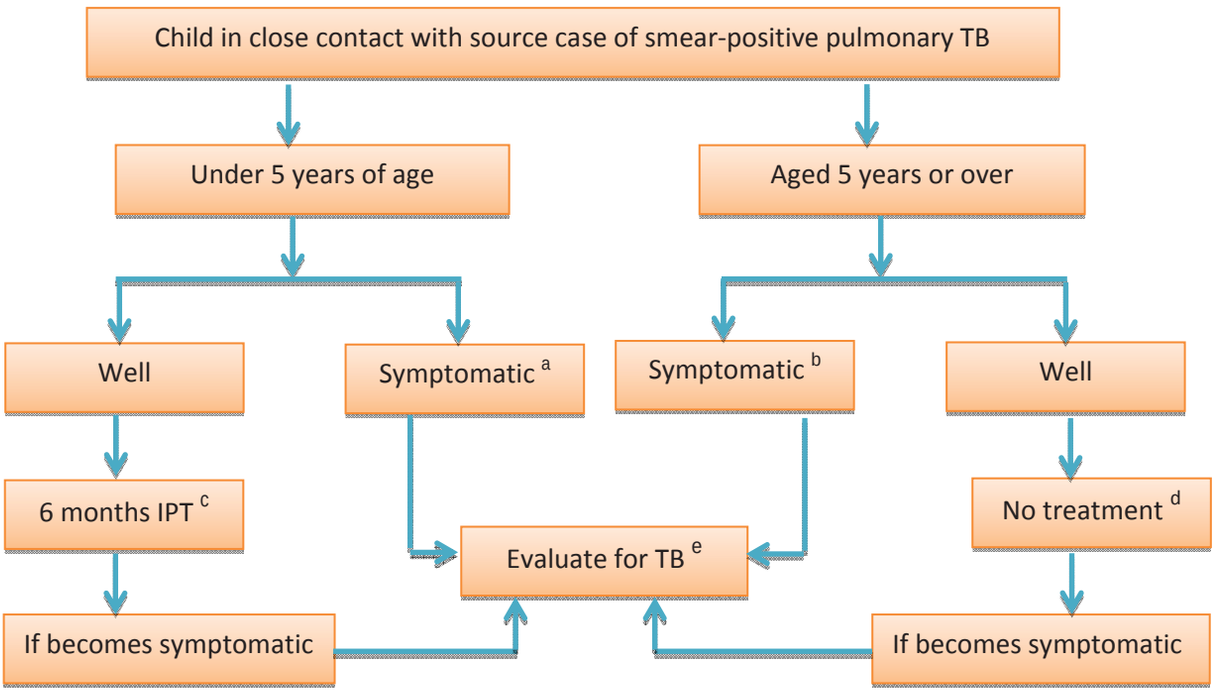
In addition to asking about weight loss or failure to thrive, it is important to look at the child's growth chart if available. Other or additional symptoms will be present in various forms of extra-pulmonary TB (i.e. TB of organs other than the lungs) and will depend on the site of disease (e.g. enlarged lymph nodes, back swelling, seizures).

The specificity of symptoms for the diagnosis of TB depends on how strict the definitions of the symptoms are. However, no definite cut-offs, e.g. duration of symptoms, have been validated and accuracy will depend on context. Strict symptom criteria have lower sensitivity and specificity in those at greatest risk of severe disease and poor outcome such as infants or very young children (under 3 years), children living with HIV, or severely malnourished children. These groups pose the greatest challenge for clinical diagnosis.

Approach to contact management:

The best way to detect TB infection is the TST and CXR to screen for TB disease among contacts. These tests should be used where they are available to screen exposed contacts. If the TST and CXR are not readily available, this should not preclude contact screening and management, as this can be conducted on the basis of simple clinical assessment.

Figure 1: Approach to contact management when chest X-Ray and TST are not readily available



- All children diagnosed with TB disease should be promptly treated and reported to the NTP.
- If TB disease is suspected, refer for further diagnosis.
- Isoniazid 10 mg/kg (7−15 mg/kg) daily for 6 months.
- If HIV-positive, isoniazid daily for 6 months is indicated regardless of age.
- If the child is diagnosed with TB disease, anti-TB treatment is started and the child is registered with the NTP.
- If TB disease is excluded, the child needs to be considered for eligibility for IPT.

2.5.2 Clinical assessment (including growth monitoring)

There are no specific features on clinical examination that can confirm that the presenting illness is due to pulmonary TB. Some clinical signs, although uncommon, are highly suggestive of extra-pulmonary TB. Other signs are less specific, but should still prompt a diagnostic evaluation for TB. Important physical signs are:

- Physical signs highly suggestive of extra-pulmonary TB:
  - gibbus, especially of recent onset (resulting from vertebral TB);
  - non-painful enlarged cervical lymphadenopathy, with or without fistula formation.
- Physical signs requiring investigation to exclude extra-pulmonary TB:
  - meningitis not responding to antibiotic treatment, with a sub-acute onset and/or raised intracranial pressure;
  - pleural effusion;
  - pericardial effusion;
  - distended abdomen with ascites;
  - non-painful enlarged lymph nodes without fistula formation;
  - non-painful enlarged joints.

Children who are receiving therapeutic nutritional treatment or nutritional supplementation but are still not gaining weight, or are continuing to lose weight, should be considered as having a chronic disease, such as TB.

Danger signs requiring urgent hospital referral:

Although TB is usually a chronic disease, there are certain danger signs that require urgent hospital referral.

- Severe forms of PTB and EPTB for further investigation and initial management.
- Severe respiratory distress (TB pneumonia with/without bacterial super infection, Pleural effusion).
- Severe wheezing not responding to bronchodilators (signs of severe airway compression).
- Headache (especially if accompanied by vomiting), irritability, drowsiness, neck stiffness and convulsions (signs of TB meningitis).
- Acutely ill with big liver and spleen and ascites (signs of disseminated TB).
- Breathlessness and peripheral edema (signs of pericardial effusion).
- Acute angulation (bending) of the spine (sign of TB spine - gibbus).
- Other co-morbidities e.g. severe anemia, severe malnutrition.

Note: Hospital referral should also be considered if there is any diagnostic uncertainty that requires further investigations.

Uncommon signs indicative of recent TB infection:

- Phlyctenular conjunctivitis - Raised patch at the junction of the sclera and cornea surrounded by a red area of conjunctivitis.
- Erythema nodosum - Raised, tender, purple patches on the shin.

2.5.3 Diagnostic tests

Tuberculin Skin Test:

A positive TST indicates that a person is or was infected with M. tuberculosis but does not necessarily indicate TB disease. It is a test that measures immune response, not the presence/absence of bacteria. The TST can be a useful tool in the assessment of a child with suspected TB, especially when there is no positive history of TB contact, because a positive TST indicates that the child has been infected at some point. It may therefore be used as an adjunct in diagnosing TB in children with signs and symptoms of TB and in conjunction with other diagnostic tests. The TST can also be used to screen children exposed to TB (such as household contact with TB), although contact screening and management can still be undertaken even if the TST is not available.

There are a number of methods for performing TSTs, but the Mantoux method is recommended. The TST should be standardized for each country using either 5 tuberculin units (TU) of tuberculin purified protein derivative (PPD-S) or 2 TU of tuberculin PPD RT23, which give similar reactions in children infected with M. tuberculosis. Health care workers must be trained in performing and reading TSTs. (Annex-I)

A TST should be regarded as positive:

- in children who are immune-suppressed (including HIV-positive children and severely malnourished children, i.e. those with clinical evidence of marasmus or kwashiorkor): >5 mm diameter of induration;
- in all other children (whether they have received a BCG vaccination or not): >10mm diameter of induration.

There can be false-positive as well as false-negative TST results; possible. It is important to note that a negative TST does not rule out infection with M. tuberculosis or the possibility of a diagnosis of TB in a child. (Annex-I)

Chest X-Ray (CXR):

Chest radiography is useful in the diagnosis of TB in children. In the majority of cases, children with pulmonary TB have CXR changes suggestive of TB. Good-quality CXRs are essential for proper evaluation. CXRs should preferably be read by a radiologist or a healthcare worker trained in their reading. A lateral chest X- ray is helpful to evaluate hilar lymphadenopathy.

Chest X-ray changes are often non-specific. CXR changes suggestive of TB are summarized below.

The most common radiological signs of TB in children

- Increased density in the hilar region due to enlarged hilar lymph nodes, and/or abroad mediastinum due to enlarged mediastinal lymph nodes.
- Persistent opacity in the lung.

Less common radiological signs

- Compression of the airways due to enlarged lymph nodes. Partial occlusion may lead to segmental or lobar hyperinflation. Complete airway occlusion may cause collapse of a lung segment or lobe.
- Miliary pattern of opacification.
- Pleural effusions (usually in children > 5 years old).

Adolescent patients with TB often have CXR changes similar to adult patients. Pleural effusions and apical infiltrates with cavity formation are the most common presentations.

Persistent opacification, which does not improve after a course of antibiotics, should be investigated for TB.

Radiological features require urgent hospital referral

- Widespread fine millet-sized (1-2 mm) lesions indicative of disseminated or miliary TB.
- Severe airway obstruction (always evaluate the airways).
- Severe parenchymal involvement.
- Acute angulation of the spine (TB spine, gibbus).

Bacteriological confirmation whenever possible:

Every effort should be made to confirm diagnosis of TB in a child using whatever specimens and laboratory facilities are available. Appropriate specimens from the suspected sites of involvement should be obtained for microscopy and culture (and histopathological examination in extra-pulmonary TB whenever possible), although this will depend on the availability of facilities and resources. Appropriate clinical samples include sputum (expectorated or induced), gastric aspirates and other specimens depending on the site of TB disease (e.g. lymph node biopsy). Fine-needle aspiration of enlarged lymph glands - for staining of acid-fast bacilli (AFB), culture and histology - has been shown to be useful, with a high bacteriological yield.

In young children TB is usually a paucibacillary disease, meaning that culture is much more likely than microscopy to yield a positive diagnosis. In addition, culture differentiates M. tuberculosis from non-tuberculosis mycobacteria and allows drug susceptibility testing. Similarly, use X-pert if strongly suspicion of TB and use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV.

Bacteriological confirmation is especially important for children who have:

- suspected drug-resistant TB
- HIV infection
- complicated or severe cases of TB disease
- an uncertain diagnosis
- been previously treated.

Note that TB in older children and adolescents is often similar to adult-type disease (and so is not paucibacillary). In this age group, sputum is often readily available and is often AFB-positive.

HIV testing

Most HIV infections in children occur through mother-to-child transmission. Other associated risk factors include blood transfusions and injections with infected blood. Although sexual transmission is not usually the cause of HIV/AIDS among children, it may be in cases of sexual abuse or rape.

In areas with low HIV prevalence, HIV counseling and testing is indicated for TB patients with symptoms and/or signs of HIV-related conditions, and in TB patients with a history suggestive of a high risk of HIV exposure.

In areas with a high prevalence of HIV infection in the general population, where TB and HIV infection are likely to coexist, HIV counseling and testing is indicated for all TB patients as part of their routine management. Routine HIV testing should be offered to all patients, including children, with presumptive and diagnosed TB.

Investigations relevant for suspected pulmonary TB and suspected extra-pulmonary TB:

Suspected pulmonary TB

Chest radiography is useful in the diagnosis of TB in children. In most cases, children with pulmonary TB have radiographic changes suggestive of TB; the commonest picture is one of persistent opacification in the lung together with enlarged hilar or subcarinal lymph glands. A miliary pattern of opacification in HIV-negative children is highly suggestive of TB.

Adolescent patients with TB have radiographic changes similar to adult patients, with large pleural effusions and apical infiltrates with cavity formation being the most common forms of presentation. Adolescents may also develop primary disease with hilar adenopathy and collapse lesions.

Good-quality chest radiographs (including lateral view, if and where possible) are essential for proper evaluation and should preferably be read by a radiologist or a health care worker trained in their reading. A practical guide for interpreting chest radiographs of children with suspected TB has been developed.

Suspected extra-pulmonary TB:

Table 1 shows the investigations normally used to diagnose the common forms of extra-pulmonary TB. In most of these cases, TB will be suspected from the clinical picture and confirmed by histology or other special investigations.

Table 1: Common forms of extra-pulmonary TB in children:

Note: All fluid (CSF, pleural, ascitic, joint or pericardial) must be subjected to biochemical analysis (protein and glucose concentrations), cell count, cell type AFB stain and culture whenever possible.

Site Practical approach to diagnosis

Site	Practical approach to diagnosis
Peripheral lymph node (especially cervical)	Lymph node biopsy or fine needle aspiration
Miliary TB (e.g. disseminated)	Chest radiograph and lumbar puncture {follow diagnostic rule for tuberculous meningitis (TBM)}
Tuberculous meningitis	Lumbar puncture (and imaging where available)
Pleural effusion (older children and adolescents)	Chest radiograph, pleural tap for biochemical analysis (protein and glucose concentrations), cell count and culture
Abdominal TB (e.g. peritoneal)	Abdominal ultrasound, ascitic tap and analysis
Osteoarticular	Radiograph of joint/bone, joint tap or synovial biopsy
Pericardial TB	Ultrasound and pericardial tap and analysis

Other tests:

Specialized tests, such as computerized chest tomography and bronchoscopy, are not recommended for the routine diagnosis of TB in children. Some countries use scoring systems for diagnosing TB in children. However, these systems have rarely been evaluated or validated against a "gold standard"; when they have been evaluated; they have performed poorly and variably. They perform particularly poorly in children suspected of pulmonary TB (the most common form) and in children who are also HIV-positive. At this point, therefore, WHO cannot give a recommendation regarding the use of scoring systems to diagnose TB.

3 Treatment of Childhood TB

3.1 Introduction:

Children with TB usually have paucibacillary disease and are not a risk to other children or adults. However, some children, mainly school-aged children and adolescents, have smear-positive TB with cavities on chest x-ray. These children are as infectious as smear-positive adults and their contacts must be investigated as well. Children develop extra pulmonary TB more often than adults.

All children who have been diagnosed with TB disease must receive directly observed TB treatment (DOT) with the appropriate regimen and 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, even in young and immune compromised children who are at higher risk of disease progression and disseminated disease. Children with TB usually respond to treatment and tolerate anti-TB drugs well. The parents should receive advice on the infection control measures to implement in the house to prevent further transmission of infection. A nutritional assessment of the child must be conducted and parents advised on appropriate diet and where necessary nutritional supplements must be provided.

3.2 Objectives of treatment of TB

1. Cure individual patient;
2. Prevent death from active TB or its late effects;
3. Prevent relapse of TB (by eliminating the dormant bacilli);
4. Reduce transmission;
5. Prevent the development of drug resistance.

Important things to do in a child diagnosed with TB:

- Exclude HIV infection
- Assess all co-infections, do baseline CD4 and plan for ART
- Provide psycho-social support to child and parents/ guardian
- Consider referral for nutritional support
- Complete the TB Register
- Ask about other children or adults in the household and screen them for TB

3.3 TB treatment:

TB treatment is the same in both HIV-infected and HIV-uninfected children. Possible causes for failure, such as non-compliance with therapy, poor drug absorption, drug resistance and alternative diagnoses should be investigated in children who are not improving on TB treatment.

3.3.1 Categories of TB patients

Based on type of patients and sputum results, patients are treated in two categories:

New cases (Category-I)	This includes a) New cases of pulmonary TB. b) New extra-pulmonary TB.
Re-treatment cases (Category-II)	This includes relapses, treatment after failure, and treatment after loss to follow-up, others previously treated (positive & negative) & patients with unknown previous TB treatment history.

3.3.2 Drugs and Regimens

Prescribing standardized drug regimen according to the category of a diagnosed patient is the responsibility of the clinician at health facility level. The treatment period for new TB cases lasts 6 months and for re-treatment cases is 8 months. The five essential anti-TB drugs is used with their mode of action and dosage (in mg per kg body weight), are given in the table below.

Uninterrupted availability of ATT drugs must be ensured to every TB patient free of cost and compliance of patient to complete treatment should also be ensured. The most important drugs used in the treatment of Tuberculosis are Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Streptomycin (S), and Ethambutol (E). Fixed dose combinations with proven bio-availability are preferred over individual drugs preparations. The use of Rifampicin or Streptomycin, for diseases other than mycobacterial diseases, should be avoided or limited to very carefully considered indications.

3.3.2.1 Treatment Regimen for Category I (New cases)

- During the initial intensive phase a combination of four drugs (Isoniazid, Rifampicin, Pyrazinamide and Ethambutol "HRZE") are administered under observation daily for a period of two months (sixty doses).
- When the patient has completed the initial intensive phase of two months, first follow up sputum test is done, and continuation phase will start irrespective of sputum smear result.
- Similarly for smear negative cases, initial intensive phase (HRZE) is administered for two months.
- Sputum smear is done at the end of 2 month, if smear is negative, the continuation phase will start.
- However if sputum smear is positive, then X-pert test will be done and if Mycobacterium is detected but RR not detected by test result, continuation phase will start.
- During the continuation phase, isoniazid and rifampicin (HR) are administered daily for four months.

3.3.2.2 Treatment Regimen for re-treatment cases (Category II):

- During the initial intensive phase Rifampicin, Isoniazid, Pyrazinamide and Ethambutol, supplemented with streptomycin (HRZES) are given for the first two months, followed by the same drugs without streptomycin (HRZE) for another one month administered daily under observation. The initial intensive phase should be continued for three months.
- If the sputum smear is negative at the end of 3rd month, the continuation phase is started.
- If the sputum smear is positive at the end of 3rd month, X-pert test will be done. If RR is detected, patient will be shifted to DR register and if RR is not detected, the patient should then start the continuation phase.
- During the continuation phase, Isoniazid, Rifampicin, and Ethambutol (HRE) are administered daily for five months under observation.
- If the patient remains smear-positive after the end of five months, he/she is no longer eligible for the re-treatment regimen. Such patients are regarded as CAT-II treatment failure & refer as MDR presumptive cases.

Table 2: Recommended dosages

The following dosages of anti-TB medicines should be used daily for the treatment of TB in children:

Drug	Daily dose and range (mg per kg body weight)
Isoniazid (H)	10 mg/kg (range 7–15 mg/kg); maximum dose 300 mg/day
Rifampicin (R)	15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day
Pyrazinamide (Z)	35 mg/kg (range 30–40 mg/kg)
Ethambutol (E)	20 mg/kg (range 15–25 mg/kg)

Young age influences drug metabolism: a particular dose of a drug in mg/kg when given to a young child (under 5 years) may not reach the same level in the blood as when given to an older child or adult. Higher mg/kg dosages are therefore required in young children to achieve levels that are considered to produce effective bactericidal activity.

The revised dosages will result in higher blood levels in young children, including those under 2 years of age. The revised dosages have an excellent safety profile and are not associated with an increased risk of toxicity (including no increased risk of drug induced hepatotoxicity due to isoniazid or pyrazinamide, or of optic neuritis due to ethambutol.

Using an FDC of three essential drugs (rifampicin, isoniazid, pyrazinamide), for many children it would be impossible to provide an isoniazid dosage in the 10-15 mg/kg range without using a pyrazinamide dosage that exceeded the recommended range (thereby increasing the risk of hepatotoxicity) or without requiring additional tablets of isoniazid alone (thereby imposing an additional pill burden and increasing the risk of incorrect dosing). A minimal isoniazid dosage of 7 mg/kg will provide adequate levels in almost all children. Even children who are younger than 2 years and/or are isoniazid fast acetylators 2 (the two subgroups most likely to not reach optimal levels for drug action) will respond well to this dosage. Therefore, recommended dose for isoniazid is range from 7-15 mg/kg, with the mid-range of 10 mg/kg. **Table 3** shows the recommended doses and dose ranges for first-line anti-TB drugs; these recommendations are independent of HIV status.

Table 3: Recommended daily doses of first-line anti-TB drugs for children

Anti-TB drug	Dose and range (mg/kg body weight)	Maximum dose (mg)
Isoniazid	10 (7-15) [a]	300
Rifampicin	15 (10-20)	600
Pyrazinamide	35 (30-40)	2000
Ethambutol	20 (15–25)	1200

[a] The higher end of the range for isoniazid dose applies to younger children; as the children grow older the lower end of the dosing range becomes more appropriate.

Note: As children approach a body weight of 25 kg, clinicians can use adult dosing recommendations.

3.4 Recommended treatment regimens:

Anti-TB treatment is divided into two phases: an intensive phase and a continuation phase. The purpose of the intensive phase is to rapidly eliminate the majority of organisms and to prevent the emergence of drug resistance. This phase uses a greater number of drugs than the continuation phase. The purpose of the continuation phase is to eradicate the dormant organisms. Fewer drugs are generally used in this phase because the risk of acquiring drug resistant is low, as most of the organisms have already been eliminated. Regular weight-based dose adjustment is important, particularly in young and/or malnourished children during the intensive phase of treatment, when weight gain may be pronounced.

WHO Recommendations:

1. Children with suspected or confirmed pulmonary TB or tuberculosis peripheral lymphadenitis who live in settings with low HIV prevalence or low prevalence of isoniazid resistance and children who are HIV-negative can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug (HR) regimen for 4 months at the dosages specified in **table 2**.

   Note: The regimen for new patients should contain rifampicin for 6 months. Wherever feasible, the optimal dosing frequency for new patients is daily throughout the course of therapy.

2. Infants aged 0–3 months with suspected or confirmed pulmonary TB or tuberculosis peripheral lymphadenitis should be promptly treated with the standard treatment regimens, as described in recommendation 1. Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in managing pediatric TB.

   Note: There are very limited data to inform drug dosages for neonates, who have certain characteristics - especially in the first week of life - that are likely to affect drug metabolism. Treatment of neonates may require dose adjustment to reconcile the effect of age and possible toxicity and should therefore be undertaken by a clinician experienced in managing pediatric TB. If such expertise is not available, and TB has either been definitively diagnosed or is strongly suspected, treatment with the standard drug regimen may be considered.

3. During the continuation phase of treatment, thrice-weekly regimens can be considered for children known not to be HIV-infected and living in settings with well-established directly-observed therapy (DOT).

4. Streptomycin should not be used as part of first-line treatment regimens for children with pulmonary TB or tuberculosis peripheral lymphadenitis.

5. Children with suspected or confirmed tuberculosis meningitis and children with suspected or confirmed osteoarticular TB should be treated with a four drug regimen (HRZ) plus streptomycin for 2 months, followed by a two-drug regimen (HR) for 10 months, the total duration of treatment being 12 months. The doses recommended for the treatment of tuberculosis meningitis are the same as those described for pulmonary TB. For easier understanding, **Table 4** lists all current recommended treatment regimens.

Table 4: Recommended treatment regimens for new cases of TB in children

<table>
<tr><th rowspan="2">TB diagnostic category</th><th colspan="2">Anti-TB drug regimens [a]</th></tr>
<tr><th>Intensive phase</th><th>Continuation phase</th></tr>
<tr><td colspan="3">Low HIV prevalence (and HIV-negative children) and low isoniazid resistance settings</td></tr>
<tr><td>Smear-negative pulmonary TB</td><td rowspan="3">2HRZ</td><td rowspan="3">4HR</td></tr>
<tr><td>Intrathoracic lymph node TB</td></tr>
<tr><td>Tuberculous peripheral lymphadenitis</td></tr>
<tr><td>Extensive pulmonary disease</td><td rowspan="3">2HRZE</td><td rowspan="3">4HR</td></tr>
<tr><td>Smear-positive pulmonary TB</td></tr>
<tr><td>Severe forms of extra-pulmonary TB (other than tuberculous meningitis/osteoarticular TB)</td></tr>
<tr><td colspan="3">All SAARC countries</td></tr>
<tr><td>Tuberculous meningitis and osteoarticular TB</td><td>2HRZ+SM</td><td>10HR</td></tr>
<tr><td>MDR-TB</td><td colspan="2">Individualized regimens (MDR section)</td></tr>
</table>

NB: The standard code for anti-TB treatment regimens uses an abbreviation for each anti-TB drug: isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E). A regimen consists of two phases - the initial and continuation phases. The number at the front of each phase represents the duration of that phase in months. Example, 2HRZ: Duration of this phase is 2 months and drug treatment is daily (no subscript numbers after the abbreviations) with isoniazid, rifampicin and pyrazinamide.

3.5 Directly Observed Therapy (DOT)

The DOTS strategy is a very important component of the internationally recommended policy package for TB control. DOT means that an observer watches the patient swallowing their drugs, which is essential for completion of treatment and recovery from TB. This ensures 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 should be used as a fixed drug combination (FDC). Ethambutol needs to be added with the FDC when indicated. Drug dosages, depending on the body weight of the child, are given daily (7 days per week). The dose should be adjusted as the weight changes during the course of treatment. Children should therefore be weighed at least after 1, 2, 3 and 6 months of therapy (or at a lesser interval when necessary), and 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), children should be referred for urgent assessment. Parents and caregivers should be counseled about TB and the importance of treatment adherence to ensure a good outcome.

3.6 Referrals:

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

- All children with severe forms of TB (TB meningitis, miliary TB, TB peritonitis, spinal or skeletal TB);
- Children suspected of having MDR TB, XDR TB (in contact with MDR TB, XDR TB case or not responding to first-line therapy);
- If there is poor response to therapy (no weight gains, persistent symptoms after 2-3 months of treatment).

3.7 Treatment response and follow-up during treatment:

Treatment outcomes in children are generally good provided that treatment starts promptly and adherence is maintained until completion. The risk of serious adverse events in children associated with use of the recommended treatment regimens is very low. Severe disseminated disease such as tuberculosis meningitis is associated with high mortality and with high morbidity among survivors.

Ideally, each child should be assessed at the following intervals:

- 2 weeks after the start of treatment,
- at the end of the intensive phase, and
- every 2 months until completion of treatment.

The assessment should include, as a minimum: symptom assessment, assessment of treatment adherence, enquiry about any adverse events, and weight measurement. Dosages should be adjusted to take account of any weight gain. Adherence should be assessed by reviewing the treatment card. A follow-up sputum sample for smear microscopy at 2 months after the start of treatment should be obtained from any child who was smear-positive at diagnosis. Follow-up chest X-rays are not routinely required in children who are improving with treatment, particularly as many children will have a slow radiographic response to treatment.

A child who is not responding to anti-TB treatment should be referred for further assessment and management. This child may have a drug-resistant TB, an unusual complication of pulmonary TB, a lung disease from another cause or problems with treatment adherence.

3.8 Treatment adherence:

Children, their parents, other family members and other caregivers should be educated about TB and the importance of completing treatment. The support of the child's parents and immediate family is vital to ensure a satisfactory outcome of treatment. Often a health care worker can observe or administer treatment but, if this arrangement is not convenient for the family, a trained community member (preferably someone other than the child's parent or immediate family member) can assume this responsibility. All children should receive treatment free of charge. Whenever possible, FDCs of drugs should be used to simplify drug administration and adherence. Patient treatment cards are recommended for documenting treatment adherence.

Adherence to the full course of therapy is frequently a challenge, especially as clinical improvement can be rapid; most children with TB will start to show signs of improvement after 2-4 weeks of anti-TB treatment.

On assessment at 2 months after the start of treatment, the possibility of treatment failure should be considered if a child who is receiving anti-TB treatment has following:

- has no symptom resolution or has worsening symptoms;

- shows continued weight loss;

- is sputum smear-positive

Poor adherence is a common cause of "treatment failure". Treatment failure suggests the possibility of MDR-TB and needs careful assessment (see DR section). It may also be more common in children living with HIV (see HIV section).

3.9 Causes of deterioration during TB treatment:

Children may sometimes deteriorate or experience a worsening of symptoms despite adequate therapy. The most important questions to answer are:

- Is the drug dosage correct?
- Is the child taking the drugs as prescribed (good adherence)?
- Is the child HIV-infected?
- Is the child severely malnourished?
- Is there a reason to suspect drug-resistant TB (the index case has drug resistant TB or is a re-treatment case or is also not responding to therapy)?
- Is there another reason for the child's illness other than TB?

Severely malnourished children, children following nutritional rehabilitation or HIV-infected children on highly active antiretroviral therapy may sometimes develop a temporary worsening of symptoms due to the recovery of their immune responses. This is referred to as immune reconstitution inflammatory syndrome (IRIS). Any child with severe persistent symptoms should be referred for assessment.

3.10 Treatment issues specific to adolescents:

The treatment of TB in adolescents follows the same guidelines as for adults. As regards dosage requirements, risk of MDR-TB, and drug tolerance, adolescents show greater similarity to adults than to young children. Thus, it is recommended that adolescents and older children (once they reach a body weight of 25 kg) be treated at adult dosages. Adolescents are at particular risk for poor adherence, which can be

exacerbated by the unique challenges for this age group of access to, and support from, either child health services or adult health services when they are often seen as belonging to neither. Treating adolescents with TB requires that special attention be paid to ensuring adherence. Involving adolescents in their care may help to engage them as active participants in their treatment plan. For example, individualized and family counseling and "brainstorming" on adherence strategies may empower adolescents and motivate them to adhere to treatment.

3.11 Management of adverse events:

Adverse events caused by TB drugs are much less common in children than in adults. The most serious adverse event is hepatotoxicity, which can be caused by isoniazid, rifampicin or pyrazinamide. Serum liver enzyme levels should not be monitored routinely, as asymptomatic children started on TB children have commonly a mild elevation of serum liver enzymes (<5 times the normal values). This is not an indication to stop treatment. However, the occurrence of liver tenderness with vomiting, hepatomegaly or jaundice during the course of treatment should lead to immediate stopping of all the drug and urgent referral for further investigation.

3.12 Other management issues:

3.12.1 Corticosteroids

Corticosteroids may be used for the management of some complicated forms of TB, e.g. tuberculosis meningitis, complications of airway obstruction by TB lymph glands, endobronchial TB and pericardial TB. Corticosteroids have been shown to improve survival and reduce morbidity in advanced tuberculous meningitis and are thus recommended in all cases of tuberculous meningitis. According WHO, prednisone is used most frequently, in a dosage of 2 mg/kg daily, increased to 4 mg/kg daily in the case of the most seriously ill children, with a maximum dosage of 60 mg/day for 4 weeks. The dose should then be gradually reduced over 1–2 weeks before stopping.

3.12.2 Pyridoxine supplementation

Isoniazid may cause symptomatic pyridoxine deficiency, which presents as neuropathy, particularly in severely malnourished children and HIV-positive children on antiretroviral therapy (ART). Supplemental pyridoxine (5–10 mg/day) is recommended in HIV-positive or malnourished children being treated for TB. This drug should be included in the treatment regimen and ensure supply from system.

3.12.3 Nutritional support

Severe malnutrition is associated with increased mortality in TB patients - children and adults - and a child's nutritional status should be assessed regularly during treatment of TB. All children diagnosed with TB who do not need treatment for severe acute malnutrition require nutritional support. This includes efforts to continue breastfeeding (until at least 24 months of age where possible) and to ensure adequate nutrient intake on the basis of locally available and affordable foods. Additional energy is particularly important during the intensive phase of treatment and is best given through additional household foods, provided as part of a balanced varied diet. Infants under 6 months of age causing concern about malnutrition or growth failure require referral to a therapeutic feeding programme. If this is not available or feasible, breastfeeding mothers should be given support to optimize breastfeeding. Nutritional supplementation cannot be given directly to an infant under 6 months of age but can be provided for the lactating mother.

4 Management of drug-resistant TB in Pediatric and TB/HIV Co-infection

4.1 Introduction

The burden of childhood tuberculosis (TB) reflects ongoing TB transmission in a community. About one million children fall sick with TB every year. The pattern of drug resistance in children in a community generally mirrors that of the adult population. Among adults, 3.7% of new cases and 20% of previously treated cases were estimated to have multi-drug-resistant TB (MDR-TB) worldwide in 2012. In 2010, an estimated one million children developed TB disease, among whom 32000 had MDR-TB. Difficulties in diagnosis due to insensitive tools for microbiological confirmation in children hamper the estimation of the burden of drug-resistant TB in this population. Thus, accurate information on mortality and morbidity due to drug-resistant TB in children is lacking.

Drug-resistant tuberculosis (DR-TB) is a growing global health crisis; DR-TB is defined as strains of TB with in vitro resistance to at least isoniazid and rifampin, and it is estimated there are more than five million people infected and sick with drug-resistant forms of TB in the world today (World Health Organization, 2011). Children represent a significant proportion of these cases yet they lack the same access to diagnosis and treatment as their adult counterparts. A recent meta-analysis of treatment for MDR-TB among children showed that more than 80% had positive outcomes when treated for MDR-TB and that pediatric patients tolerated second-line medications well (Ettehad, D. *et al.*, 2012).

Whenever possible, management of children with DR-TB should take place within the activities of a National TB Control Program (NTP). There are multiple advantages to doing this, including a contextual approach, integration with other health initiatives, and health systems strengthening. If activities occur outside the auspices of an NTP, all efforts should be made to report standardized outcomes and to collaborate with the NTP whenever possible.

The term “children” encompasses a broad range of individuals and ages with widely different needs. A 2-year-old child requires a different approach to a 12-year-old, and the treatment of children with DR-TB will never be a “one size fits all” approach. In essence, children older than 12 years of age can be managed as adults, although the specific emotional needs of adolescent children and their caregivers should be considered.

4.2 Types of Drug Resistant TB in children:

4.2.1 Mono Drug Resistance

Mono drug resistance means M. tuberculosis is resistant to only one first-line anti-TB drug, for example, EMB or INH or SM. Resistance to INH is usually the first step in the development of DR-TB. Evidence suggests that CAT I regimen (INH, RMP, PZA, EMB) should be sufficient for effective cure in most patients with INH mono-resistant TB. The risk of acquiring MDR-TB is increased in patients with high bacillary loads.

4.2.2 Poly Drug Resistance

When M. tuberculosis develops resistance to more than one first line anti-TB drugs, the organism is then called poly drug resistant. Examples of poly drug resistance are INH-EMB or EMB- SM or SM- RMP-EMB resistance, etc.

4.2.3 Multi Drug Resistance (MDR)

Multi drug resistant TB (MDR-TB) occurs when TB is caused by organism that is resistant to isoniazid and rifampicin, the two most potent first line anti-TB drugs, with or without resistance to other anti-TB drugs. The principles guiding disease management remain unchanged. Accurate disease classification and drug susceptibility test results should guide therapy. Second-line drugs are generally more toxic but with correct dosing, few serious adverse events have been reported in children. Hearing loss is a major concern with prolonged use of injectable agents such as kanamycin or amikacin, and careful monitoring for adverse events such as depression and/or hypothyroidism is indicated. Table 6 provided a summary of the main toxicities associated with second-line drugs. Optimal treatment should be discussed with an expert in the field, and parents and children require regular counseling and support to complete treatment.

4.2.4 Extensively Drug Resistance (XDR)

Extensively drug resistant TB, or XDR-TB, can be defined as MDR-TB that is also resistant to anyone of the fluoroquinolones and to at least one of three injectable second line anti TB drugs (amikacin, capreomycin or kanamycin). Usually XDR-TB develops when second-line drugs are misused or mismanaged and therefore become ineffective. XDR-TB has been identified in all regions of the world since 2006. Treatment options for these patients are limited and should be discussed with an expert in the field.

Is drug resistant TB infectious?

Drug-resistant TB is as infectious as drug-susceptible TB. Children usually become infected from adult or adolescent MDR-TB contact. It is evident that current control efforts are not adequately containing the spread of the drug-resistant TB epidemic.

How to recognize a drug resistant suspect?

Drug-resistant TB is a laboratory diagnosis, but should be suspected if any of the following features are present:

- Features in the index case suggestive of drug resistant TB
  - Index case remaining smear-positive after 3 months of treatment
  - History of previous TB treatment interruption or recurrence after completion of TB treatment
- Features in a child suggestive of having drug resistant TB
  - Contact with a known case of MDR-TB
  - Child not responding to adhered standard TB treatment
  - Child with TB recurrence after completing TB treatment

4.3 Diagnosis of DR-TB in Children:

A diagnosis of TB in children can be made on clinical and radiological grounds in the majority of cases, even though bacteriological confirmation may not be possible. Furthermore, most children over the age of 7 years can provide sputum for bacteriologic confirmation and drug susceptibility testing (DST). Since children may have paucibacillary disease or extra pulmonary disease, and since sputum samples may be difficult to obtain in younger children, a bacteriologically confirmed TB diagnosis may be difficult

to make, and testing for drug resistance may not be possible. Thus, a high index of clinical suspicion is needed, as well as the readiness to initiate DR-TB treatment even in the absence of bacteriologically confirmed disease. Systematic approaches to the management of pediatric contacts of DR-TB patients are needed.

Recognition and Initial Management of a Child with Suspected DR-TB

TB should be included in the differential diagnosis list of any child with a persistent non-remitting cough or fever, weight loss, or focal findings that are suggestive of TB, such as lymphadenitis, spinal deformities, ascites, and joint effusions. Diagnosis of DR-TB among children is challenging and requires a high index of suspicion. The algorithm on the next page suggests a diagnostic strategy for determining risk factors for DR-TB among children who have confirmed or suspected TB.

Abbreviations for drugs used in this guideline

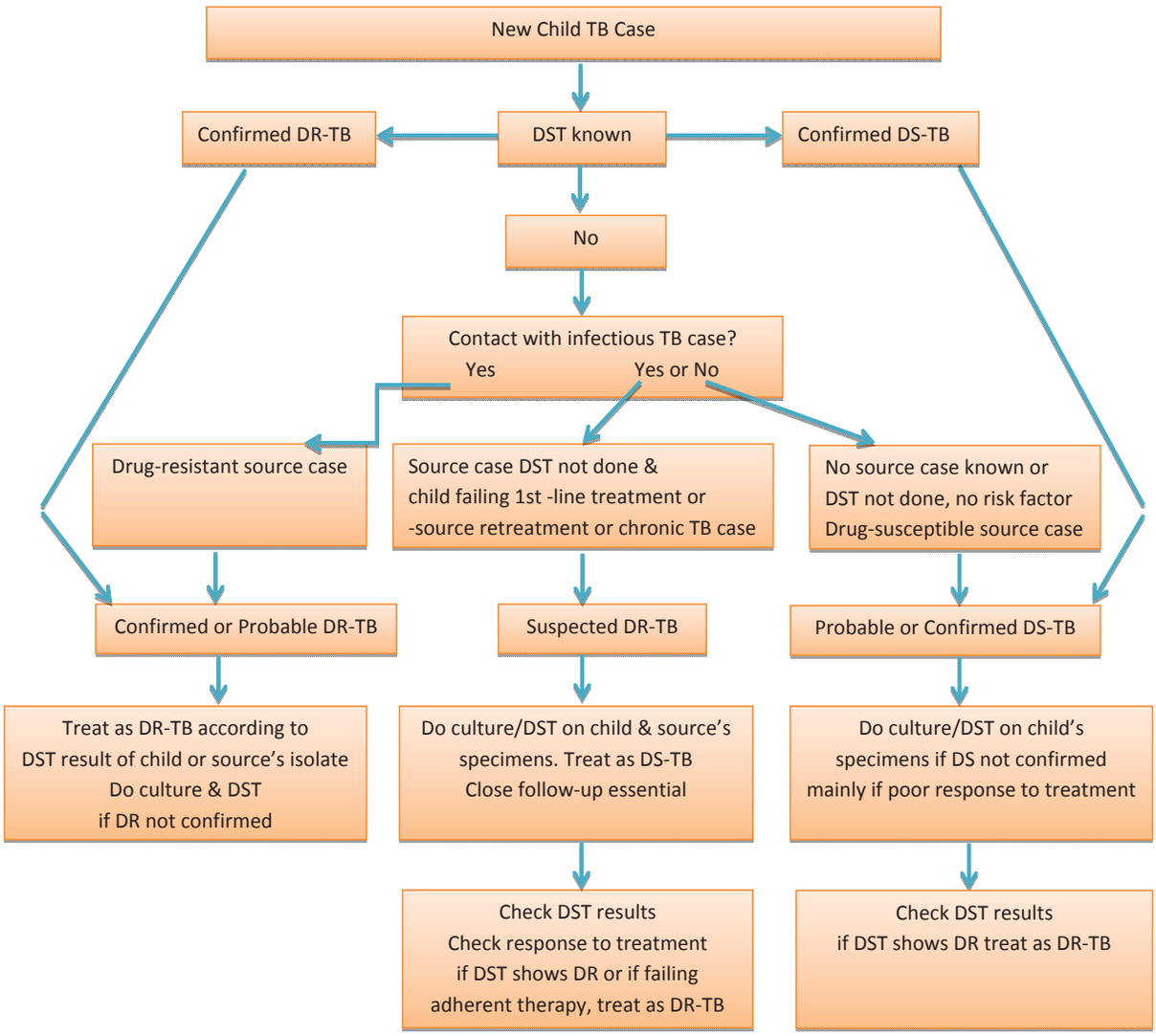
INH	isoniazid	THA	ethionamide
RIF	rifampicin	PTO	protionamide
EMB	ethambutol	LVX	levofloxacin
PZA	pyrazinamide	MFX	moxifloxacin
SM	streptomycin	OFX	ofloxacin
CM	capreomycin	CS	cycloserine
KM	kanamycin	TZD	terizidone
AMK	amikacin	PAS	para-aminosalicylic acid

Drug-resistant TB should be suspected when:

- there is contact with known DR-TB;
- there is contact with suspected DR-TB, i.e. source case is a treatment failure or a retreatment case or recently died from TB;
- a child with TB is not responding to first-line therapy despite adherence;
- a child previously treated for TB presents with recurrence of disease.

When DR-TB is suspected, every effort should be made to confirm the diagnosis by obtaining specimens for culture and drug susceptibility testing (DST). Rapid DST of isoniazid and rifampicin or of rifampicin alone is recommended over conventional testing or no testing at the time of diagnosis. The use of molecular tests (line probe assay and Xpert MTB/RIF) may provide evidence of resistance within hours to 1-2 days of specimen testing and is endorsed by WHO; conventional DST, by contrast, may take 1-3 months to yield results. Rapid DST may therefore provide a cost-effective means of achieving early treatment, increased cure rates, reduced mortality, reduced development of additional drug resistance and a lowered probability of failure and relapse. In all cases of confirmed MDR-TB, second-line DST should be performed to exclude XDR-TB and to help establish an effective treatment regimen.

Figure 2: Diagnostic algorithm for the diagnosis of DR-TB in children.

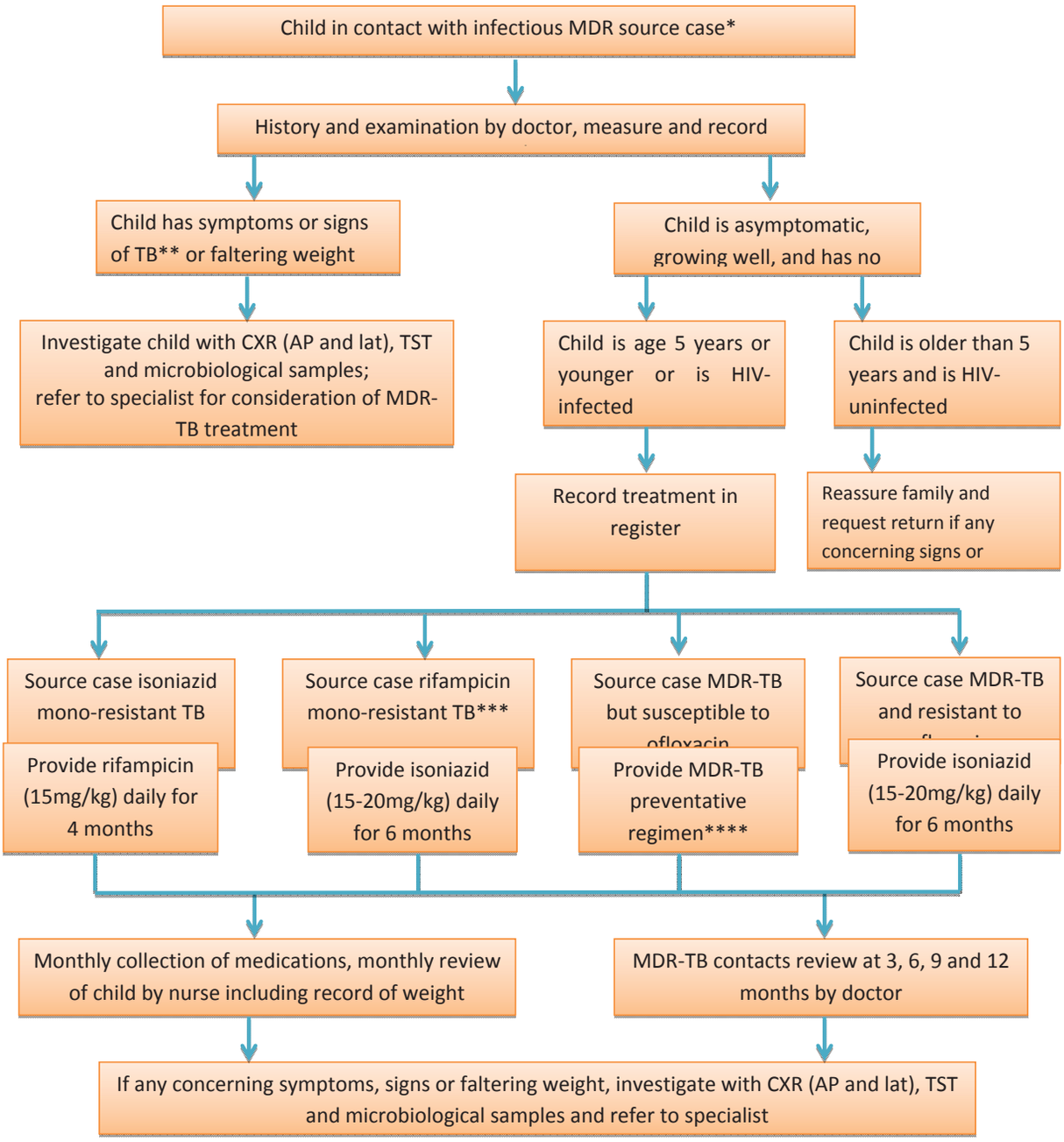


*DST = drug susceptibility test; DR = drug-resistant; DS = drug-susceptible
*Reference to culture and DST implies that facilities are available

4.4 Management of TB disease in child contacts of drug-resistant TB

Current WHO guidelines do not recommend preventive therapy for contacts of DR-TB patients. No clinical trials have been done to inform policy, but observational studies have been reported. The management of contacts of DR-TB cases, whether the contacts are children or adults, is an important research topic. Close contacts of DR-TB patients who develop TB disease usually have drug-resistant disease. All children with an infectious TB contact should be screened for TB disease, especially children living with HIV and child household contacts of DR-TB. Careful clinical follow-up of asymptomatic children (every 2-3 months for the first 6 months, then6-monthly for at least 2 years) is recommended. If TB disease develops, treatment with an appropriate DR-TB regimen based on the DST pattern of the presumed source case should be initiated. Care providers should note that younger children are more at risk of progressing to TB disease.

Figure 3: Management Algorithm for Child Contacts of MDR-TB Cases.



* Infectious is defined as smear or culture-positive pulmonary TB

** Cough, reduced playfulness, fever, lethargy, abnormal bones or joints, faltering weight

*** If diagnosed by GeneXpert, consider MDR until confirmation by line probe assay (LPA) or DST

**** The composition of the preventive regimen will depend on the national program, but could be: (1) a fluoroquinolone and high dose INH, (2) a fluoroquinolone, high dose INH and EMB, (3) a fluoroquinolone and EMB, (4) high dose INH alone, or (5) a fluoroquinolone alone. Additional studies are underway to provide a strong evidence base for preventive therapy recommendations. In the largest observation cohort of children given prophylaxis for MDR-TB, a regimen of INH (15-20 mg/kg/day), EMB (20-25mg/kg/day) and OFX (15-20mg/kg/day) for a total of 6 months was given (Seddon, J. et al. Clin Infect Dis, 2013)

4.5 Treatment

The treatment of MDR-TB and XDR-TB in children is guided by the same principles and uses the same second-line drugs as the treatment in adults, although optimal durations of regimens are not known. MDR-TB is associated with poorer treatment outcomes and higher mortality than drug-sensitive TB in children.

Dosing of Second-Line Anti-tuberculosis Agents for Pediatrics

Proper dosing of second-line agents for children is key to ensure good outcomes and to prevent the development of additional resistance. Unfortunately, dosing recommendations for children can be somewhat complicated. This is due to the fact that there are limited pharmacokinetic data (i.e. the way the body metabolizes a drug) on most second-line drugs in children, and optimal doses are yet to be determined. An ongoing pharmacokinetic study in South Africa will provide data on all second-line drugs in children; results from the injectables, ethionamide, and the fluoroquinolones have been presented at the Union TB meetings in Kuala Lumpur (2012) and Paris (2013). The second problem is that there are not pediatric-friendly formulations of most of the drugs used to treat MDR-TB in children (with the exception of some of the fluoroquinolones and PAS); most programs split adult tablets, which can lead to inconsistent dosing.

Treatment of mono-resistant TB

Where mono-resistance to isoniazid is known or suspected when treatment is initiated, or when there is high background prevalence of isoniazid resistance, the addition of ethambutol to isoniazid, rifampicin and pyrazinamide in the intensive phase is recommended (see Chapter Treatment). For patients with more extensive disease, consideration should be given to the addition of a fluoroquinolone and to prolonging treatment to a minimum of 9 months. Mono-resistance to rifampicin should be treated as MDR TB.

Treatment of poly-resistant TB

Poly-resistance refers to resistance to two or more first-line drugs but not to both ionized and rifampicin.

Treatment of multidrug-resistant TB

Children with MDR-TB are treated in a similar way to adults with MDR-TB. One practical difference is that confirmation and DST may not possible, so that empirical treatment is often required for children with suspected MDR-TB. Management should adhere to the following principles:

- Never add a single drug to a failing regimen; this may lead to amplification of resistance.
- All treatment should be given daily and under direct observation.
- Treat the child according to the DST results from the likely source case, unless M. tuberculosis culture and DST results are available from the child.
- Do second-line DST in all MDR-TB cases to exclude resistance to the fluoroquinolones and/or second-line injectables, as this may call for additional drugs early in therapy.
- Give at least three (only in early primary disease) or preferably four drugs to which the patient or adult source case is naive or their isolates susceptible.
- Caregivers need counselling and support at every follow-up visit regarding adverse effects, treatment duration and importance of adherence. In addition, the following assessment of the child should be undertaken as a minimum:
    - symptom assessment;
    - assessment of treatment adherence;
    - enquiry about any adverse events; and weight measurement.

- Drug dosages should be adjusted to account for any weight gain. Clinical, radiographic and culture response to treatment should be monitored. Monthly smear microscopy and cultures should be done until confirmed negative on three consecutive occasions; thereafter, follow-up cultures can be done every 2-3months.
- Clinical monitoring for adverse effects should be done at every visit. Special investigations should be guided by the adverse effect profile of the drugs used.

While any of the drugs described in Table 4 might be used in the treatment of children with MDR-TB, safety data in children currently exist only for fluoroquinolones, and so the WHO recommendation on the treatment of MDR-TB in children addresses the use only of fluoroquinolones. There is a need for safety data on other drugs that are being used for treatment of children with MDR-TB.

Note: Children with proven or suspected pulmonary TB or tuberculosis meningitis caused by multi-drug resistant bacilli can be treated with a fluoroquinolone in the context of a well-functioning MDR-TB control programme and within an appropriate MDR-TB regimen. The decision to treat should be taken by a clinician experienced in managing pediatric TB.

Building a treatment regimen for MDR-TB

Treatment regimens for children with MDR-TB follow the same principles as in adults. With extensive pulmonary or disseminated extra-pulmonary disease, a minimum of four to six drugs should be included in the regimen, based on susceptibilities of the isolate, as outlined in the following progression:

1. Use any **Group 1 first-line oral drugs** (see Table 4) that have certain, or almost certain, efficacy, for example, drugs showing susceptibility in DST. These drugs should be administered for the duration of therapy.

2. Add one **Group 2 injectable agent** based on DST results and treatment history. This agent is normally given for a minimum of 6 months and for 4 months after culture conversion. Preferably, it should be an aminoglycoside such as amikacin. Do not use streptomycin (unless other Group 2 drugs are unavailable) because of high rates of resistance with DR-TB strains and higher incidence of toxicity.

3. Add **one Group 3 fluoroquinolone** based on DST results and treatment history, for the duration of therapy. Levofloxacin and moxifloxacin are preferred to ofloxacin. Note that ciprofloxacin is not recommended.

4. **Group 4 second-line oral drugs** should be added for the duration of therapy, until there are at least four drugs in the regimen to which the isolate is likely to be susceptible. The Group 4 drugs should be chosen on the basis of treatment history, adverse effect profile and cost. DST is not standardized for Group 4 drugs.

5. If a regimen of four effective drugs cannot be built from Groups 1-4, consider adding, in consultation with an MDR-TB expert, at least two **Group 5 third-line drugs**. DST is not standardized for Group 5 drugs. Drug groups used to treat drug-resistant TB are summarized in Table 4.

Table 4: Summary of drug groups used to treat drug-resistant TB

Drug group Daily	Drug name	adult dose in mg/kg	Maximum adult daily dose (mg)	Daily paediatric dose in mg/kg (max. dose in mg)[a]
Group 1: first-line oral drugs [b]	Ethambutol	20-25	2000	20-25 (2000)
	Pyrazinamide	30-40	2000	30-40 (2000)
Group 2: injectable agents[c]				
Aminoglycosides	Amikacin Kanamycin	15-20 15-20	1000 1000	15-22.5 (1000) 15-30 (1000)
Cyclic polypeptide	Capreomycin	15-20	1 000	15-30 (1000)
Group 3: fluoroquinolones	Ofloxacin	15-20	800	15-20 (800) 2x daily
	Levofloxacin	7.5-10	750	7.5-10 (750)
	Moxifloxacin	7.5-10	400	7.5-10 (400)
Group 4: second-line oral drugs[d]	Ethionamide (or prothionamide)	15-20	1 000	15-20 (1000) 2x daily
	Cycloserine (or terizidone)	10-20	1000	10-20 (1000) 1x/2x Daily
	p-aminosalicylic acid [e] (PAS; 4-g sachets)	150	12000	150 (12000) 2x/3x Daily
Group 5: third-line drugs of unclear efficacy (not recommended by WHO for routine use in MDR-TB patients) [f]	High-dose Isoniazid [g] Linezolid [h] Amoxicillin/ clavulanate Clarithromycin Thioacetazone[i] Imipenem/cilastatin Clofazimine	15-20 10-12, 2x daily 80mg/kg 3x daily 7.5-15, 2x daily 3-4 (only IV) 3-5	400 300, 1x/2x daily 500, 2x daily 150 300	

a. In children, doses of all drugs, including the fluoroquinolones, should be at the higher end of the recommended ranges wherever possible, *except* ethambutol. Ethambutol should be dosed at 15 mg/kg, and not at 25 mg/kg as sometimes used in adults with DR-TB, as monitoring for optic neuritis is more difficult in children.

b. DST could be unreliable – use an additional drug if DST is not done or result is susceptible.

c. Choose one drug in each of these groups; amikacin is preferred to kanamycin in children. Intramuscular injection of amikacin is very painful -intravenous infusion should be preferred.

d. Choose one or more of these drugs to make up total of four new drugs.

e. PAS (including PAS Na) is administered in acidic medium (e.g. yoghurt or orange juice) for improved absorption.

f. Consider use of these drugs if there are insufficient drugs in other groups to build an acceptable regimen. Each drug is considered as only half a drug - therefore two drugs in this group count as one additional drug.

g. In adults, high-dose isoniazid is defined as 15-20 mg/kg per day.

h. Linezolid dosage for TB is uncertain, but lower doses (300 mg twice daily or even 300 mg daily in adults) cause fewer adverse effects and still seem effective.

i. Thioacetazone should not be used in people living with HIV because of the serious risk of life-threatening adverse reaction and use shorter MDR TB Regimen.

4.6 Duration of treatment

There is little evidence on treatment of MDR-TB in children; typically, therefore, programmes treating children with MDR-TB use WHO guidelines for treatment of adult patients. Treatment duration depends on the extent of the disease; in most cases the intensive phase will last at least 8 months and total duration of treatment will be at least 18 months. All treatment should be given daily and under direct observation. The optimal duration of treatment for MDR-TB in children is unknown. It may be that children with early, non-extensive disease require treatment for shorter periods than adults, but this is an area that requires research.

4.7 Monitoring

Diagnosing children with DR-TB and designing an appropriate treatment regimen can be major obstacles in the management of pediatric DR-TB. Another challenge is maintaining the patient on therapy for 18-24 months and making sure that he or she is closely followed by physicians, nurses, health care workers, and caregivers. Children have been successfully treated for DR-TB, but only with appropriate monitoring and follow-up. Monitoring is needed to evaluate therapeutic efficacy and to mitigate the development of adverse events. This section will discuss:

- Timing and types of monitoring
- Adverse events and management strategies
- Management of co-morbid conditions
- Adherence support

Table 5: A proposed monitoring schedule

All children	Baseline	Month												Ongoing
		1	2	3	4	5	6	7	8	9	12	15	18	
HIV status														
Toxicity (symptoms, signs)														
Height and weight														
Audiology[1]														
Color vision testing[2]														
CXR[3]														
TB culture and DST[4]														
Creatinine and potassium[1]														
TSH, T4[5]														
Hematology (FBC, diff)[6]														
HIV-infected children														
LFTs, cholesterol[7]														
CD4 count and viral load														

[1] Monthly while on injectable and at 6 months following termination of injectable

[2] If on ethambutol

[3] If any pulmonary involvement

[4] Monthly if old enough to expectorate; if unable to expectorate and initially smear or culture positive, monthly until culture-converted then every three months; if initially smear and culture negative, perform if clinically indicated

[5] If on ethionamide, prothionamide or PAS

[6] If on linezolid or HIV-infected

[7] For patients on ART, depending on the regimen

4.8 Identification and Management of Adverse Events

Table 6: Identification and Management of Adverse Events

Type of adverse event	Likely culprit drugs	Identification	Management
Hepatotoxicity	INH, PZA, RIF, THA, PAS, Clofazimine (CFZ)	Tender liver, visible jaundice	Stop all drugs; Wait for liver function to return to normal; Re-introduce drugs one-by-one sequentially, every 2 days with monitoring of liver function before introducing the next drug.
Visual problems	EMB	Regular testing with Ishihara Chart	Stop EMB or substitute for alternative drug.
Hearing problems	AMK, KM, CM	Identified through audiometry or problems in communication	Consider stopping the injectable drug, substituting for an alternative drug, reducing dose or increasing dose interval.
Thyroid dysfunction	THA, PAS	Regular blood testing, clinical hypothyroidism or goitre	Consider thyroxine supplementation (0.05mg daily) if (a) clinical hypothyroidism, or (b) raised TSH and decreased fT4; If raised TSH and normal fT4 repeat test in 1 month.
Renal impairment	AMK, KM, CM	Regular blood testing, symptoms of high potassium	If creatinine rises or potassium is elevated, stop injectable, substitute for alternative drug, dose three times a week or reduce dose.
Severe rash (SJS)	Any drug	Severe rash, peeling mucus membranes, child unwell	Stop all drugs; Wait until clinical condition has improved; Re-introduce drugs one-by-one sequentially, every 2 days, monitoring clinically.
Nausea and vomiting	THA, EMB, PAS	Clinically	Consider separating the dosing of THA from the other drugs by giving it in the evening; Consider reducing the dose of THA and building the dose up to full dose over 2 weeks.

Type of adverse event	Likely culprit drugs	Identification	Management
Diarrhea	PAS	Clinically	Split dose of granules to give small doses throughout day; Reduce dose; Consider loperamide.
Peripheral neuropathy	INH	Clinically	Give or increase pyridoxine; If persistent or severe, stop INH.
Neuropsychiatric problems	INH, OFX, LVX, MFX, TZD, CS	Seizures, headache, behavior changes, sleep disturbances	Verify correct dosing; Stop likely culprit drug; If symptoms persist, reintroduce and stop next most likely drug; If symptoms severe or persistent, stop all likely drugs or reduce dose.
Joint problems	PZA, OFX, LVX, MFX	Clinically	Verify correct dosing; Consider reducing dose/ stopping possible culprit drug; Consider trial of allopurinol.
Painful injection sites	AMK, KM, CM	Clinically	Add local anesthetic to drug in equal volumes; Vary site of injection on a daily basis; If severe, consider splitting dose and giving half into two different sites.

4.9 Co-Morbid Conditions

Children with DR-TB often suffer from other conditions. These may be pre-existing, or develop as a result of their DR-TB, or may be in conjunction with their DR-TB. Common co-morbid conditions seen in children with DR-TB include HIV, diabetes mellitus, orthopedic problems, and reactive airway disease. In each of these cases, children do better in terms of DR-TB outcomes when their co-morbid conditions are also aggressively treated and controlled. Management of co-morbid conditions should follow these principles:

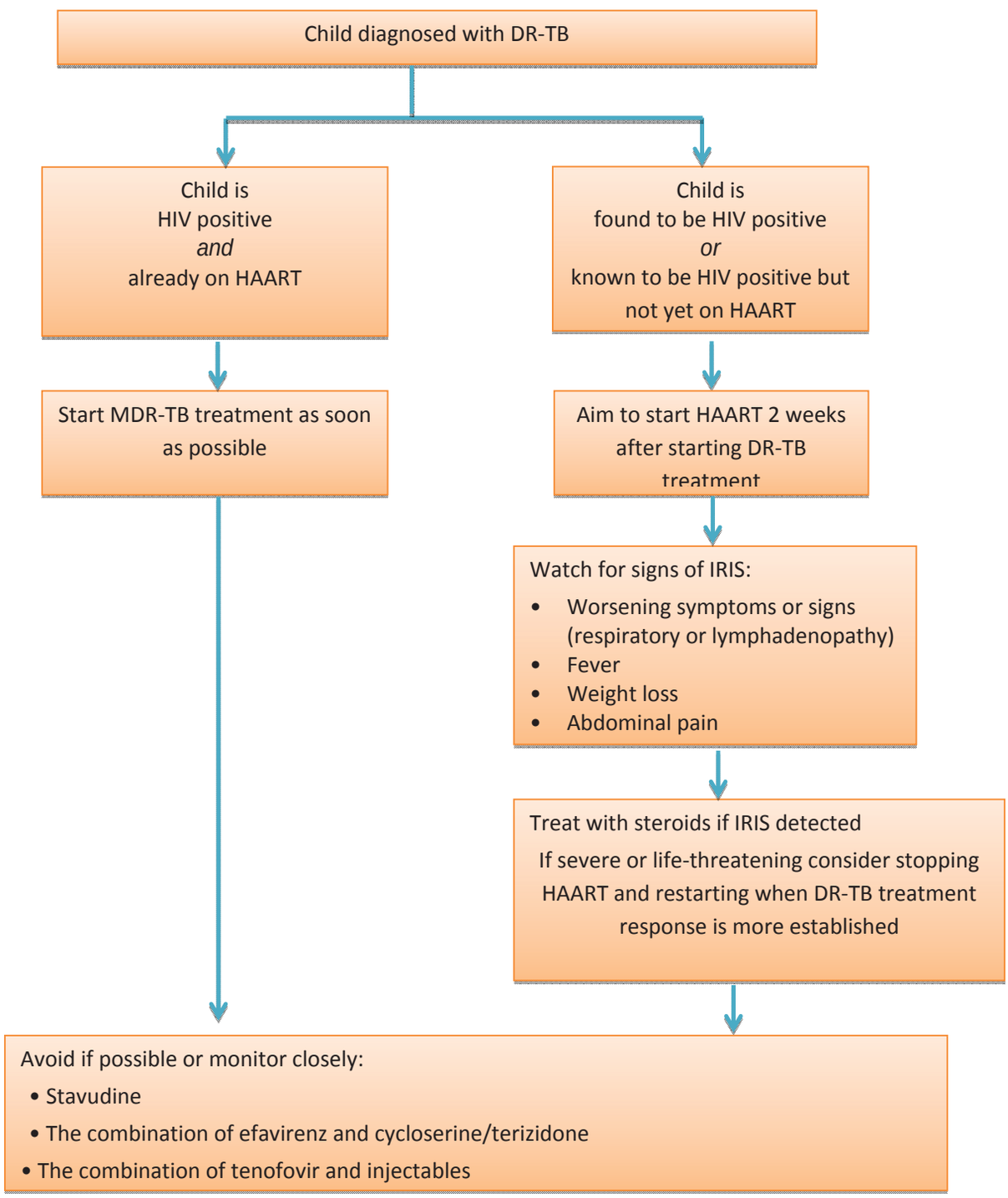
- Management should occur at the same time as treatment for DR-TB; waiting for DR-TB treatment to finish or move to a "continuous" phase puts the patient at risk for poor outcomes from both conditions.
- Management should be provided in an integrated setting making care easy for the patient and reducing the risk of DR-TB in other clinical settings (i.e. diabetes clinic, asthma clinic).
- Care should be taken to avoid giving drugs with overlapping toxicities when possible.

A detailed algorithm on the management of children with co-morbid HIV is included in this field guide. For other co-morbid conditions, we recommend the following (Figure-4)

- Diabetes mellitus: Blood sugar results may fluctuate in the setting of acute DR-TB, and thus, more frequent monitoring of blood sugars is necessary. In addition, common drugs used to treat TB may exacerbate glucose control problems and could have overlapping toxicities with both the disease itself (e.g. peripheral neuropathy) and with diabetes treatment regimens (e.g. oral antihyperglycemics). Patients may need to adjust their insulin dosing for tighter control, especially in the early stages of treatment. In addition, patients should be provided with adequate calories to ensure healthy weight gain.

- Reactive airway disease: Active DR-TB can exacerbate existing reactive airway disease or cause reactive airway disease. Bronchodilators should be used for both maintenance and rescue situations. Inhaled corticosteroids can be safely used in children with MDR-TB.
- Orthopedic problems: Children may develop TB of the spine or joints, requiring the use of braces or other support devices. Children may also need physical therapy as part of their recoveries. When possible, local materials should be used for devices, and simple physical therapy regimens (e.g. chest clapping) that can be done at home should be designed.
- All children with DR-TB should have a full complement of immunizations. It is important to verify immunizations at each appointment.

Figure 4: Algorithm for Management of Children on Treatment for DR-TB and HIV



4.10 Adherence

Adherence to DR-TB therapy is one of the cornerstones of treatment success. Hospitalization is not necessary for most children with DR-TB and may actually decrease rates of adherence. As with adults, all children should be given treatment under DOT for each dose. Clinic-based DOT may place undue burdens on patients and their families, and where feasible, community-based DOT should be considered. If community-based DOT is not feasible, patients should be given incentives (e.g. food baskets) and enablers (e.g. transportation vouchers) to assist in treatment adherence.

Pediatric DR-TB patients face special challenges with adherence. Very young children may not be able or willing to swallow tablets. Adolescent patients may use non-adherence as a way of asserting their independence. It is important to recognize that adherence strategies will need to be tailored to the individual patient and may change over time, even for the same patient. Some common principles should be followed in improving adherence among pediatric DR-TB patients. These include:

- Age-appropriate patient education for the child and the caregiver. This is an extremely important part of adherence. The level of information given, and the manner in which it is delivered will need to be tailored according to the age of the child and where they are in their treatment course.
- Avoid the use of physical restraints and nasogastric tubes when possible. Avoidance may not be possible in all settings. Where restraints or nasogastric tubes are required, a daily assessment of ongoing need should be made.
- Adherence should be approached as a relationship, and pediatric patients offered some control over the process whenever possible (i.e. holding the medication spoon or dispenser with the provider; deciding the order in which to take the medications).
- It may be convenient to dose all medications at the same time, but this may be overwhelming for children. Twice or thrice daily dosing can be considered for some medications. Even with once daily dosing, half of the pills could be given in the morning and half in the evening, provided patients are not dosed the same medication more than once in 24 hours.
- Drug substitution to improve adherence (i.e. the changing of one effective medication for another in a successful treatment regimen to assist with adverse event management) can be considered, provided the substitution does not compromise the integrity of the regimen.
- Pediatric adherence depends on the caregivers. They should be involved at all stages and help make decisions about improving adherence.
- Incentives should be provided to children on a daily or weekly basis, depending on age. This could be as simple as a positive mark on a wall chart, singing a favorite song, or eating a special food. For adolescents, mobile phone minutes have been shown to be a powerful incentive. Incentives should also be provided to caregivers.

It is important to remember that children are often far more adherent than providers imagine them to be. Non-adherence may also be a sign of psychological or emotional distress, and social support should be given to both the child and the caregiver.

5 Management of TB in Pediatric living with HIV

5.1 Background

Globally, tuberculosis (TB) 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. HIV infection is a major threat in the global resurgence of tuberculosis (TB), especially for tuberculosis control in many developing countries. People living with HIV are at least 26 times more likely to develop TB disease as people without HIV. TB is the biggest killer of people with HIV/AIDS, shortening their lives by 6 to 24 months. Globally, 12% of the 9.6 million new TB cases in 2014 were HIV- positive. The World Health Organization estimates that the prevalence of HIV among children with TB in moderate to high prevalence countries ranges between 10% and 60%.

Tuberculosis, although curable, is one of the most common causes of HIV- related illness and death. 1.2 million People living with HIV/AIDS (PLHIV) are estimated to be co-infected with Mycobacterium tuberculosis, with 74% of those co-infected living in sub-Saharan Africa.

The annual risk of developing TB in a PLHIV who is co-infected with M tuberculosis ranges from 5 to 15 percent. HIV increases the rate of recurrent TB, which may be due to either endogenous reactivation (true relapse) or exogenous re-infection. Increasing tuberculosis cases in PLHIV poses an increased risk of TB transmission to the general community regardless whether they are infected with HIV or not.

The World Health Organization (WHO) has recommended the package of "collaborative TB/HIV activities" since 2004. To reduce the burden of TB in PLHIV, the WHO recommended the 3I's approach in addition to early antiretroviral therapy. Treatment of latent TB infection with 6 months of isoniazid preventive therapy (IPT) which can reduce the progression to active TB in PLHIV by 32-62%.[12] It is estimated that about 34% of children aged <15 years needing ART in low- and middle-income countries receive treatment compared with about 68% of adults.

Children living with HIV infection have increased risk of TB exposure, infection, progression to disease, and TB-related morbidity and mortality. This risk is influenced by the degree of immune suppression. All children living with HIV infection in a TB-endemic setting should therefore be regularly screened for TB by clinical assessment at each visit to a health facility or contact with a health worker. Evaluation should aim to identify those patients who are likely to have TB disease, requiring anti-TB treatment, and those who should start IPT. Suspicion of TB disease in children with HIV is initially based on the presence of clinical symptoms. Clinical evaluation may be followed up with further investigations as appropriate (e.g. chest radiography). As for any child with suspected TB, attempts should be made to confirm diagnosis (e.g. culture, Xpert MTB/RIF assay) whenever possible.

Childhood HIV infection is particularly common in settings where antenatal HIV prevalence is high and PMTCT interventions are not widely implemented. The prevalence of HIV is therefore particularly high among infants and young children, an age-group also at risk for TB. In regions endemic for TB/HIV, TB is common in children living with HIV, and HIV infection is common in children with TB. It is recommended that HIV testing be routinely offered to all children with suspected or diagnosed TB.

5.2 Diagnosing TB in HIV-Infected Children

In HIV-infected children the diagnosis of TB disease is more complex because:

- Clinical features consistent with pulmonary TB are common in children living with HIV but may be due to other diseases and therefore lack specificity for a diagnosis of TB.
- Most children living with HIV are infected by mother-to-child transmission. The peak age prevalence for HIV is therefore in infants and young children (<5 years), who also make up the age group in which it is most difficult to confirm the cause of acute or chronic lung disease, including TB.
- TST is less sensitive in children living with HIV than in HIV-negative children; **induration of >5 mm is considered positive if the child is living with HIV.**
- Children living with HIV have a very high incidence of acute and chronic lung diseases other than TB.
- Children living with HIV may have lung disease of more than one cause (co-infection), which can mask response to therapy.
- There is an overlap of radiographic findings in TB and other HIV-related lung disease.

There is the dual risk that TB may either be over-diagnosed, resulting in unnecessary TB treatment, or under-diagnosed, resulting in increased morbidity and mortality. LIP is the most difficult condition to distinguish from TB, due to radiological similarities, although it is usually associated with typical clinical signs, such as clubbing and/or parotid enlargement. TB can occur in children with an underlying diagnosis of LIP, bronchiectasis, or any other lung infection. In spite of the difficulties described, TB can usually be diagnosed with a fair degree of accuracy in the majority of HIV-infected children. The diagnostic approach in HIV-infected children is essentially the same as for HIV-uninfected children. Since the symptoms of TB can be confused with the symptoms of HIV disease and the CXR is more difficult to interpret, if possible every effort should be made to try and establish a bacteriological diagnosis.

5.3 Treatment of TB in HIV-Infected Children

Children living in settings where the prevalence of HIV is high should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months at the dosages. Children with suspected or confirmed pulmonary TB or tuberculosis peripheral lymphadenitis in settings with a high HIV prevalence (or with confirmed HIV infection) should not be treated with intermittent regimens (that is, twice- or thrice-weekly doses).

Each child should be assessed 2 weeks after the start of TB treatment then reviewed monthly with clinical monitoring, which should include symptom assessment, weight measurement, assessment of adherence to treatment and enquiry about any adverse events. Dosages of anti-TB drugs should be adjusted to account for any weight gain. Most children living with HIV with drug-sensitive TB who are compliant with therapy have a good response to the 6-month regimen. Possible reasons for treatment failure are non-compliance with therapy, drug-resistant TB or alternative diagnoses (incorrect diagnosis of TB).

All children living with HIV who have successfully completed treatment for TB disease should receive isoniazid for an additional 6 months. When compared with HIV-negative children, responses to TB treatment and outcome are poorer for children living with HIV. Before the availability of ART, many deaths in children with TB/HIV occurred in the first 2 months following the start of TB treatment. Medical risk factors for poor treatment response and mortality include severe malnutrition, co-infections, severe immune-suppression and high viral load. Additional therapy recommended for HIV-infected children with TB, which may help to improve TB treatment outcomes, includes co-trimoxazole preventive therapy, the early start of ART (see below) and pyridoxine supplementation along with nutritional support. (See details in Chapter 3).

5.4 Co-trimoxazole preventive therapy

Co-trimoxazole is a broad-spectrum antimicrobial agent that prevents a range of secondary bacterial and parasitic infections in eligible adults and children living with HIV. Daily prophylaxis – co-trimoxazole preventive therapy (CPT) - prolongs survival in children living with HIV and reduces the incidence of co-morbidities. It also reduces the risk of co-infections such as pneumocystis pneumonia in HIV-exposed infants. CPT is therefore recommended for all HIV-exposed infants and children living with HIV, including those with TB, and should be implemented as an integral component of a package of HIV related services.

Table 7: Cotrimoxazole prophylaxis

Age	Recommended daily cotrimoxazole prophylaxis
Under 6 months of age	20 mg trimethoprim (TMP) + 100 mg sulfamethoxazole (SMX)
Under 5 years	40 mg TMP + 200 mg SMX
5 years or older	80 mg TMP + 400mg SMX

5.5 Antiretroviral therapy

Antiretroviral therapy (ART) in children living with HIV aims to improve the length and quality of life, reduce HIV-related morbidity and mortality by reducing the incidence of opportunistic infections (including TB), reduce the viral load, restore and preserve immune function, and restore and preserve normal growth and development. ART improves TB treatment outcomes for children living with HIV.

Appropriate arrangements for access to ART should be made. All children with TB disease and HIV infection require ART. In HIV-infected children with confirmed or presumptive TB disease, initiation of TB treatment is the priority. The decision on when to initiate ART after starting TB treatment should consider the child's immune status and clinical severity of disease, the child's age, pill burden, potential drug interactions, overlapping toxicities and possible IRIS.

This should be weighed up against the risk of further HIV disease progression and immunesuppression with associated increase in mortality and morbidity in the absence of ART. **TB treatment should be started first, followed by ART as soon as possible thereafter (and within 8 weeks of the start of TB treatment). For those with a CD4 count below 50 cells/mm3, ART should be provided within 2 weeks of the start of TB treatment.**

Table 8: Use of first-line ART

Age	Treatment regimen
Children younger than 3 years	Protease inhibitor (PI)-based regimen in combination with ABC or zidovudine (AZT)
Adolescents and children older than 3 years	Regimens comprising a non-thymidine nucleoside reverse-transcriptase inhibitor (NRTI) backbone (tenofovir disoproxil fumarate (TDF) or abacavir (ABC) + lamivudine (3TC)) and one non-nucleoside reverse-transcriptase inhibitor (NNRTI) efavirenz (EFV)

Note: For first-line ART, use of simplified and less toxic regimens – as fixed-dose combinations whenever possible – is recommended as the most effective and convenient approach.

Table 9: When to start ART in children

Age	When to start
Infants (<1 year)	Treat all individuals regardless of CD4 count
1 year to <5 years	Treat all individuals (children ≤2 years or with WHO stage 3 or 4 or CD4 count ≤750 cells/mm³ or <25% as a priority)
5 years and above	WHO stage 3 or 4 or CD4 ≤500 cells/mm³ (CD4 ≤350 cells/mm³ as a priority)

NB: Given its complexity, it is important to refer to the latest national HIV guidelines for current recommendations regarding the co-treatment of TB and HIV in children.

6 Prevention of TB in Children

6.1 Screening for Child Contacts of Known TB Cases and Management

Contact screening is a mechanism of active or intensified case-finding. Early identification of disease among contacts can reduce both disease severity - thereby improving outcomes- and subsequent rates of transmission. If the index case is a child, contact screening includes efforts to identify the likely source case.

Young children living in close contact with an index case of smear positive pulmonary TB is at a high risk of TB infection and disease. The risk of infection is greatest if the contact is close and prolonged. The risk of developing disease after infection is much greater for malnourished children, children under 5 years and HIV infected children than it is for HIV un-infected children and those over 5 years. If the disease develops it usually does so within 1 years of infection, but in infants the time lag can be as short as a few weeks. Isoniazid preventive therapy (IPT) for young children with infection who have not yet developed disease will greatly reduce the likelihood of developing TB during childhood. Children of any age who are household contacts of MDR-TB index cases are at especially high risk of contracting MDR-TB, and so their prompt evaluation and treatment if necessary, is important.

Contact screening refers to the screening or evaluation for TB infection or disease of all close contacts of smear positive PTB index case

Purpose of contact screening and management

The main purpose of child contact screening is to:

1. Identify symptomatic children (i.e. children of any age with undiagnosed TB disease) and treat them for TB.
2. Provide Isoniazid preventive therapy (IPT) for the high risk children who have no signs or symptoms of TB disease i.e.
    - all children under 5 years of age; and,
    - HIV-positive children of any age.

The best way to detect TB infection is the TST, and CXR is the best method to screen for TB disease in symptomatic children contacts who are not able to produce sputum for AFB microscopy. Where these two tests are unavailable contact screening and management can be conducted on the basis of a simple clinical assessment. Generally clinical assessment is sufficient to decide whether the contact is well or symptomatic.

Clinical evaluation of household and close contacts for active TB should be done on the basis of their risk for having or developing active TB or for the potential consequences of the disease if it develops. Priority should be given to contacts who are:

- children with symptoms suggestive of TB,
- children <5 years of age,
- children with known or suspected immune-compromising conditions (especially those living with HIV), and
- child contacts of index cases with MDR-TB or XDR-TB (proven or suspected)

Contact investigation should be conducted for household and close contacts when the index case has any of the following characteristics:

- has sputum smear-positive pulmonary TB,
- has MDR-TB or XDR-TB (proven or suspected);
- is a person living with HIV;
- is a child <5 years of age.

Symptoms for Child Contact Screening

A symptom-based approach means that screening can be done by health workers at a peripheral level: access to a district-level health facility is not needed. Only symptomatic contacts may require referral to the secondary level for further assessment.

1. Non remitting cough for more than 2 weeks
2. Persistent fever for more than 2 weeks
3. Loss of weight/poor weight gain
4. Lethargy/malaise/reduced play
5. Enlarged cervical LN

In the resource-constrained setting, screening of contacts of sputum smear-positive cases is prioritized; sputum smear-positive cases are the most likely to transmit infection with exposure. NTPs may decide to include contacts of all TB index cases for screening, depending on available resources.

In some settings, screening of child contacts includes TST to screen for infection and chest X-ray (CXR) to screen for disease. However, routine assessment of exposed contacts does not require CXR or TST. These tests have limitations and are often not readily available or possible in low- and middle-income settings. In the absence of TST or CXR, clinical assessment alone is sufficient to decide whether the contact is well or symptomatic.

Note: Symptom-based screening approach to child contact management (See Diagnosis chapter 2 and Figure 1) which provides a simple algorithmic approach that can be applied in any setting and requires information only on age, HIV status and the presence or absence of symptoms.

Isoniazid preventive therapy

Preventive therapy is indicated for an asymptomatic contact or a contact in whom TB disease has been excluded if the contact is less than 5 years of age or who is living with HIV (regardless of age). Preventive therapy for young children with TB infection who have not yet developed TB disease will greatly reduce the likelihood of TB disease developing during childhood. While this treatment is called “preventive therapy”, it is actually treatment for latent TB infection.

Children <5 years of age who are household or close contacts of people with TB and who, after an appropriate evaluation, are found not to have TB disease should be given 6 months of IPT (10 mg/kg per day, range 7-15mg/kg, maximum dose 300 mg/day). Single isoniazid dispersible tablets, 100 mg, can be obtained from the Global Drug Facility (GDF). Follow-up should be carried out at least every 2 months until treatment is complete. There is no risk of isoniazid resistance developing in children receiving IPT, even if the diagnosis of active TB is missed.

Child contact known to be HIV-infected

If the child contact is HIV-infected and asymptomatic, then IPT should be considered for all ages, including those 5 years and older. As with other contacts, active disease should be ruled out before providing HIV-infected children with IPT. HIV infected children who have symptoms should be carefully evaluated for TB, and if found to have TB should be started on TB treatment.

Suspected HIV infection of contact

If the index case is a parent and is HIV infected, their children may be at risk of both TB and HIV infection. It is important to counsel and test for HIV as we screen for TB infection in all the contacts. (Consider joint TB/HIV contact investigations)

Tracing of TB Source

Where the child is the first person in the household diagnosed to have TB, the household members and other close contacts of the child should be evaluated in order to identify the index case of TB. Evaluation should include screening for classic TB symptoms: cough, fever, weight loss and lethargy.

Note: The index case may have transmitted TB to the child several months earlier, and may not currently be living in the household.

Table 10: Sample contact screening register

Name	Age (years)	Symptoms (Y/N)	HIV status	IPT (Y/N)	Anti-TB treatment (Y/N)	TB registration number	Treatment Outcome

6.2 BCG Vaccination in Children

Bacillus Calmette- Guerin (BCG) is a live attenuated (weakened) form of the cow TB organism (M. bovis). Neonatal BCG vaccination provides substantial protection against the more severe types of disseminated TB, such as miliary TB and tuberculous meningitis, to which infants and young children are particularly susceptible. All children should be given the BCG vaccine as soon as possible after birth except those with suspected TB infection at birth. If the baby has TB, the baby should receive a full course of TB treatment. Similarly, if the baby is asymptomatic TB, withhold BCG at birth and give BCG after completion of 6 months INH therapy. Many children continue to get TB despite routine BCG vaccination and the youngest remain the most vulnerable. Nevertheless, the BCG vaccination is recommended to avoid life threatening diseases. There is no evidence that revaccination with BCG affords any additional protection, and revaccination is therefore not recommended. In settings where TB is highly endemic or where there is high risk of exposure to TB, a single dose of BCG vaccine should be given to all infants.

Adverse Events following BCG Immunization

Adverse events include suppurative adenitis, local BCG abscess, lymphadenopathy, wart-like nodules, large ulcers, osteomyelitis, local bacterial infections and lupoid reactions. The most common complication is BCG adenitis. BCG adenitis is best left alone. Needle aspiration or total excision is necessary only if the lump is very painful.

BCG and HIV

BCG vaccine should not be used in children who are known to be HIV-positive because of the increased risk of severe and often fatal disseminated BCG disease. In infants whose HIV status is unknown and who are born to HIV-positive mothers and who lack symptoms suggestive of HIV, BCG vaccine should be given after considering local factors. The diagnosis of BCG disease is difficult and the treatment is specialized: M. bovis is inherently resistant to pyrazinamide and thus all forms of BCG disease must be treated using higher doses of other first-line TB medications. For example, a daily isoniazid dose of up to 20 mg/kg (maximum 300 mg) and a daily rifampicin dose of up to 20 mg/kg (maximum 600 mg) for at least 9 months of therapy, as well as continuous monitoring for drug toxicity and response to therapy. Children living with HIV and suspected of having BCG disease should be referred to an appropriate expert for management.

BCG-induced immune reconstitution inflammatory syndrome (BCG-IRIS) is increasingly reported in infants living with HIV who have started ART early in infancy. BCG-IRIS can cause significant morbidity although - unlike disseminated BCG disease – it is rarely fatal. However, BCG is given routinely to newborns in TB-endemic settings and it is difficult to establish HIV infection status before the vaccine is administered.

HIV infection cannot be reliably determined at birth. Infants who are HIV-exposed but uninfected will be at increased risk of disseminated TB disease if not vaccinated with BCG. In settings endemic for TB/HIV, BCG should therefore continue to be given to infants who are born to HIV-positive mothers but who do not have any symptoms suggestive of HIV infection.

The following factors are likely to be important determinants of the risk-benefit balance of such an approach:

- coverage and success of the prevention of mother to child transmission of HIV (PMTCT) programme;
- possibility of deferring BCG vaccination in HIV-exposed infants until HIV infection status has been established;
- availability of early diagnosis of HIV infection in infants;
- provision of early ART to HIV-positive infants.

Guideline while using BCG vaccine:

Decisions at national and local level should be taken based on the following guideline on the use of BCG vaccine in infants at risk for HIV infection:

- In general, populations with high prevalence of HIV also have the greatest burden of TB; in such populations, HIV-negative children will particularly benefit from the use of BCG vaccine.
- Benefits of BCG vaccination outweigh the risks for infants born to women of unknown HIV status. These infants should be immunized.
- Benefits of BCG vaccination usually outweigh the risks for infants whose HIV infection status is unknown and who have no signs or reported symptoms suggestive of HIV infection but who are born to HIV-positive women. These infants should be immunized after consideration of the aforementioned locally determined factors.
- Risks of BCG vaccination outweigh the benefits for infants who are known to be HIV-positive with or without signs or reported symptoms of HIV infection. These infants should not be immunized.
- Risks of BCG vaccination usually outweigh the benefits for infants whose HIV infection status is unknown but who have signs or reported symptoms suggestive of HIV infection and who are born to HIV-positive mothers. These children should not be immunized. However, this guideline will be applicable only to children who have not received BCG in the first few weeks of life, since clinical

manifestations of HIV infection typically occur after 3 months of age. If infection status can be established with early virological testing, BCG may then be administered once HIV infection has been ruled out.

6.3 TB Infection Control

Infection control is of paramount importance in the management of DR-TB in children. Children should be protected from becoming infected with DR-TB in both the health facility and home setting. Children with DR-TB should be safely managed in a way that does not cause unnecessary psychosocial stress and avoids making them victims of stigma. Children with DR-TB usually do better in a home setting and when they are able to resume normal activities, such as going to school. In most cases, as long as the child is on appropriate therapy for DR-TB, the risk of transmitting DR-TB is low. This section offers practical guidance on facility-based infection control and home/community-based infection control that acknowledges the need to reduce DR-TB transmission risk while at the same time acknowledging the important developmental needs of a growing child. This section will discuss:

- All family members of children with DR-TB should themselves be actively screened for TB by a trained provider;
- Facility-based infection control;
- Community-based infection control.

Facility-Based Infection Control

Although negative pressure airflow isolation rooms and precautions are the gold standard in TB infection control, there are simple infection control measures that can be easily put into place to make nosocomial transmission of DR-TB less likely. These include:

- Having patients wait outdoors
- Using windows for natural ventilation
- Having separate waiting areas for TB and DR-TB patients with separate entrances and air supplies
- Considering separate waiting areas for patients with cough if space allows
- Separating waiting areas for HIV patients, who are exceptionally vulnerable to TB, when possible
- Avoiding scheduling patients for well visits on days when known DR-TB patients are being seen
- Ensuring that appropriate therapy be given and maintained for all TB patients
- Having patients with active cough wear surgical masks to decrease transmission
- Avoiding unnecessary hospitalizations
- Discharging patients on treatment from the wards as quickly as possible once effective therapy has been started and can be maintained in the community. This can be within days to weeks of starting DR-TB therapy.
- Taking special infection control measures during highly infectious diagnostic procedures such as induced sputum collection

Community-Based Infection Control

Patients with DR-TB can be safely treated in the community setting, and the risk for ongoing transmission is low, once the patient is on appropriate DR-TB therapy. Some community and household measures should be taken to decrease transmission in the household and community. These include:

- DR-TB patients should ideally sleep in a separate room.
- Windows in the home of a DR-TB patient should be kept open as often as possible.

- DR-TB patients should spend as much time outside whenever possible, including visits with friends and family members.
- DR-TB patients should be provided with social support to be able to stay on DR-TB therapy.

Household and community members often fear becoming infected with DR-TB when a child with DR-TB is returned to the community. As long as the child is maintained on appropriate treatment for DR-TB, his or her risk of infectiousness is low. Once his or her smear is negative, he or she should return to normal activities—including school and sporting teams—provided his or her clinical status allows. Education should be provided to family members and key community members (i.e. teachers, coaches, ministers). This will decrease stigma and discrimination. Specific points to address include:

- Once the child is on DR-TB treatment, he or she is unlikely to transmit disease.
- If smear-negative, the child doesn't need to wear a mask in public.
- Children with DR-TB can share bathrooms, utensils, balls, tools, crayons, etc.
- Children with DR-TB feel better physically and psychologically when they can return to their usual environments and activities.

Annex 1

Weight-Based Dosing in Children

Group 1: Oral first-line anti-TB drugs

Isoniazid (10–15 mg/kg)	
kg	**100 mg tablet**
1.0–2.9	not recommended
3.0–4.9	0.5 tab
5.0–8.9	1 tab
9.0–12.9	2 tabs
13.0–20.9	3 tabs
21.0–26.9	4 tabs
27.0–29.9	5 tabs

Older children over 14 kg can use the adult 300 mg tablet in combination with the 100 mg tablet to reduce the pill count.

Rifampicin (10–20 mg/kg)		
kg	**150 mg tablet**	**300 mg tablet**
1.0–2.9	not recommended	
3.0–3.9	0.5 tab	-
4.0–4.9	0.5 tab	-
5.0–7.9	1 tab	-
8.0–12.9	1.5 tabs	-
13.0–17.9	2 tabs	1 tab
18.0–25.9	3 tabs	1.5 tabs
26.0–29.9	4 tabs	2 tabs

Ethambutol(15–25 mg/kg)	
kg	**100 mg tablet**
1.0–2.9	not recommended
3.0–7.9	1 tab
8.0–12.9	2 tabs
13.0–15.9	3 tabs
16.0–26.9	4 tabs
27.0–29.9	5 tabs

Older children over 16 kg can use the adult 400 mg tablet in combination with the 100 mg tablet to reduce the pill count.

Pyrazinamide (30–40 mg/kg)		
kg	**400 mg tablet**	**500 mg tablet**
1.0–2.9	not recommended	
3.0–4.9	0.25 tab	0.25 tab
5.0–5.9	0.5 tab	0.25 tab
6.0–9.9	0.5 tab	0.5 tab
10.0–11.9	1 tab	0.5 tab
12.0–14.9	1 tab	1 tab
15.0–18.9	1.5 tabs	1 tab
19.0–20.9	1.5 tabs	1.5 tabs
21.0–25.9	2 tabs	1.5 tabs
26.0–26.9	2 tabs	2 tabs
27.0–29.9	2.5 tabs	2 tabs

Group 2: Injectable anti-TB drugs (injectable agents or parental agents)

Drug	Daily dose	Maximum daily dose
Streptomycin	15-20 mg/kg once daily	1000 mg
Amikacin	15-22.5 mg/kg once daily	1000 mg
Kanamycin	15-30 mg/kg once daily	1000 mg
Capreomycin	15-30 mg/kg once daily	1000 mg

To illustrate dose calculation, take the example of a child that weighs 6.9 kg.

• Both the low and high doses for the child's weight are calculated.

For kanamycin:

Low dose: 15 mg/kg x 6.9 kg = 103 mg

High dose: 30 mg/kg x 6.9 kg = 207 mg

• A convenient dosing is then chosen between the two numbers.

Select a dose between the two numbers and towards the higher number. In this case, choose: 150 mg per day, single dose.

• Calculate the number of mL to draw up in the syringe based on the mg/mL concentration of the preparation.

Group 3: Fluoroquinolones

Levofloxacin (5 years and under: 7.5-10 mg/kg twice daily; over 5 years: 7.5-10 mg/kg once daily)		
kg	**250 mg tablet**	**25 mg/mL suspension**
1.0–2.9	not recommended	
3.0–4.9	0.25 tab	2.5 mL
5.0–8.9	0.5 tab	5 mL
9.0–11.9	0.75 tab	7.5 mL
12.0–16.9	1 tab	10 mL
17.0–24.9	1.5 tabs	15 mL
25.0–29.9	2 tabs	20 mL

Levofloxacin is dosed twice daily for children 5 years of age and under (total daily dose: 7.5-10mg/kg/day) and once daily for children over 5 years of age (total daily dose: 7.5-10mg/kg/day). This is done because children under five metabolize the levofloxacin faster than those older than five. Therefore, give the dose indicated in the table twice per day for children under five.

Moxifloxacin(7.5–10 mg/kg)		
kg	**400 mg tablet**	**20 mg/mL suspension**
1.0–2.9	not recommended	
3.0–3.9	not recommended	1.5 mL
4.0–4.9	not recommended	2 mL
5.0–7.9	not recommended	2.5 mL
8.0–13.9	not recommended	5 mL
14.0–14.9	0.5 tab	5 mL
15.0–19.9	0.5 tab	7.5 mL
20.0–26.9	0.5 tab	10 mL
27.0–29.9	0.5 tab	12.5 mL

The moxifloxacin suspension is not available commercially and must be prepared.

Ofloxacin(15–20 mg/kg)	
kg	**200 mg tablet**
1.0–2.9	not recommended
3.0–7.9	0.5 tab
8.0–14.9	1 tab
15.0–20.9	1.5 tabs
21.0–26.9	2 tabs
27.0–29.9	2.5 tabs

Later generation quinolones such as levofloxacin and moxifloxacin are preferred over ofloxacin.

Group 4: Oral bacteriostatic agents

Cycloserine / Terizidone(10–20 mg/kg)		
kg	**250 mg capsule**	**1 capsule in 10 mL water**
1.0–2.9	not recommended	
3.0–4.9	0.25 cap	2.5 mL
5.0–8.9	0.5 cap	5 mL
9.0–11.9	0.75 cap	7.5 mL
12.0–16.9	1 cap	10 mL
17.0–24.9	1.5 caps	15 mL
25.0–29.9	2 caps	20 mL

For older children who cannot swallow capsules, the capsules can be opened and dissolved in 10 mL water to aid administration.

PAS (150–200 mg/kg)		
kg	**PASER granules (4g sachet)**	
	Daily	**Twice daily**
1.0–2.9	not recommended	
3.0–3.9	500 mg	250 mg
4.0–5.9	1000 mg	500 mg
6.0–8.9	1500 mg	750 mg
9.0–12.9	2000 mg	1000 mg
13.0–15.9	2500 mg	1250 mg
16.0–20.9	3000 mg	1500 mg
21.0–24.9	4000 mg	2000 mg
25.0–28.9	5000 mg	2500 mg
29.0–29.9	6000 mg	3000 mg

PASER® is stable for up to 8 weeks at 40^0C and 75% humidity, and therefore can be distributed to the patient on a monthly basis in most environments with no cold chain. If storage of longer than 8 weeks is needed, refrigeration below 15^0C is required.

Prothionamide / Ethionamide (15–20 mg/kg)	
kg	**250 mg tablet**
1.0–2.9	not recommended
3.0–4.9	0.25 tab
5.0–8.9	0.5 tab
9.0–11.9	0.75 tab
12.0–16.9	1 tab
17.0–24.9	1.5 tabs
25.0–29.9	2 tabs

Group 5: Anti-TB drugs with unclear efficacy or unclear role in MDR-TB treatment

Group 5 drugs are not recommended by the WHO for routine use in MDR-TB treatment because their contribution to the efficacy of MDR regimens is unclear. Their role in pediatric MDR-TB treatment is even more unclear. Most of these drugs are expensive, and in some cases, they require intravenous

administration, and/or have severe side effects. However, they can be used in cases where adequate regimens are impossible to design with the medications from Groups 1-4. **They should be used in consultation with an expert in the treatment of DR-TB.**

Finally, some of the newer anti-tuberculosis agents, such as delaminid and bedaquiline, have not yet been evaluated in children but could be considered in cases of extreme resistance or severe adverse events.

Drug	Daily dose	Maximum daily dose
Clofazimine (CFZ)	3-5 mg/kg once daily; if the child is <25 kg, give 100 mg every second day	200 mg
Amoxicillin-clavulanate (AMX-CLV)	80 mg/kg in two divided doses based on the amoxicillin component	4000 mg amoxicillin and 500 mg clavulanate
Meropenem (MPN)	20–40 mg/kg IV every 8 hours	6000 mg
Linezolid (LZD)	10 mg/kg/dose twice daily for children <10 years of age; 300 mg daily for children ≥10 years of age. Also give vitamin B6.	600 mg
Clarithromycin (CLR)	7.5 -15 mg/kg twice daily	1000 mg

Annex 2

Tuberculin Skin Test (Mantoux test): Administering, reading and interpreting

A TST is the intradermal injection of a combination of mycobacterial antigens that elicit an immune response (delayed-type hypersensitivity), represented by induration, which can be measured in millimeters. The standard method of identifying people infected with M. *tuberculosis* is the TST using the Mantoux method. Multiple puncture tests should not be used as these tests are unreliable (because the amount of tuberculin injected intradermally cannot be precisely controlled).

This annex describes how to administer, read and interpret a TST using 2 tuberculin units (TU) of tuberculin PPD RT 23.

Administration

1. ***Locate and clean injection site 5–10 cm (2–4 inches) below elbow joint***

- Place forearm palm-up on a firm, well-lit surface.
- Select an area free of barriers (e.g. scars, sores, veins) to placing and reading.
- Clean the area with an alcohol swab.

2. ***Prepare syringe***

- Check expiry date on vial and ensure vial contains tuberculin PPD (2 TU/0.1 ml).
- Use a single-dose tuberculin syringe with a short (.- to .-inch) 27-gauge needle with a short bevel.
- Clean the top of the vial with a sterile swab.
- Fill the syringe with 0.1 ml tuberculin.

3. Inject tuberculin

- Insert the needle slowly, bevel up, at an angle of 5–15°.
- Needle bevel should be visible just below skin surface.

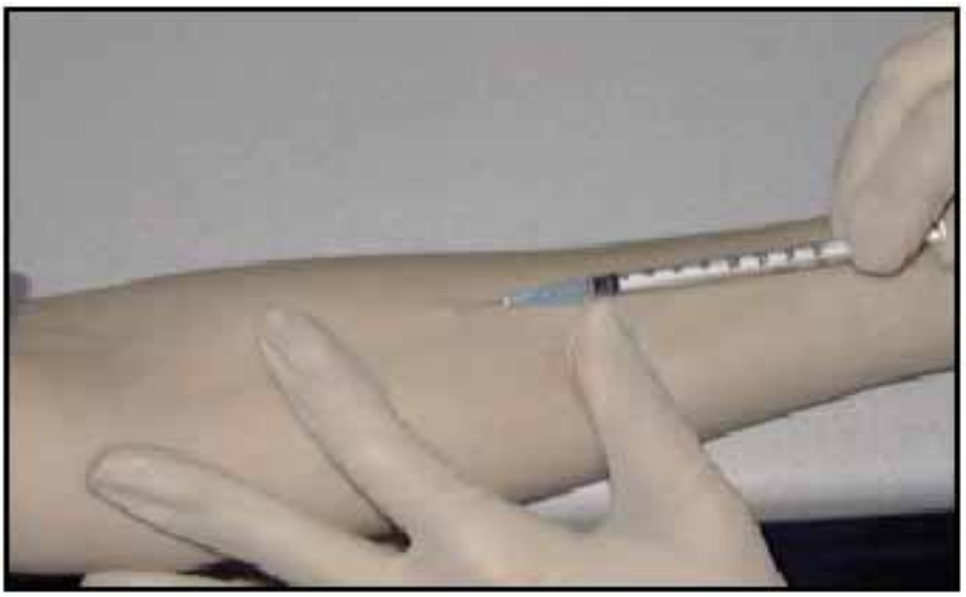
4. Check injection site

- After injection, a flat intradermal wheal of 8–10 mm diameter should appear. If not, repeat the injection at a site at least 5 cm (2 inches) away from the original site.

5. Record information

- Record all the information required by your institution for documentation (e.g. date and time of test administration, injection site location, lot number of tuberculin).

Figure: Administration of the tuberculin skin test using the Mantoux method



Reading

The results should be read between 48 and 72 hours after administration. A patient who does not return within 72 hours will probably need to be rescheduled for another TST.

1. ***Inspect site***

- Visually inspect injection site under good light, and measure indurations (thickening of the skin), not erythema (reddening of the skin).

2. ***Palpate indurations***

- Use fingertips to find margins of indurations.

3. ***Mark indurations***

- Use fingertips as a guide for marking widest edges of indurations across the forearm.

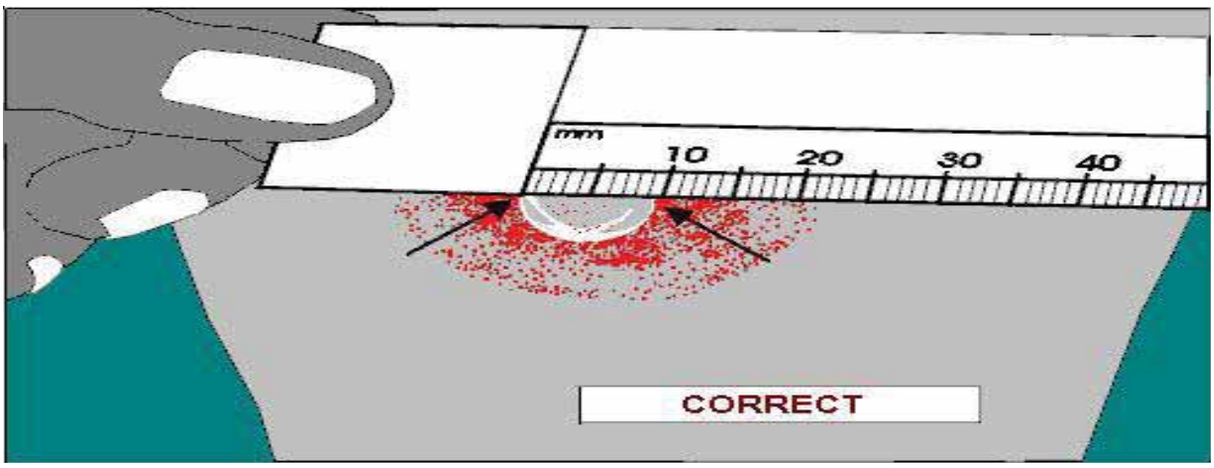
4. ***Measure diameter of indurations using a clear flexible ruler***

- Place "0" of ruler line on the inside left edge of the indurations.
- Read ruler line on the inside right edge of the indurations (use lower measurement If between two gradations on mm scale).

5. Record diameter of indurations

- Do not record as "positive" or "negative".
- Only record measurement in millimeters.
- If no indurations, record as 0 mm.

Figure: Reading of the tuberculin skin test



Interpretation

Interpretation of TST depends on two factors:

- diameter of the induration;
- person's risk of being infected with TB and of progression to disease if infected.

Induration of diameter ≥5 mm is considered positive in:

- HIV-positive children;
- severely malnourished children (with clinical evidence of marasmus or kwashiorkor).

Induration of diameter ≥10 mm is considered positive in:

- all other children (whether or not they have received BCG vaccination).

Causes of false-negative and false-positive TSTs are listed in below table.

Table 11: Causes of false-negative and false-positive tuberculin skin tests

Causes of false-negative TST	Causes of false-positive TST
Incorrect administration or interpretation of test	Incorrect interpretation of test
HIV infection	BCG vaccination
Improper storage of tuberculin	Infection with non-tuberculous mycobacteria
Viral infections (e.g. measles, varicella)	
Vaccinated with live viral vaccines (within 6 weeks)	
Malnutrition	
Bacterial infections (e.g. typhoid, leprosy, pertussis)	
Immunosuppressive medications (e.g.corticosteroids)	
Neonatal patient	
Primary immunodeficiencies	
Diseases of lymphoid tissue (e.g. Hodgkin disease, lymphoma, leukemia, sarcoidosis)	
Low protein states	
Severe TB	

Annex 3

TB case and treatment outcome definitions

Case and outcome definitions

Presumptive TB refers to a patient who presents with symptoms or signs suggestive of TB (previously known as a TB suspect).

Bacteriologically confirmed or clinically diagnosed cases of TB are also classified according to:

- anatomical site of disease;
- history of previous treatment;
- drug resistance;
- HIV status.

TB case definitions

- **A bacteriologically confirmed TB case** is one from whom a biological specimen is positive by smear microscopy, culture or WHO-approved rapid diagnostics (such as X-pert MTB/RIF). All such cases should be notified, regardless of whether TB treatment has started.
- **A clinically diagnosed TB case** is one who does not fulfill the criteria for bacteriological confirmation but who has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. This definition includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extra-pulmonary cases without laboratory confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

Classification based on anatomical site of disease

Pulmonary TB (PTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Miliary TB is classified as PTB because there are lesions in the lungs. Tuberculosis intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculosis pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extra-pulmonary TB. A patient with both pulmonary and extra-pulmonary TB should be classified as a case of PTB.

Extra-pulmonary TB (EPTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.

Classification based on history of previous TB treatment (patient registration group)

Classifications based on history of previous TB treatment are slightly different from those previously published. They focus only on history of previous treatment and are independent of bacteriological confirmation or site of disease. Note also that the registration groups for DR-TB are slightly different.

New patients have never been treated for TB or have taken anti-TB drugs for less than 1 month.

Previously treated patients have received 1 month or more of anti-TB drugs in the past. They are further classified by the outcome of their most recent course of treatment as follows:

Relapse patients have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).

Treatment after failure patients are those who have previously been treated for TB and whose treatment failed at the end of their most recent course of treatment.

Treatment after loss to follow-up patients have previously been treated for TB and were declared lost to follow-up at the end of their most recent course of treatment. (These were previously known as treatment after default patients.)

Other previously treated patients are those who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.

Patients with unknown previous TB treatment history do not fit into any of the categories listed above.

New and relapse cases of TB are incident TB cases.

Classification based on HIV status

HIV-positive TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a positive result from HIV testing conducted at the time of TB diagnosis or other documented evidence of enrolment in HIV care, such as enrolment in the pre-ART register or in the ART register once ART has been started.

HIV-negative TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a negative result from HIV testing conducted at the time of TB diagnosis. Any HIV-negative TB patient subsequently found to be HIV-positive should be reclassified accordingly.

HIV status unknown TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV testing and no other documented evidence of enrolment in HIV care. If the HIV status is subsequently determined, the patient should be reclassified accordingly.

Classification based on drug resistance

Cases are classified on the basis of drug susceptibility testing (DST) of clinical isolates confirmed to be M. tuberculosis:

- **Mono-resistance:** resistance to one first-line anti-TB drug only.
- **Polydrug resistance:** resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin).
- **Multidrug resistance:** resistance to at least both isoniazid and rifampicin.
- **Extensive drug resistance:** resistance to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.
- **Rifampicin resistance:** resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether mono-resistance, multidrug resistance, polydrug resistance or extensive drug resistance.

These categories are not all mutually exclusive. When enumerating rifampicin-resistant TB (RR-TB), for instance, multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) are also included. While it has been the practice until now to limit the definitions of mono resistance and poly drug resistance to first-line drugs only, future drug regimens may make it important to classify patients by their

strain resistance patterns to fluoroquinolones, second-line injectable agents and any other anti-TB drug for which reliable DST becomes available.

Treatment outcome definitions

For purposes of consistency of reporting by NTPs, the same outcome definitions apply for children as for adults.

Treatment response in a child with sputum smear-negative PTB, smear not done PTB or EPTB is assessed through regular monthly assessment and recording of weight gain and symptom improvement. In children with smear-positive TB, sputum smears should be repeated at 2 and 5 months.

The new treatment outcome definitions make a clear distinction between two types of patients:

- patients treated for drug-susceptible TB;
- patients treated for drug-resistant TB using second-line treatment (defined as combination chemotherapy for drug-resistant TB, which includes drugs other than those in Group 1).

The two groups are mutually exclusive. Any patient found to have drug-resistant TB and placed on second-line treatment is removed from the drug-susceptible TB outcome cohort. This means that management of the standard TB register and of the second line TB treatment register needs to be coordinated to ensure proper accounting of the outcomes of treatment.

All bacteriologically confirmed and clinically diagnosed TB cases should be assigned an outcome from the list in Table 1, except those with RR-TB or MDR-TB, who are placed on a second-line drug regimen (Table 2).

Patients found to have an RR-TB or MDR-TB strain at any point in time should be started on an adequate second-line drug regimen. These cases are excluded from the main TB cohort when calculating treatment outcomes and included only in the second-line TB treatment cohort analysis (Table 2). If treatment with a second-line drug regimen is not possible, the patient is kept in the main TB cohort and assigned an outcome from among those in Table 1.

Table 12: Treatment outcomes for TB patients (excluding patients treated for RR-TB or MDR-TB)

Outcome	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion
Treatment Completed	A TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable
Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment
Died	A TB patient who dies for any reason before starting or during the course of treatment
Loss to follow-up	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more
Not evaluated	A TB patient for whom no treatment outcome is assigned. This includes cases “transferred out” to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.
Treatment success	The sum of cured and treatment completed

Table 13:Treatment outcomes for RR-TB/MDR-TB/XDR-TB patient streatedusing second-line treatment

Outcome	Definition
Cured	Treatment completed as recommended by the national policy without evidence of failure and three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase[a]
Treatment Completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase[a]
Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: - lack of conversion by the end of the intensive phase a, or - bacteriological reversion in the continuation phase after conversion[b] to negative, or - evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or - adverse drug reactions (ADRs)
Died	A patient who dies for any reason during the course of treatment.
Loss to follow-up	A patient whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown.
Treatment success	The sum of cured and treatment completed

[a] For treatment failed, lack of conversion by the end of the intensive phase implies that the patient does not convert within the maximum duration of the intensive phase applied by the programme. If no maximum duration is defined, an 8-month cut-off is proposed. For regimens without a clear distinction between intensive and continuation phases, a cut-off 8 months after the start of treatment is suggested to determine when the criteria for Cured, Treatment completed and Treatment failed start to apply.

[b]The terms "conversion" and "reversion" of culture as used here are defined as follows:

Conversion (to negative): culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.

Reversion (to positive): culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining Treatment failed, reversion is considered only when it occurs in the continuation phase.

Annex 4

Protocols for Specimen Collection

Gastric Aspiration

Gastric aspiration can be used in children when sputa cannot be spontaneously expectorated nor induced using hypertonic saline. Since gastric aspiration is not an aerosol-generating procedure, it poses a low risk for transmission. Normal infection control measures should be in place, and staff should use respirators (as coughing in the patient can be accidently induced by the procedure), eye protection, and non-sterile gloves.

Procedures for gastric aspiration adapted from WHO guidelines, 2006. An instructive video on the procedure can be found at the following website:

https://www.youtube.com/watch?v=IWl_TY_LbZk&feature=youtu.be

Contraindications

- Child not fasted for 4 hours
- Low platelet count or bleeding tendency

Material required

- Non sterile gloves
- Nasogastric tube (10F)
- Syringe 5-30 cc with appropriate connector for the nasogastric tube
- Litmus paper
- Specimen container
- Lab request forms
- Pen
- Sterile water or normal saline
- Sodium bicarbonate solution (8%)
- Alcohol/chlorhexidine

Procedure

- Position child on his/her back or side.
- Have an assistant to hold the child.
- Measure the distance between the nose and stomach to estimate the distance that will be required to insert the tube into the stomach.
- Attach a syringe to the nasogastric tube.
- Gently insert the nasogastric tube through the nose and advance it into the stomach. Management of Drug-Resistant Tuberculosis in Children 49
- Withdraw gastric contents (2-5 mL) using the syringe attached to the nasogastric tube.

- To check that the position of the tube is correct, test the gastric contents with litmus paper: blue litmus turns red in response to acidic stomach contents. Tube position can also be checked by pushing 3-5 mL of air into the stomach and listening with a stethoscope over the stomach.
- If no fluid is aspirated, insert 5-10 mL of sterile water or normal saline and attempt to aspirate again. If still unsuccessful, attempt this again. Do not repeat more than three times.
- Withdraw gastric contents (ideally at least 5-10 mL).
- Transfer gastric fluid from the syringe into a sterile container.
- Add an equal volume of sodium bicarbonate to the specimen in order to neutralize the acidic gastric contents and prevent destruction of tubercle bacilli.

After the procedure

- Wipe the specimen container with alcohol/chlorhexidine to prevent cross-infection and label the container.
- Fill out the lab request forms.
- Transport the specimen in a cool box to the lab for processing as soon as possible (within 4 hours).
- Give the child his or her usual food.

Sputum Induction

Sputum induction (SI) is a useful procedure for obtaining sputum specimens in situations where suspected or known TB patients cannot self-expectorate, and where a bacteriological result is desired for diagnosis or follow up.

Practice points

- The procedure can be repeated twice on the same day, at least 4 hours apart, in order to obtain the specimens.
- Due to the risk of bronchospasm, only trained health staff must conduct the procedure, preferably a nurse.
- Sputum induction is an aerosol-generating procedure. Therefore, appropriate infection control measures must be taken. Specifically:
    - An appropriate site must be available. The minimum requirement is a small room with good ventilation.
    - Staff must use respirators, eye protection and non-sterile gloves.

Material required

General

- Mask (respirator) for the operator and caregiver (if present)
- Eye protection and non-sterile gloves for operator
- Oxygen (on standby in case of emergency)
- Pulse oximeter
- Request form

Preparation Pre-nebulization

- Spacer device (holding chamber) and mask
- Salbutamol metered dose inhaler

Nebulization

- Mask, chamber and tubing
- Antibacterial filter
- Nebulizer (Ultrasonic is the preferred type)
- Sterile solution of 3-6% sodium chloride, refrigerated if possible (more irritant)

Aspiration

Suction material usually required only for children under 5 years old.

- Suction catheter (7 or 8F)
- Mechanical suction device & mucus trap or 50 mL syringe if not available
- Sputum collection container
- Sterile solution of 0.9% sodium chloride

Infection control measures

Management of materials

- Spacer devices (holding chambers) should either be sterilized after each patient (preferred) or disinfected after each patient by soaking in hexanios for at least 15 minutes, then rinse, then soak again in a new bath of hexanios for 15 minutes. Rinse well and then wipe dry.
- All masks, tubing, suction catheters and syringes should be disinfected with 2% chlorine and then discarded.
- Antibacterial filters should be fitted and changed for each patient to protect the nebulizer, oxygen cylinder (if used), and any aspiration device (if used).

Management of the environment

The site must be left unused with the windows open or extraction fan on for at least 30 minutes after the procedure to allow adequate replacement of air in the room. No one should enter this room during the period without a respirator.

Contraindications

- Patient not fasted for 2 hours
- Severe respiratory distress
- Oxygen saturation less than 92% in room air
- Bleeding – low platelet count, nose bleeds or other bleeding source
- Reduced level of consciousness
- History of significant asthma or chronic obstructive airways disease

Procedure

Prior to nebulization

- Explain the procedure to the patient and the accompanying adult.
- Have the patient in a sitting position.
- Ask older children to rinse their mouth with water.
- Use pulse oximeter to obtain baseline oxygen saturation.
- Administer 2 puffs of salbutamol 10 seconds apart. Use a holding chamber for all children. Wait 5 minutes before starting nebulization.
- Prepare a sputum container.

Nebulization

- Fill the nebulizer with 5 mL 3-6% hypertonic saline solution.
- Put on an N95 or FFP2 respirator and provide one for any accompanying adult.
- Place the nebulizer mask over the patient's face.
- Leave the patient to inhale.
- Stop the procedure and obtain a sample as soon as the patient starts to cough productively. In young children careful attention, with suctioning at the right moment is critical to avoid the sample being swallowed. If sputum is not induced during the procedure, continue until the reservoir is empty (not longer than 15 minutes), then attempt sample collection.

The patient should be observed for respiratory distress and the procedure should be stopped at any time if severe cough or wheeze develops.

Nasopharyngeal suction (usually required for children < 5 years)

- Do 1 to 2 minutes of clapping on the chest.
- Lay the child flat on his or her side, facing away from the operator.
- If a mechanical suction device and mucus extractor are available, use these. If not:
    - Fit a suction catheter to a 50 mL syringe. Lubricate the end of the catheter.
    - Measure the distance from the tip of the nose to the tragus of the ear. Insert the suction catheter to that depth.
    - When inserting and withdrawing the tube, pull on the plunger of the syringe to create suction.
    - Once the syringe is filled with air and mucus, disconnect it from the suction catheter and purge the air (tip facing upward), so that only mucus is left in the syringe.
    - To collect the mucus, draw 2 mL of 0.9% saline into the syringe to rinse, then empty contents into the sample container.

Note that sputum may sometimes not be produced until up to 24 hours later. Therefore if a good sputum sample is not immediately produced, older children can be given a collection container to take home.

All patients should be observed for at least 15 minutes after the procedure to ensure there are no signs of respiratory distress. Recheck the oxygen saturation post procedure. Give oxygen if saturation has dropped below 90%.

Possible adverse effects to anticipate

In all cases, try to obtain a specimen only if the patient condition permits. Do not repeat the procedure in the case of severe adverse effects.

- Coughing spells (~40%)
- If severe, stop the procedure and administer salbutamol. Oxygen should be available and can be administered in severe cases.
- Nosebleeds (~8%)
- Stop the procedure and apply constant pressure to the mid portion of the nose until the bleeding stops. Note that it is very common to see blood in the specimens collected from nasopharyngeal suction; this in itself is not an adverse effect.
- Wheezing (<1%)
- Monitor the child closely. Stop the procedure if wheeze increases. Administer salbutamol, and oxygen if severe.
- Vomiting (<1%)

  Stop the procedure and observe the child closely until the vomiting stops.

Annex 5

Contact Management Form for Children Exposed to MDR-TB

CHILD PERSONAL INFORMATION			
Child name:		Clinic name:	
Child date of birth:		Clinic phone number:	
Child folder number:		Clinic fax number:	
Child address:			
SOURCE CASE INFORMATION			
Source case name:		Date of sample production:	
Relationship to child:		Sputum smear result:	
DST results:			
Drugs	Resistant	Susceptible	Not tested
Isoniazid			
Rifampicin			
Ofloxacin			
Amikacin			
Ethionamide			
PHYSICAL EXAM			
Weight:	HIV test date:	Mantoux test date:	CXR date:
Height/length:	HIV test result:	Mantoux test size (mm):	CXR impression:
Symptoms: □ Cough > 2 weeks □ Fever □ Losing weight □ Reduced energy □ Night sweating □ Abnormal joints/spine		Management: □ Refer □ Prophylaxis □ Discharge/observe	
PREVENTIVE TREATMENT			
	Date started	Dose	Number of tablets
Isoniazid			
Ofloxacin			
Ethambutol			
Other:			

MONITORING CHART			
Month	**Weight**	**Height**	**Clinical review completed**
1			
2			
3			
4			
5			
6			

Annex 6

Sample Intake Form

<table>
<tr><th colspan="2">PERSONAL DATA</th></tr>
<tr><td>Name:</td><td>Date of evaluation:</td></tr>
<tr><td>Caregiver:</td><td>Date of birth:</td></tr>
<tr><td rowspan="2">Place of Residence:</td><td>Age:</td></tr>
<tr><td>Sex:</td></tr>
<tr><td>Telephone:</td><td rowspan="2">Medical record number:</td></tr>
<tr><td colspan="2">Address and mobile phone number (if different than above):</td></tr>
<tr><td colspan="2">Name of evaluator:</td></tr>
<tr><td colspan="2">Health establishment:</td></tr>
<tr><th colspan="2">TB HISTORY</th></tr>
<tr><td>□ Never diagnosed</td><td>Year first diagnosed with TB:</td></tr>
<tr><td>Ever received BCG?
□ Yes, year(s):_____
□ No
□ Unknown</td><td>Diagnosed by:
□ AFB □ Other (specify):
□ Culture
□ CXR</td></tr>
<tr><td colspan="2">Suspect primary MDR-TB
□ Yes □ No</td></tr>
<tr><td colspan="2">Check all risk factors that apply:
□ Close contact with known MDR-TB
□ Close contact with person who died of TB or failed TB treatment
□ Previous treatment
□ Failure to improve on current TB treatment</td></tr>
<tr><td colspan="2">Summary of previous anti-tuberculosis drug use
(mark each drug patient has received for >1 month)
□ INH □ SM □ FQ □ AMX-CLV
□ RIF □ KM □ THA/PTO □ CFZ
□ EMB □ AMK □ CS □ Other:_____
□ PZA □ CM □ PAS □ Other:_____</td></tr>
<tr><th colspan="2">IMMUNIZATION HISTORY</th></tr>
<tr><td>Has the child been fully immunized for age:
□ Yes
□ No
If no, what vaccines are missing?</td><td>Has patient had BCG?
□ Yes
□ No
Is BCG scar present?
□ Yes
□ No</td></tr>
</table>

<table>
<tr><th colspan="3">SOCIO-DEMOGRAPHIC DATA</th></tr>
<tr><td colspan="2">Currently in school:
□ Yes
□ No
□ N/A</td><td rowspan="4">Who are the primary caregivers?
Are the caregivers employed?
□ Yes
□ No
If yes, what is their work?</td></tr>
<tr><td colspan="2">Number of household members:</td></tr>
<tr><td colspan="2">Number of household members
when diagnosed with TB:</td></tr>
<tr><td colspan="2">Number of household members
when diagnosed with MDR-TB:</td></tr>
<tr><td colspan="2">How far does patient live from health facility?</td><td rowspan="3">Have parent(s) been tested for HIV?
□ Yes
□ No
If yes, date and result:</td></tr>
<tr><td colspan="2">How did patient get to the health facility?</td></tr>
<tr><td colspan="2">How long does it take patient to get to the health facility?</td></tr>
<tr><th colspan="3">REVIEW OF SYSTEMS</th></tr>
<tr><td colspan="3">Check all that apply
□ Cough □ Dyspnea at rest □ Swelling or “lumps” in neck, arms or groin
□ Sputum □ Dyspnea on exertion □ Vertebral pain
□ Poor appetite □ Tired, listless, not playing□ Back pain
□ Weight loss □ Other:_____
□ Bronchospasm</td></tr>
<tr><td colspan="3">□ Hemoptysis
Largest quantity in mL: Date of first episode of hemoptysis:

Most recent quantity in mL: Date of most recent hemoptysis:</td></tr>
<tr><td colspan="2">Current medications:</td><td>Allergies or adverse reactions:</td></tr>
<tr><th colspan="3">PAST MEDICAL HISTORY</th></tr>
<tr><td>Diabetes
□ Yes□ No</td><td>Asthma
□ Yes □ No</td><td rowspan="3">Previous hospitalization(s)?
□ Yes □ No
Hospitalization(s) in pulmonary ward?
□ Yes □ No
Reason for hospitalization(s):
Name of hospital(s):</td></tr>
<tr><td colspan="2">Other:</td></tr>
<tr><td colspan="2">Has patient been tested for HIV?
□ Yes
□ No
If yes, date and result:</td></tr>
<tr><td colspan="3">Prior transfusion(s) Date of transfusion(s):
□ Yes Indication for transfusion(s):
□ No</td></tr>
</table>

BIRTH HISTORY AND PAST SURGICAL HISTORY	
Was patient born at home? □ Yes □ No Did the mother receive prenatal care? □ Yes □ No Were there any problems at birth? □ Yes □ No If yes, describe:	Prior surgery? □ Yes □ No Procedure(s): Date(s) of surgery: Complications:

PHYSICAL EXAM			
Temp:	BP:	HR:	RR:
Weight:	Height:	**BMI:**	
GENERAL APPEARENCE			
HEENT Conjunctiva: Sclera: Oropharynx:	Lymphadenopathy present? JVD: Thyromegaly:	CVS Tachycardic? Murmurs? Extra heart sounds?	Lungs Wheezing? Crackles? Bronchial breathing sounds?
Abdomen Bowel sounds? Organomegaly? Tender?	Extremities Edema? Cyanosis? Pulses:	Neuro Mental status: Reflexes: Strength: Gait:	Developmental Describe development for age:

TEST RESULTS						
Drug susceptibility testing:						
Sample number	Date of sample collection	Date of results	AFB results (**P**os, **N**eg, **U**nknown)	Laboratory	Resistant to	Susceptible to
1			P N U			
2			P N U			
3			P N U			
4			P N U			
5			P N U			
6			P N U			
Chest radiograph:						
Other lab results:						
Impression/plan:						

SUMMARY OF KNOWN TB CONTACTS									
Name of contact	Relation to patient	Date of TB diagnosis	Lived in same household when contact had TB?	History of multiple treatments?	Died during treatment?	History of documented MDR-TB?	Current AFB status*	Current status of TB contact**	Resistant to which drugs?
			Y N U	Y N U	Y N U	Y N U	P N U	C D T U S	
			Y N U	Y N U	Y N U	Y N U	P N U	C D T U S	
			Y N U	Y N U	Y N U	Y N U	P N U	C D T U S	
			Y N U	Y N U	Y N U	Y N U	P N U	C D T U S	

Unless stated otherwise, indicate **Y**es, **N**o or **U**nknown

* For AFB status, indicate **P**ositive, **N**egative or **U**nknown

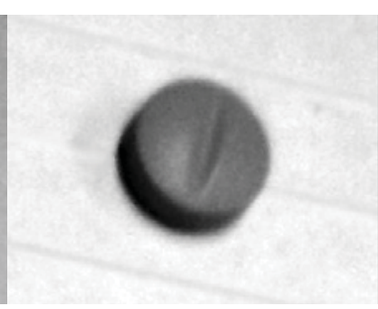
** For current status, indicate **C**ured, in **T**reatment, **S**ymptomatic but not in treatment, **D**eceased, or **U**nknown

Annex 7

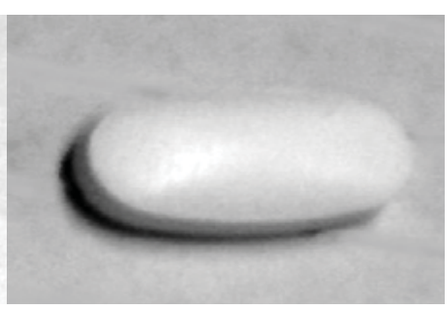
Medications Used to Treat MDR-TB

Photo: Damien Schumann

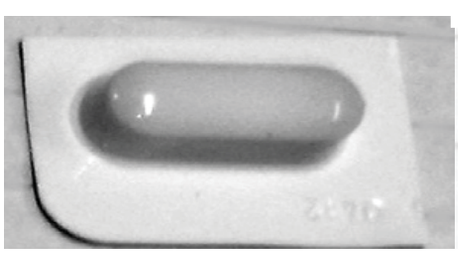
Clarithromycin (CLR)
Form: tablet
Dose: 500 mg



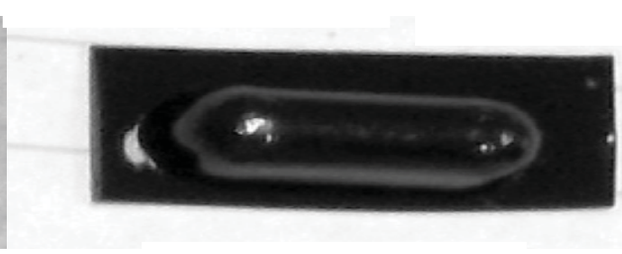
Prothionamide (PTO)
Form: tablet
Dose: 250 mg



Amoxicillin-clavulanic acid (AMX-CLV)
Form: tablet
Dose: 500 mg



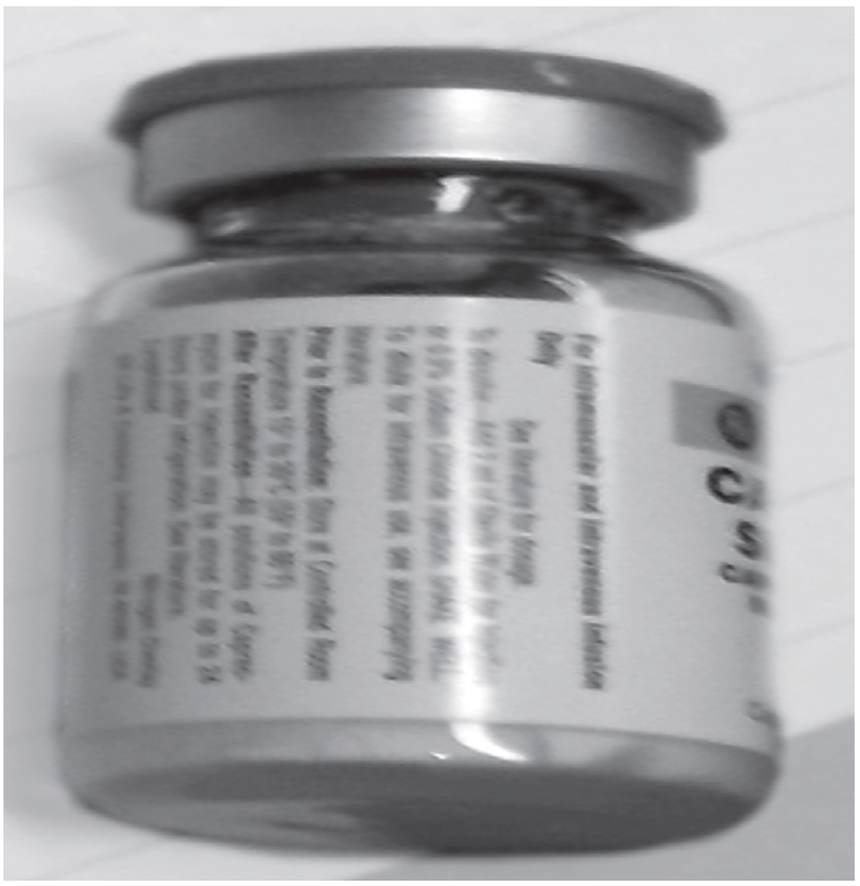
Moxifloxacin (MFX)
Form: tablet
Dose: 400 mg



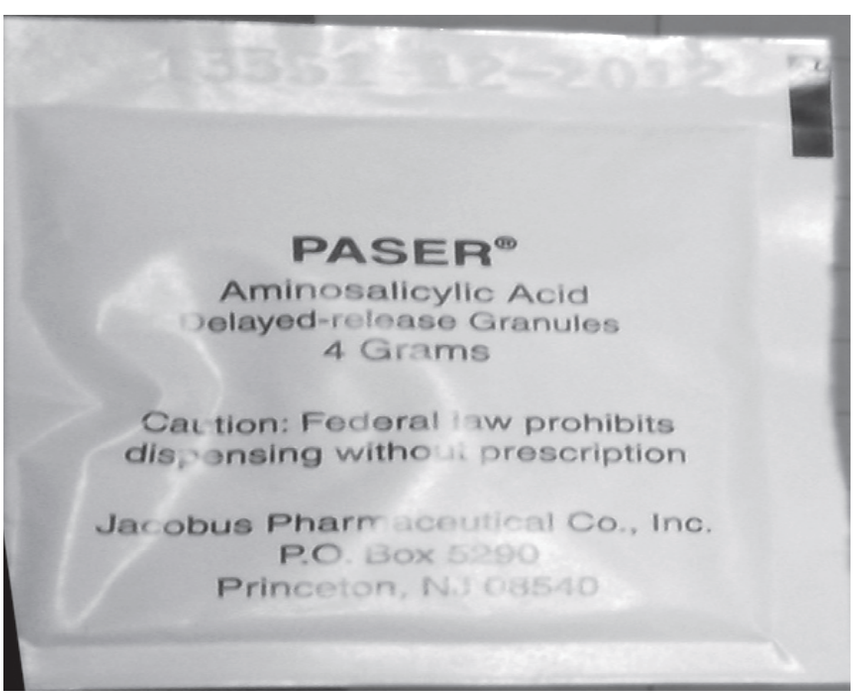
Clofazimine (CFZ)
Form: soft gel
Dose: 100 mg

Cycloserine (CS)
Form: capsule
Dose: 250 mg

Kanamycin (KM)
Form: solution for injection
Dose: 500 mg



Capreomycin (CM)
Form: lyophilized powder
Dose: 1 g



Para-Aminosalicylic acid (PAS)
Form: granules
Dose: 4 g

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