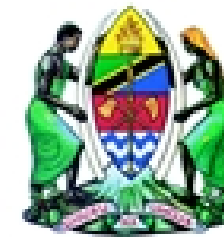


THE UNITED REPUBLIC OF TANZANIA



MINISTRY OF HEALTH AND SOCIAL WELFARE

Management of Tuberculosis in Children

Manual for Health Care
Workers

National Tuberculosis and
Leprosy Programme (NTLP)
October, 2012

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Figure 8.3 Indicators for NTLP Routine Recording and Reporting

	Significance
Proportion of children with TB amongst all TB cases notified	May indicate over- or under-reporting of TB cases in children
Proportion of children with pulmonary TB amongst childhood TB cases	May indicate over- or under-diagnosis of pulmonary TB
Proportion of children with TB who are cured amongst smear-positive childhood TB cases (demonstrated by end-of-treatment smear conversion from positive to negative)	Demonstrates the quality of management of children with TB in the program
Proportion of children who complete treatment amongst smear-positive childhood TB cases (those who complete a full course of anti-TB treatment in whom smear conversion is not demonstrated)	Demonstrates the quality of management of children with TB in the program
Proportion of children who are successfully treated amongst smear-positive childhood TB cases (cured + treatment completed)	Demonstrates the quality of management of children with TB in the program
Proportion of children with miliary TB or TB meningitis amongst childhood TB cases	This proportion should be very low where BCG vaccination coverage is high

TB/HIV Indicators

TB/HIV indicators are listed below. These are the measures used to determine if program activities are successful and identify where improvement might be needed.

- Number and proportions of children counseled and tested for HIV among all children notified
- Number and proportions of children who tested HIV positive
- Number and proportions of children who tested HIV positive and referred to CTC
- Number and proportions of children who tested HIV positive registered at CTC
- Number and proportions of children who tested HIV positive initiated CPT
- Number and proportions of children who tested HIV positive initiated ART

Key Points

- Recording and reporting are essential to a facility's success, as they help health care workers to:
 - Assess patient progress
 - Ensure quality of care, sharing of information between patient and health workers
 - Conduct monitoring and evaluation activities
 - Assess program performance
 - Plan programs
 - Demonstrate accountability
- Learning how to use all of the different TB data forms is key to successful reporting
- The more accurate and complete reporting is, the more likely it is that health care workers will meet TB control objectives

Figure 8.2 Definitions of Treatment Outcomes

Treatment outcome	Definition
Cured	A patient whose sputum smear or culture was positive at the beginning of treatment but who was smear or culture negative in the last month of treatment and on at least one previous occasion.
Treatment completed	A patient who completed a treatment course but who does not have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion. Note: The sputum examination may not have been done or the results may not be available.
Failure	A patient whose sputum smear or culture is positive at 5 months or later during treatment. Also included in this definition are patients found to harbor a multidrug-resistant strain at any point of time during the treatment, whether they are smear negative or positive.
Died	A patient who dies for any reason during the course of TB treatment.
Default	A patient whose treatment was interrupted for 2 consecutive months or more.
Transferred out	A patient who has been transferred to another recording and reporting unit and whose treatment outcome is unknown.

Since most children have sputum smear negative and/or have extrapulmonary TB it is impossible to show bacteriological cure so most will be classified as treatment completed.

Cohort Analysis

Cohort analysis is a key tool for evaluating program effectiveness. It is the review of the outcomes for a cohort or group of patients that were started on treatment during the same timeframe. Outcomes for children are analyzed based on the following age groups: under 5 years, from 5 to under 10 years, and from 10 to under 15 years.

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As it is not easy to mention each individual and organisations which participated in the development of this document the MoHSW extends similar gratitude to all those who constructively played a role in one way or another during the development of this manual.



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TB/HIV Forms

- TB/HIV 01 - TB/HIV notification form
- TB/HIV 02 - TB/HIV treatment outcome form
- TB/HIV 03 - TB/HIV referral/transfer form
- CTC2

Registers

Two types of TB registers exist, paper and electronic. The paper version is filled out at the facility and district, and the electronic version is filled out at the district level. Registers include:

- TB 03 - The TB unit register. List of all patients taking TB drugs in the clinic. Data from this register provide the foundation for the District TB register and forms the basis for major decisions. It is filled out by health care workers in TB clinics who provide drugs, treatment, and counseling to patients.
- TB 04 - TB district register, contains the list of all TB patients at notified in the district and the transferred in the district.
- TB 05 - TB laboratory register, Is a register found in laboratory where all TB suspected provided sputum are registered including their sputum examination results
- TB 10 - TB culture and DST register. All pa

Assigning and Evaluating Treatment Outcomes

Health workers at health facility level fill in the treatment outcomes of each patient on treatment card and in the unit register, the DTLC fill in treatment outcome in the district unit and compile quarterly report for notification and treatment outcomes. The NTLP compiles all case and treatment outcome data for national recording and reporting purposes.

New Cases

- A child with smear negative pulmonary TB or extrapulmonary TB cases, is considered to have completed treatment after 6 months of continuous therapy, or 168 doses. This includes 56 doses in the intensive phase and 112 doses in the continuation phase. Since most children have sputum smear negative and/or extrapulmonary TB, it is impossible to show bacteriological cure and most cases will be classified as treatment completed.
- New smear positive or culture positive patients with negative sputum smear or culture results at 5 months should be classified as cured. However, the patient should still complete a full course of treatment (total of 168 doses/6 months treatment).
- New smear positive patients with positive sputum smear or culture results at 5 months should be classified as treatment failures. Request a sputum specimen for mycobacterial culture and drug susceptibility testing (DST). Close their treatment card (outcome = failure) and open a new treatment card (type of patient = treatment after failure).

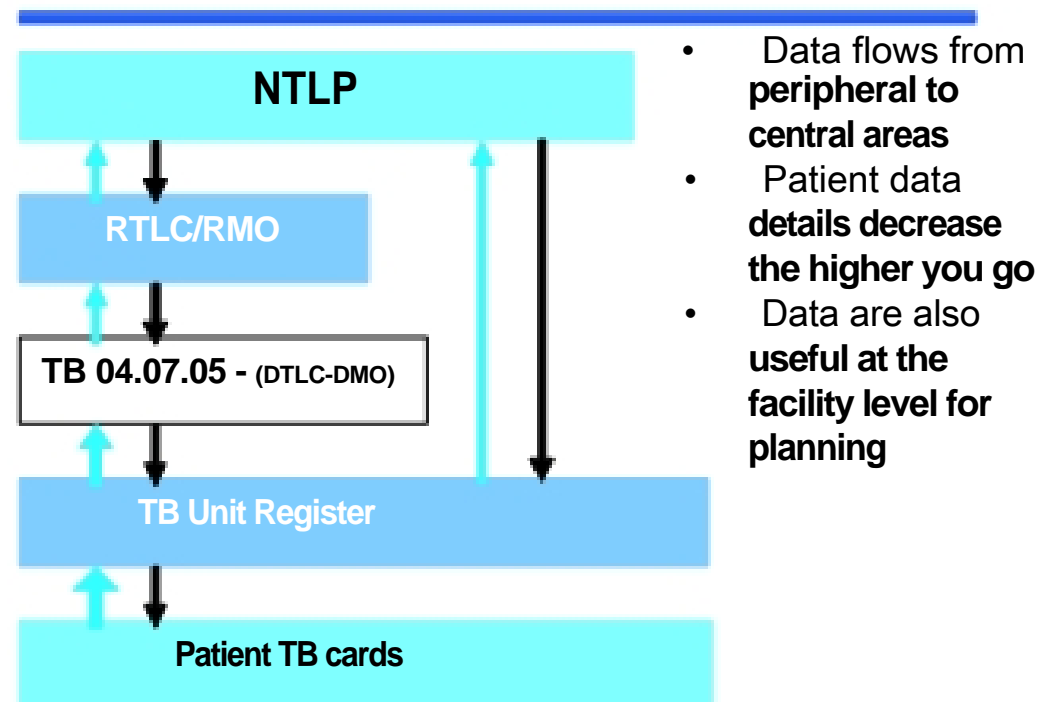
Retreatment Cases

- Retreatment sputum smear positive cases with negative sputum smear or culture results at 7 months should be classified as cured after taking 244 doses (8 months of treatment).
- Retreatment sputum smear positive cases with positive sputum smear or culture results at 5 months are classified as treatment failures. Request a sputum specimen for mycobacterial culture and drug susceptibility testing (DST). Close their treatment card (outcome = failure) and check results from sputum culture and DST that were requested previously per NTLP guidelines. If drug resistance is identified, refer the patient to the MDR TB Treatment Centre.

complete, accurate, and reliable. Data collected at any level should be used locally for planning and monitoring purposes, and for making evidence-based decisions.

ABBREVIATIONS

Data Flow for TB



Data flow from peripheral to central areas, with data volume and detail decreasing as it moves up the next higher level. Data are also useful at the clinic level for planning purposes.

Recording and Reporting of Child Cases

Children with TB should be included in routine recording and reporting. Notify all identified TB cases in children and register the child for treatment. If smear positive, record their smear status at months 2, 5 and at the end of treatment. Record the child's treatment outcome as well.

TB Forms and Cards

- TB 01 - Tuberculosis treatment card. The health care worker who manages the patient's treatment fills out this card at every patient visit. It focuses on the clinical aspects of patient care.
- TB 02 - TB Identity card (Kadi ya Mgonjwa). The health care worker fills out this card when treatment is started. It is kept by the patient, provides evidence of previous treatment history, and enables the patient to collect their medicines.
- TB/LEW 01TB - Laboratory request form for AFB microscopy
- TB 06 - Culture and susceptibility request form
- TB 07 - TB quarterly notification form
- TB 08 - TB drugs and supplies form
- TB 09 - TB treatment outcome form
- TB 11 - Treatment outcome of transferred in TB patients

MDR TB Forms

- District DR TB suspect register
- MDR TB Patient Identity Card
- MDR TB Treatment Card

AFB	Acid-Fast Bacillus
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
BCG	Bacille Calmette-Guérin
CPT	Cotrimoxazole preventive therapy
CSF	Cerebral spinal fluid
CT	Computed tomography
CTRL	Central Tuberculosis Reference Laboratory
CXR	Chest x-ray
CXT	Chemotherapy
DBS	Dried blood spot
DOT	Directly observed therapy
DST	Drug susceptibility testing
DTLC	District Tuberculosis and Leprosy Coordinator
FDC	Fixed-dose combination
HIV	Human Immunodeficiency Virus
IGRA	Interferon-gamma release assay
IPT	Isoniazid preventive treatment
IRIS	Immune Reconstitution Inflammatory Syndrome
LFT	Liver function test
LTBI	Latent tuberculosis infection
MDR TB	Multidrug-resistant tuberculosis
MRI	Magnetic resonance imaging
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NTLP	National Tuberculosis and Leprosy Programme
PCR	Polymerase chain reaction
PI	Protease inhibitor
PITC	Provider-initiated testing and counseling
PTB	Pulmonary tuberculosis
RTLC	Regional Tuberculosis and Leprosy Coordinator
RUTF	Ready-to-eat therapeutic food
TB	Tuberculosis
TSH	Thyroid-stimulating hormone
TST	Tuberculin skin test
WHO	World Health Organization
XDR TB	Extensively drug-resistant tuberculosis

Anti-Tuberculosis Drug Abbreviations

E	Ethambutol
H	Isoniazid
PAS	Para-Aminosalicylic Acid
R	Rifampicin
S	Streptomycin
Z	Pyrazinamide

HIV Drug Abbreviations

ABC	Abacavir
AZT	Zidovudine
D4T	Stavudine
EFV	Efavirenz
LPV/r	Lopinavir/ritonavir
NVP	Nevirapine
SMZ	Sulfamethoxazole
TMP	Trimethoprim
3TC	Lamivudine

8

RECORDING AND REPORTING CHILDREN WITH TUBERCULOSIS

Introduction

The goal of this unit is for participants to understand the different types of data collection tools and to appreciate the importance of proper record keeping regarding childhood TB.

By the end of this unit you should be able to:

- Explain the importance of recording and reporting
- Explain the data flow from health facilities through districts, regions to the national level
- Describe how to use the different TB forms and registers to record and report cases of TB in children

Recording and Reporting

Definitions:

Recording - capturing data on patient management over time and across clinical sites. Information is written directly on paper forms or entered into a computer.

Reporting - routine tracking (monitoring) of priority program management information of summary patient outcome data (evaluation) at facility, district, regional, and national levels over a period of time.

Health care workers must report both new and re-treatment TB cases and their treatment outcomes in accordance with international and Tanzanian standards of TB care. Additionally, recording and reporting are essential for good program management and patient care. They involve accurately recording all individual patients started on treatment, making use of information at the facility, updating registers, and sending reports to district, regional, and national levels for decision making. Recording and reporting are used to assist in case holding and patient monitoring (e.g. attendance and treatment outcome), establishment of baseline information, planning, establishment of trend, notification, or treatment outcomes, decision making on treatment, and improving services.

Importance of Keeping Good Records

Good record keeping is part of good patient care. Accurate and complete records are important because these records are used to assess patient progress and aid staff in providing adequate services to each patient. Accurate and complete records also ensure high quality patient care, support continuity of care, and enable sharing of information with the patient and transfer of information between health facilities.

For program purposes, good record keeping is equally important because program managers at different levels use recording and reporting records as monitoring and evaluation tools. Records are used to assess program performance, program planning and budgeting, accountability, and decision-making. Health care workers should make sure that cards and registers are up-to-date,

Aim of the training

The aim of this training is to build the capacity of healthcare workers to provide the best available care to children with tuberculosis.

Objectives of the Pediatric TB Course

By the end of this course, you will be able to:

- Explain what tuberculosis (TB) is and how it presents in children
- Suspect TB in a child appropriately and know how to diagnose it.
- Collect sputum specimens from a child
- Explain how to effectively treat TB in children at all ages
- Explain how to manage TB treatment interruptions and adverse reactions,
- Explain how to provide effective counseling
- Explain how to monitor TB treatment in a child
- Explain what tuberculosis (TB) is and how it presents in children
- Suspect TB in a child appropriately and know how to `diagnose it.
- Collect sputum specimens from a child
- Explain how to effectively treat TB in children at all ages
- Explain how to manage TB treatment interruptions and adverse reactions,
- Explain how to provide effective counseling
- Explain how to monitor TB treatment in a child

Course Organization

The course is a facilitator-led program and consists of 5 days of didactic training. Units include the following teaching/learning methods:

- Lecture discussions
- Case studies
- Review exercises
- Role-plays
- Large- and small-group activities and discussions
- Field site visit

Course Materials

Your Participant Manual contains the course content in a reference manual format and corresponds to the slides that the facilitators will present to you during the training. Your Participant Workbook includes the case studies, key tables, and the worksheets that you will need for the group activities.

Course Evaluation

Your Participant Workbook includes the pre- and post-tests that will be used to evaluate the knowledge you gained from this course. In addition, there is a course evaluation so you can provide feedback that will help improve this course for future trainings.

Training Schedule

Day 1

	Topic/Activity	Duration
8:00 - 8:30 am	Registration	30 minutes
8:30 - 10:30 am	Unit 1: Welcome and Overview of the Training Programme, Pre-course Evaluation (Pre-Test)	120 minutes
10:30 - 11:00 am	Break	30 minutes
11:00 - 12:30 pm	Introduction to TB and TB in Children	90 minutes
12:30 - 1:30 pm	Lunch	60 minutes
1:30 - 3:15 pm	Diagnosis of TB Disease in Children	105 minutes
3:15 - 3:30 pm	Break	15 minutes
3:30 - 4:45 pm	Diagnosis of TB Disease in Children (continued, resume with Diagnosis of Extrapulmonary TB in Children)	80 minutes
4:50 - 5:05 pm	Conclusion and Evaluation	15 minutes
5:05 - 5:35 pm	Facilitators Debrief	30 minutes

Day 2

	Topic/Activity	Duration
8:00 - 8:30 am	Review Previous Day	30 minutes
8:30 - 10:30 am	Management of TB in Children	120 minutes
10:30 - 10:45 am	Break	15 minutes
10:45 - 12:30 pm	Management of TB in Children (continued, resume with Nutrition for Children with TB)	105 minutes
12:30 - 1:30 pm	Lunch	60 minutes
1:30 - 2:45 pm	Prevention of Tuberculosis in Children	75 minutes
2:45 - 3:15 pm	Break	30 minutes
3:15 - 5:15 pm	Pediatric TB in Special Situations: TB/HIV in Children	120 minutes
5:15 - 5:30 pm	Conclusion and Evaluation	15 minutes
5:30 - 6:00 pm	Facilitators Debrief	30 minutes

No recommendations for chemoprophylaxis for MDR TB contacts
If disease develops, promptly refer for MDR TB treatment

Management of a newborn child of a mother with multidrug-resistant tuberculosis

A newborn should be separated from a mother with untreated MDR TB or who is still smear/culture positive despite treatment. Advise infectious mother to use an alternative feeding to avoid possible transmission drug resistant TB strains. Once a mother is no longer contagious (smears/ culture negative the infant may be cared for by the mother (separation is no longer needed), Consider early transfer of the mother to nearby clinic that can manage continuing care. Once the mother is no longer infectious but still in the intensive phase of treatment at the MDR TB center, family members may bring the infant for visits, which should occur outdoors.

Key Points

- Most children are TB culture negative, making the diagnosis of MDR TB difficult.
- All children who are contacts of an infectious MDR TB case should be screened for MDR TB disease
- Multidrug-resistant tuberculosis requires 18 to 24 months of appropriate treatment in 2 phases:
 - Intensive- inpatient (6-8 months)
 - Continuation- outpatient (12 months)
- Separate a newborn from a mother with untreated MDR TB or who has started treatment but is still infectious
- Always monitor weight in children to adjust doses as the child gains weight.
- Close and extensive monitoring is required for all patients receiving treatment with MDR TB medications.
- No chemoprophylaxis is indicated for children who are MDR TB contacts.
- Mothers with MDR TB are able to provide care for their newborns once they are no longer infectious (smears and cultures are negative).

Monitoring of children on MDR TB treatment

Children in continuation phase of the MDR TB treatment should be monitored for simple adverse effects with support from the DTLC as shown in the table below

Table 5.6. Treatment monitoring of children with MDRTB

Parameter	Frequency
Fever, cough, and loss of appetite	Monitor daily.
Sputum for smear, culture	Monthly.
Weight	Daily in hospital, monthly in the continuation phase.
Height	Monthly.
Full blood picture	Baseline and quarterly.
Creatinine	Twice monthly for the first month, then monthly in the intensive phase and in the continuation phase if indicated.
Potassium	Monthly. If low, obtain calcium and magnesium.
AST, ALT, total bilirubin	Monthly.
TSH	Baseline, then quarterly.
Audiometry and vestibular function	Monthly in the intensive phase then quarterly
X-ray investigation	At baseline, every 6 months, and at end of therapy

Monitoring treatment efficacy

Obtain a sputum specimen for smear, culture, and DST monthly until the child's sputum converts to smear and culture negative. Sputum conversion is defined as two consecutive negative smears and cultures taken 30 days apart. After conversion, obtain smears at least monthly and cultures every 2 months.

In children who are not culture positive initially, treatment efficacy or failure is difficult to assess. Always monitor weight carefully in children to adjust doses as the child gains weight. The following are the first (or only) signs of treatment failure

- Failure to gain weight adequately or
- Failure to thrive or
- Weight loss

Screening of children in contact with MDR TB patients

Close contacts of drug-resistant TB patients who develop TB disease usually have drug-resistant disease with the same resistance pattern. All children who are contacts of an infectious MDR TB case should be screened for MDR TB disease. Screening should be done even in asymptomatic children including;

- History taking
- Physical examination and
- Laboratory findings (sputum for smear and culture, and x-ray investigations).

Follow up and chemoprophylaxis

Children in contact with MDR TB patients should be followed up to enable early detection of MDR TB if the child has been infected. Follow up should be conducted as follows;

- What should be done during follow up
- HIV counseling and testing if not yet done
- Assessment of nutritional status
- History and physical examination to rule out MDR TB
- Advise on TB preventive measures

2

INTRODUCTION TO TUBERCULOSIS IN CHILDREN

Introduction

The aim of this unit is to provide participants with knowledge about TB in children. This unit will cover the definition and cause of TB as well as TB transmission and pathogenesis, differences between TB infection and TB disease, an overview of TB in children, the types of TB, and symptoms and signs of TB in children.

Unit Objectives

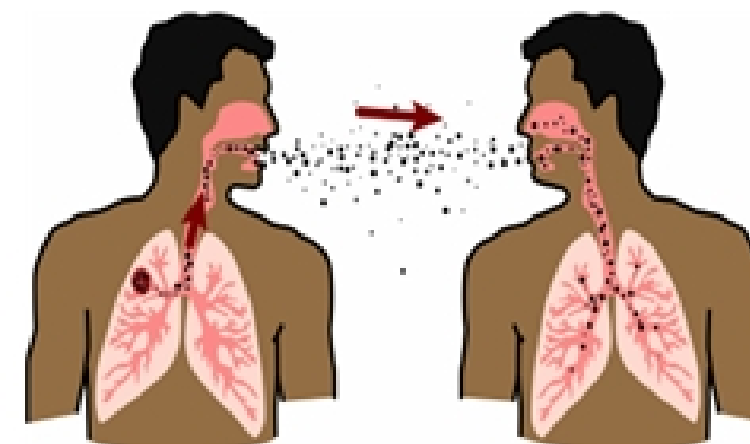
By the end of this unit, you will be able to:

- Describe what is tuberculosis (TB), its cause, mode of transmission and its magnitude.
- Identify risk factors for the transmission of TB to children
- Differentiate between TB infection and TB disease
- Recognize the types of TB, signs and symptoms of TB in children

TB Transmission

TB is a chronic infectious disease caused by *Mycobacterium tuberculosis*, which are also called Acid Fast Bacilli (AFB) as they resist decolourization with acid or alcohol. TB transmission occurs from persons with active pulmonary TB. In settings with poor airflow, TB droplets can remain suspended in the air for hours, making TB more infectious than many other respiratory pathogens. A person with pulmonary TB disease of the lungs can transmit TB through the air when he or she coughs, sneezes, or speaks (see figure 2.1). TB droplets remain suspended in the air for hours, making TB more infectious than many other respiratory pathogens. A less frequent mode of transmission is ingestion of *Mycobacterium bovis*, found in unpasteurized milk products. The closer a person is to someone who has pulmonary TB disease, the greater the chance that person has to become infected with TB.

Figure 2.1: TB transmission



Risk Factors for Transmission

- Duration of infectiousness
 - Untreated pulmonary TB patients can infect many people that they come into contact with
- Bacteriologic status of source
 - Depending upon how infectious a person's TB is, Smear positive cases are most infectious
- Immune system compromise most likely through;
 - HIV- weakens immune system and making a person more vulnerable to acquire TB disease.
 - Other condition such as measles, malnutrition and diabetes also predispose a person to acquire TB disease. However TB can also infect people without any medical condition.
- Chance of infection increases when:
 - Concentration of TB bacteria circulating in the air increases
 - More time is spent with the infectious person
 - Exposure occurs in an area where the bacteria can easily survive
 - e.g. poor ventilation in closed spaces, absence of UV light etc.

Risk factors for TB in Children

TB infection can occur in the following situations:

- Contact with an adult or older child with smear-positive Pulmonary Tuberculosis
- Extent of exposure to the infectious person

Progression from TB infection to disease is influenced by:

- Level of immune system maturity depend on the age; the younger the child the higher risk of progression from infection to TB disease.
- Weakened immune system: a child immune system may be weakened from various diseases including HIV, measles, or malnutrition

Note that; not all children with TB infection develop TB disease. TB disease can develop soon after infection, many years after infection, or never.

Pathogenesis

The primary site of infection by the *M. tuberculosis* bacilli is the alveolar macrophages in the lungs. The stages of infection include bacteria entry, multiplication (Ghon complex), and lymphatic spread (primary complex).

10% of persons with normal immune systems who become infected with latent TB will progress to TB disease at some point in their lives. HIV infection is the strongest risk factor for progressing to TB disease. The risk in HIV-infected individuals is 10% annually.

Children under the age of 2 are at greater risk for developing serious forms of TB (miliary and TB meningitis) due to their immature immune systems. Children in this age group often have non-specific symptoms. Certain medical conditions also increase the risk of progression to TB disease, such as HIV, malnutrition, measles and diabetes mellitus, prolonged use of corticosteroid therapy, and other immunosuppressive therapies.

Differences between Latent TB Infection (LTBI) and TB Disease

Latent TB infection: the person's immune system controls the infection; therefore, the bacilli do not actively multiply, the person has no signs or symptoms, is not infectious and does not need treatment.

TB disease: the bacilli actively multiply, and the person exhibits signs and symptoms, is infectious, needs treatment and can have other organ involvement such as the lymph glands.

Table 5.4. MDR TB medicines and duration of treatment

Treatment phase	Drugs	Duration
Intensive phase	Amikacin or kanamycin Ofloxacin or levofloxacin Pyrazinamide Ethionamide Cycloserine Ethambutol	Minimum of 6-8 months; can be prolonged depending on timing of culture conversion
Continuation phase	Ofloxacin or levofloxacin Ethionamide Pyrazinamide Cycloserine Ethambutol	12 months

Table 5.5. Paediatric dosing and adverse reaction of second-line anti-TB drugs

Drug	Daily dose (mg/kg)	Frequency	Maximum daily dose	Adverse reactions
Amikacin	15-22.5	Once daily, 5 times a week	1 g	Ototoxicity, nephrotoxicity
Kanamycin	15-30	Once daily	1 g	Ototoxicity, nephrotoxicity
Capreomycin	15-30	Once daily	1 g	Ototoxicity, nephrotoxicity
Ofloxacin	15-20	Twice daily	800 mg	Arthropathy, arthritis
Moxifloxacin	7.5-10	Once a day	400 mg	Arthropathy, arthritis
Levofloxacin	7.5-10	Once a day	750 mg	Arthropathy, arthritis
Ethionamide	15-20	Twice a day	1 g	Vomiting, gastrointestinal upset Central nervous system manifestations (psychosis, depression), neurological
Cycloserine	10-20	Once or twice a day	1 g	nervous system manifestations (psychosis, depression), neurological
PAS	150	Twice or thrice daily	12 g	Vomiting, gastrointestinal upset
Pyrazinamide*	30-40	Once daily	2 g	Hepatotoxicity, hyperuricemia, arthralgias, gastrointestinal upset
Ethambutol*	15-25	Once daily	2.5 g	Optic neuritis (usually reversible), decreased red-green colour discrimination, gastrointestinal upset, hypersensitivity

*First-line anti-TB drugs.

Adverse effects of second-line anti-tuberculosis drugs in children

Children generally tolerate second-line medicines well, with adverse events occurring less frequently than in adults. Caregivers should be made aware of possible adverse events and told to immediately report any possible adverse event. No second-line anti-TB drugs are absolutely contraindicated in children unless hypersensitivity or an intractable adverse reaction has been documented.

Diagnosis of multidrug-resistant tuberculosis in children

Multidrug-resistant tuberculosis should be suspected in the following situations:

- A child who is a close contact of an infectious MDR TB case.
- A child who is a close contact of a TB treatment failure or defaulter.
- A child with proven TB who is still bacteriologically positive after five months of appropriate treatment with first-line anti-TB medications. (Treatment failure).

Drug-resistant TB should be suspected under these circumstances, but confirming the diagnosis depends on sputum culture for *M. tuberculosis* strains and results of DST.

Efforts should be made to obtain specimens from all possible sources like gastric aspiration, sputum induction, or lymph node aspiration for culture and DST because MDR TB is a microbiological diagnosis even in children. Culture results can be available within two weeks (Liquid Media) and DST results are available after at least 6 weeks. The diagnosis of MDR TB in children is made by a review panel experts on MDR TB based on history, physical examination and laboratory findings. Children diagnosed with MDR TB should be reported to the DTLC for record and referred to an MDR TB Treatment Centre for further management as stipulated in the Operational Guidelines for the Management of Drug-Resistant TB in Tanzania.

Treatment of Children with Drug-resistant/MDR TB

Treatment decisions for drug-resistant/MDR TB are made by special committees at MDR TB Centres. Sufficient evidence is required because treatment requires prolonged therapy with drugs that are more toxic and less effective than the standard first-line drugs.

Before starting treatment, do the following:

- Identify children at increased risk for adverse reactions or poor outcomes
 - E.g. diabetes, HIV, congenital renal or liver disorders, and thyroid disease
- Inform caregiver/family about DR/MDR TB and its treatment and duration
- Describe the drugs to be used and possible adverse reactions
- Conduct Provider-initiated Testing and Counseling (PITC) if HIV status is unknown
- Obtain serum creatinine, potassium, FBP, thyroid stimulating hormone, liver enzymes
- Chest radiograph

Treatment of Children with Drug-resistant/MDR TB

Pretreatment screening and evaluation

Before referral for MDR TB treatment, the following interventions should be performed:

- Inform the parent/caregiver and family about MDR TB and its treatment and duration
- Evaluate nutritional status, inform mother on proper feeding practices and maintenance of a feeding chart.
- Counsel and test for HIV, if HIV status is unknown.
- Ensure the child has a baseline chest radiograph.

The Ministry of Health and Social Welfare recommends using a standardized treatment regimen approach for all identified paediatric MDR TB cases. “Therefore, all patients receive the same regimen”.

The duration of therapy for MDR TB in children is 18 to 24 months (or at least 18 months after the first negative culture). All treatment should be given daily and under facility DOT, Treatment consists of two phases:

- Intensive phase of treatment, whereby the child takes at least four effective drugs, including an injectable for a minimum of 6-8 months while admitted in an MDR TB treatment center.
- Continuation phase, in which the child takes the same drugs except for the injectable at a health facility close to their home for a total of 12 months.

Types of TB Disease

Pulmonary Tuberculosis (PTB): This is the most frequent type of TB and represents 80% of all cases. It is infectious and its classic symptoms include a cough of 2 or more weeks and sputum production. Patients may also have cavities that are rich in bacilli.

Extrapulmonary Tuberculosis (EPTB): This occurs when bacteria spread outside of the lung tissue and cause disease. With the exception of laryngeal TB, EPTB is not usually infectious. EPTB is the commonest form in people with weak immune systems, especially people with HIV and infants. Patients with EPTB can also have TB disease in their lungs.

TB bacteria can travel through the lymphatic system to regional lymph nodes and through the bloodstream to more distant tissues and organs. Organs in which TB disease can develop include the lymph nodes (most common), the brain/meninges, pleura, pericardium, abdomen, spine, other bones, kidney, adrenal glands, genital urinary tract, and the larynx. HIV-infected persons have a higher risk of disseminated TB and EPTB disease than do those without HIV.

Signs and Symptoms of Pulmonary Tuberculosis

- Most children with TB have persistent cough not improving. However, cough is less common in children less than 5 years
- Fever and /or night sweats
- Weight loss or failure to gain weight
- Loss of appetite
- Fatigue, reduce playfulness, less active and irritability
- Breathlessness
- Children greater than 5 years of age may produce sputum when they cough, sometimes with blood (haemoptysis), so sputum smear can be used to test for TB in this age group.

Signs and Symptoms of Extrapulmonary Tuberculosis

The general signs and symptoms of these patients include:

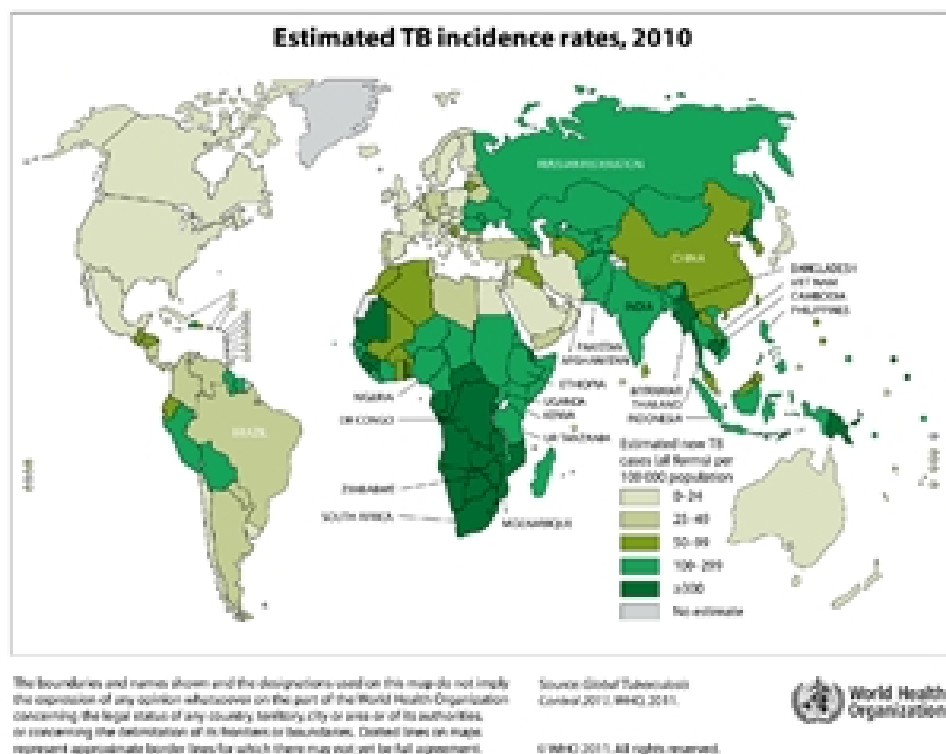
- Fever
- Loss of appetite
- Loss of weight or poor weight gain in children
- Fatigue, reduce playfulness, less active and irritability

Specific signs and symptoms depend on the site of the disease

TB Epidemiology

One-third of the world's population is infected with TB, with over 9 million new cases each year and approximately 2 million TB deaths a year. The majority of TB patients live in the 22 high burden countries as seen in Figure 2.3.

Figure 2.2



Epidemiology of Pediatric TB Global

The global burden of pediatric TB is difficult to assess. Estimates assert that TB cases in children comprise 10% of all cases worldwide, or 900,000 of the 9.2 million cases in children under the age of 15. However, in 2009, only 47,635 cases under the age of 15 had positive bacteriologic testing and were reported. There are often large discrepancies between the estimated incidence of TB and case notification rates. We know that many of these missed cases are in children but precise figures are difficult to determine. In high burden countries it is estimated that 15% of TB cases are children.

There are many steps involved in correctly diagnosing and reporting a case of TB. Improvements in health care access, social mobilization, case finding, diagnosis, standardized case definitions and monitoring could increase reporting.

Epidemiology of TB in Tanzania

Tanzania rank number 20 among 22 high TB-burden countries in TB incidence rate (Global TB report 2011). In 2010 Global TB report more than 60,000 cases of TB were identified, with an incidence rate of 177 cases per 100,000 population.

TB is the third highest cause of morbidity and mortality in Tanzania after HIV/AIDS and malaria. TB notifications in the country have increased due to HIV epidemic. Tanzania in 2010 a total of 63,453 TB patients were notified. TB/HIV co-infection rate was 38%. The magnitude of TB disease among children in Tanzania is difficult to ascertain due to challenges of diagnosis and reporting. However, data from the NTLTP for the past 8 years show that pediatric cases have constituted an average of 10 percent of all TB case notifications. In 2010, there were 5,216 TB case notifications in children (less than 15 years of age), which accounted for 8.7 percent of the total new case notifications. As the overall incidence of TB infection is decreasing in the country.

7

PAEDIATRIC TB IN SPECIAL SITUATIONS: DRUG-RESISTANT TB IN CHILDREN

Introduction

The goal of this unit is to provide participants with knowledge and skills to diagnose, treat and monitor children with drug-resistant TB, and to manage child contacts to drug-resistant TB cases.

By the end of this unit you should be able to:

- Define drug-resistant TB and multidrug-resistant TB
- Explain how to diagnose and manage children with drug-resistant TB
- Explain how to manage child contacts to a drug-resistant TB case

Introduction to Drug-resistant TB

Multidrug-resistant tuberculosis is defined as resistance to both isoniazid and rifampicin with or without resistance to other first-line anti-TB drugs (streptomycin, pyrazinamide, and ethambutol). In adults, MDR TB is more common in previously treated TB cases (acquired drug resistance); however, in children MDR TB is usually the result of direct transmission of *M. tuberculosis*-resistant strains (primary drug resistance) from an adult sick person.

Drug-resistant TB: Definitions

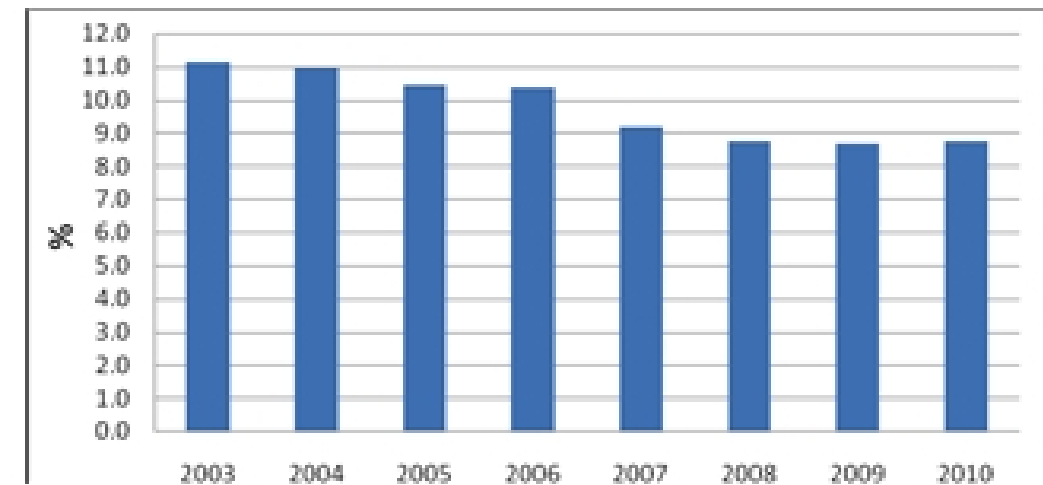
Drug-resistant TB is defined as TB caused by a strain that is resistant to one or more anti-TB medicines. This may be grouped into:

- **Mono-resistant TB:** Resistance to a single drug, most commonly isoniazid. This pattern of resistance is not usually associated with a worse outcome and does not require modification of the treatment regimen, as long as there are 4 drugs in the initial phase and rifampicin is included throughout the full duration of treatment. Rifampicin mono-resistance occurs, but is uncommon and is seen mainly in patients with HIV infection.
- **Poly-resistant TB:** Resistance to more than one drug, but not the combination of isoniazid and rifampicin.
- **MDR-TB:** Resistance to at least isoniazid and rifampicin. MDR has a major adverse effect on treatment outcome, and infected patients will generally require treatment with second-line regimens.
- **XDR-TB:** MDR-TB, plus resistance to fluoroquinolones, and at least 1 of 3 injectable agents (amikacin, kanamycin, capreomycin). XDR-TB cases are often also resistant to all 4 first-line agents, making patients significantly more difficult to treat.
- **Primary drug-resistance: "New Cases":** Drug resistance in a patient who has never been treated for TB, or received less than 1 month of TB therapy. Drug-resistant TB in children is usually primary and due to contact with an infectious adult case.
- **Acquired drug-resistance: "Previously Treated Cases":** Drug resistance in a patient who has received at least one month of anti-TB therapy.

Higher rates of TB are seen in Dar es Salaam, due mainly to the HIV epidemic. TB prevalence differs between regions and possible reasons include different rates of HIV, rural and urban migration patterns, poverty, health seeking behavior, and access to health care. TB rates and percentages of the national burden are shown in Figures 2.3 and 2.4.

According to the Drug resistance survey conducted in 2006/2007 among smear-positive notified cases, the prevalence of MDR TB in Tanzania was 1.1 percent and 3.1 percent among new and retreated TB cases respectively. In 2012 there were an estimated 510 MDR TB cases among 63,453 TB cases (chil country. No data are available on children with MDR TB; this is largely attributed to difficulties in diagnosis

Figure 2.3 Proportion of Children among new TB patients notified 2003 to 2010



Trends of paediatric (<15yrs) TB case notification (all forms) between 2003 to 2010

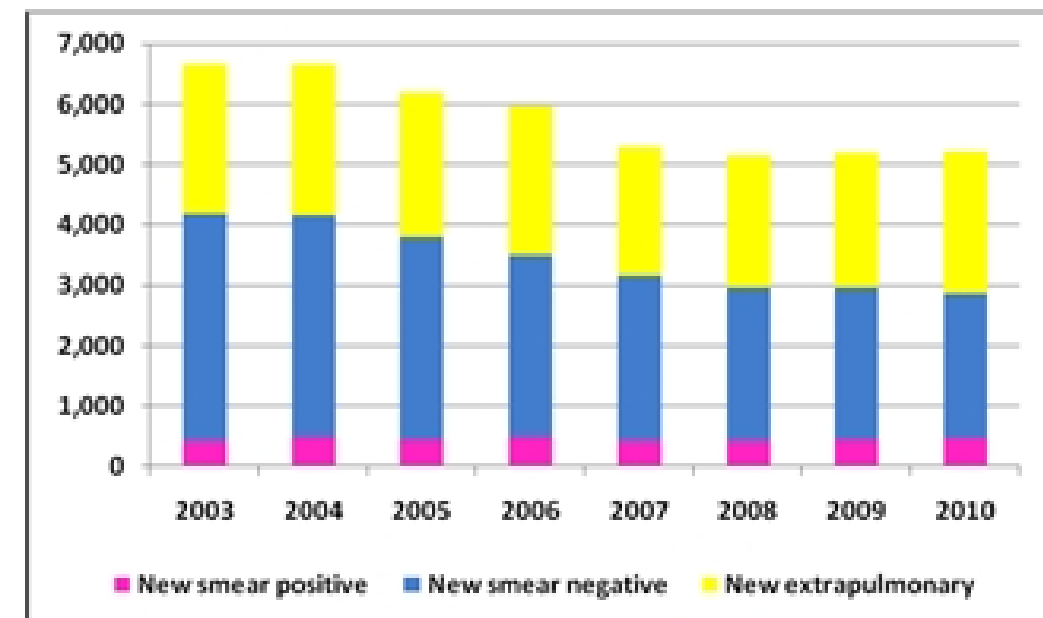
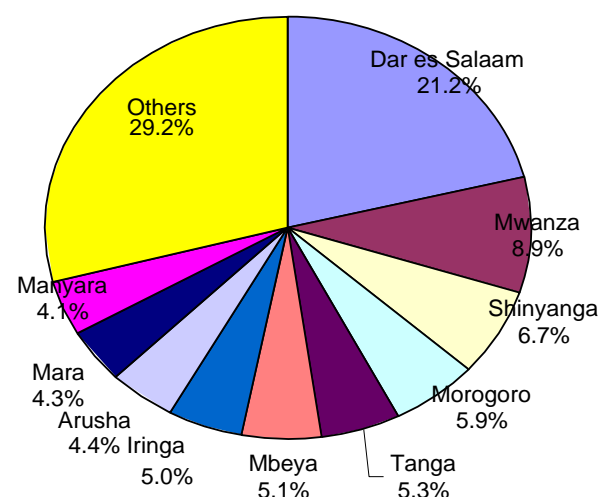


Figure 2.4: Distribution of TB notification by Regions 2010 Tanzania (Percentages)



Key Points

- TB is caused by Mycobacterium tuberculosis and its transmission is airborne.
- Persons with latent TB infection are not infectious, feel well, have normal examination and chest x-rays findings
- When TB becomes active, it causes TB disease, it usually affects the lungs but any organ system can be affected.
- Not all people with latent TB infection will develop TB disease but young children and those with compromised immune systems are at much greater risk.
- Children are usually infected by someone in their household.
- Children with TB disease are sentinel cases: they indicate recent transmission in the community or household.
- TB causes significant morbidity and mortality worldwide.
- In the last few years, effective control measures have brought down the incidence and prevalence of TB in Tanzania.

School-age children can generally handle age-appropriate information about HIV.

- For a successful disclosure process, ensure that parents/caregivers are well informed and supported beforehand and throughout. Reassure them that a child may be initially angry and upset, but is often relieved to know the truth. Support groups help parents/caregivers share emotions and experiences of disclosure.
- Psychosocial support is also important because increased stress can impair the child's immune system. Encourage parents/caregivers to talk with their children and to allow them to verbalize any fears and concerns they may have.
- Encourage proper rest, a balanced diet, and link families to social assistance. Instruct the family not to segregate the child from other family members, as this will further stigmatize the child.

Key Points

- When TB and HIV interact, the two diseases intensify and worsen each other.
- If a child has HIV infection he/she needs to be screened for TB, and if child has TB he/she needs to be tested for HIV
- If a child has HIV infection and TB disease, start him/her on anti-TB medications and, if not already on ART, start ART 2-8 weeks later.
- IRIS is NOT treatment failure but a recovery of the immune system and exaggerated presentation of unmasked infection.
- Continue anti-TB medicines and ART when HIV-infected children develop IRIS unless severe toxicity occurs.
- CPT is universally recommended for children with TB/HIV co-infection.

TB-IRIS symptoms include worsening TB symptoms, persistent fevers, and local and systemic infection/inflammation. Because TB-IRIS is characterized by the generation of an intense inflammatory response to existing infections, it is commonly associated with current or undiagnosed TB. BCG-IRIS also occurs in the setting of recent BCG vaccination.

The differential diagnosis of TB-IRIS includes TB treatment failure, side effects of anti-TB medications and/or ART, pre-existing untreated opportunistic infections. To manage TB-IRIS, it is important to continue ART and anti-TB management. In severe cases, patients can be given prednisolone 1-2mg/kg for 1-2 weeks. Supportive measures should be provided and TB treatment and ART should be stopped only if severe toxicity is suspected or confirmed (e.g., elevated liver function tests above 5 times normal).

Co-trimoxazole Preventive Therapy (CPT)

CPT is a safe and cost-effective therapy for HIV-infected children and is universally recommended for all with TB/HIV. It prevents secondary bacterial, fungal, and parasitic opportunistic infections, as well as reducing mortality and hospitalizations from these infections.

CPT should be provided to all children with TB/HIV and to HIV-exposed infants if not already given as per national HIV guidelines.

Recommended doses of cotrimoxazole by age

Age range	Trimethoprim/Sulfamethoxazole (TMP/SMZ) (Septrin®, Bactrim®)	
	4 mg/kg once daily (for prophylaxis against opportunistic illnesses; higher doses will be required for treatment)	
	Syrup: 40 mg/200 mg/5 ml	Single-strength tablet: 80 TMP/400 SMZ
Birth to 6 months	2.5 ml	¼ tablet
6 months-5 years	5 ml	½ tablet
5 years-14 years	10 ml	1 tablet
≥14 years		2 tablets

Counseling of Children with TB/HIV:

Give enough age-appropriate information to the child to ensure adherence to TB/HIV treatment. Counseling is an ongoing and lifelong activity, so more information and support must be provided as children mature. Help the parent/caregiver become a knowledgeable adviser and advocate for their children, and be sure to review the following with the patient and parent/caregiver:

- TB and HIV transmission
- Clinical care and treatment
- Good nutrition, exercise, hygiene, and rest
- Psychosocial care
- Adherence to treatment manages HIV, cures TB, and prevents resistance, thus improving the child's health and protecting others

Disclosure of TB/HIV Status to Child:

- Parents/caregivers may have strong emotions on this issue, especially if HIV infection is due to mother to child transmission (MTCT).
- Healthcare providers should help parents/caregivers overcome guilt and shame, and offer to participate in discussions when telling a child about their HIV infection. Involving the child and parent/caregiver from the beginning of the disclosure process results in better outcomes.

3

DIAGNOSIS OF TUBERCULOSIS DISEASE IN CHILDREN

Introduction

The goal of this unit is to provide participants with the knowledge and skills regarding when to suspect tuberculosis (TB) in a child and how to diagnosis TB in a child.

Unit Objectives

By the end of this unit, you will be able to:

- Explain the diagnostic approach used in children suspected of having pulmonary or extrapulmonary TB
- Describe the diagnostic tests for TB in children
- Demonstrate skills in diagnosing TB disease in children through a case study

TB Diagnosis in Children

Confirming diagnosis of TB in children is challenging. Bacteriologic confirmation is achieved in only about 30 - 40% of TB cases in children. Therefore, diagnosis is often based on the presence of the classic tetrad: 1) history of close contact with a smear positive (infectious) adult with TB; 2) signs and symptoms compatible with TB; 3) suggestive lab results or radiographic findings and or 4) a positive tuberculin skin test (TST)

Recommended Approach to Diagnose TB in Children

In order to diagnose TB in children, it is necessary to take a complete history, including any history of TB contact and symptoms of TB disease. Ask the patient/caregiver or child to describe when symptoms first started and specifically inquire about appetite and weight loss or failure to thrive. If coughing, ask about sputum production and whether blood is present. Ask about other medical conditions that predispose to TB (such as HIV) and history with details of any prior TB disease/treatment.

It is also important to perform a thorough physical examination, a TST where available and attempt bacteriologic confirmation by collecting a sputum or other relevant specimen(s). In addition, appropriate laboratory and radiologic investigations for pulmonary and extrapulmonary TB and HIV testing are recommended.

All findings must be considered carefully but when **a history of close contact with a case of TB, especially an infectious (smear positive) case, is present, this strongly supports a diagnosis of TB in a child**, especially those under age 5.

Complete a Physical Examination noting:

- Appearance: Thin or wasted
- Temperature: Normal or elevated
- Lymph nodes: Enlarged, painless, may be matted or with discharging sinus
- Chest:
 - Respiratory rate may be normal or high
 - Trachea may be displaced in massive pleural effusions
 - Breath sounds may be normal, but there may be bronchial breathing, crepitations (crackles), and wheezing/rhonchi
 - Dullness on percussion
 - Distant heart sounds in pericardial effusion
- Abdomen: masses, ascites or distension
- Joints: may be swollen or with effusion, angulation of the spine (Gibbus)

Clinical Presentation of Pulmonary TB by Age Group

Infants with TB usually have a nonproductive cough, fever, anorexia, inadequate weight gain, weight faltering, weight loss, or failure to thrive. Infants may have decreased activity, increased irritability or lethargy. Symptoms may present as severe pneumonia with fast breathing, chest indrawing, and respiratory distress.

Children with TB, pre-school and school-aged, typically have a cough for 2 or more weeks (or any cough if HIV positive), a fever for 2 or more weeks without other etiology and weight loss or failure to thrive.

Adolescents present similarly to adults with TB and typically have: a cough for 2 or more weeks (or any cough if HIV positive), a fever for 2 or more weeks and weight loss, anorexia and malaise. Adolescents are more likely to have excessive night sweats, chest pain and hemoptysis (coughing up blood)

Specimen Collection

Attempt bacteriologic confirmation in all children suspected of having TB. Sputum should be collected for smear microscopy. This can be done by 3 methods:

- expectoration (coughing up sputum)
- sputum induction
- gastric aspiration

When collecting expectorated sputum, use appropriate containers with a wide mouth to control infection. Collect the specimen in well-ventilated area, preferably outdoors in the sunlight. Ensure that no one stands in front of the patient while producing sputum and that the container is labeled and closed firmly with lid. Wash your hands with soap and water after the procedure.

Collect two expectorated sputum specimens using the spot and early morning methods. Obtain a spot sputum during their medical visit. Verify that the sample contains sputum and not saliva and send the specimen to the lab for AFB microscopy. Send the patient home with a container and instructions on how to collect the first morning sputum the next day. The morning specimen usually has the highest yield. Instruct the parent/caregiver to bring the child's morning specimen back to the health unit on the same day. All samples are sent to the lab for AFB smear microscopy (and mycobacterial culture when indicated) within 24 hours of being collected.

Figure 6.1 Recommended ART Regimens for Children Receiving Standard TB Treatment

	REGIMEN
ART regimen in children receiving anti-TB treatment	2 NRTIs + EFV (for children >3 years of age and weighing >10 kg) 2 NRTIs + NVP or triple NRTI (for children <3 years of age and/or weighing <10 kg)
Children on anti-TB treatment but not yet initiated on ART	For children <3 years of age and/or weighing <10 kg: Initiate AZT/3TC/NVP; or as an alternative, AZT/3TC/ABC For children >3 years of age and weighing >10 kg: Initiate AZT/3TC/EFV
Children already on ART and started on anti-TB treatment	Continue ART regimen For children <3 years of age and/or weighing <10 kg: substitute NVP with ABC For children >3 years of age and weighing >10 kg: substitute NVP with EFV

ABC: abacavir; **AZT:** zidovudine, **3TC:**Lamivudine, **EFV:** efavirenz, **NRTI:** nucleoside reverse transcriptase inhibitor, **NVP:** nevirapine.

Nevirapine should be used at its maximum dose (i.e. 200mg/m²) twice daily. On ART initiation, do not use nevirapine lead-in dosing since it will lead to sub-therapeutic nevirapine levels and can compromise viral suppression. For children on a lopinavir boosted with ritonavir (LPV/r) regimen, consider adding ritonavir in a 1:1 ratio to achieve a fully therapeutic dose of lopinavir. For children with anemia (Hb < 7.5g/dL) replace AZT with d4T.

Figure 6.2. Overlapping side effects of anti-TB treatment and ARVs*

Effect	Possible causes	
	Anti-TB drugs	Antiretroviral drugs
Peripheral neuropathy	Isoniazid, cycloserine	Stavudine, didanosine
Skin rash	Rifampicin, isoniazid, pyrazinamide, cycloserine	Nevirapine, efavirenz, abacavir
Gastrointestinal symptoms	All	All
Hepatitis	Pyrazinamide, rifampicin, isoniazid, ethionamide	Nevirapine, protease inhibitors
Anaemia	Rifampicin	Zidovudine

*For management of adverse reactions, refer to unit "Management of tuberculosis disease in children."

Immune Reconstitution Inflammatory Syndrome (IRIS)

TB-IRIS can occur at the beginning of anti-TB therapy and ART due to the body's capacity to mount an inflammatory response. Symptom onset is usually within a few months of starting ART, as the start of ART alone can sometimes unmask prior quiescent TB. Typically, a patient who was doing well and responding to therapy suddenly gets much worse or has new symptoms/signs -this is referred to as a paradoxical reaction. Rates of TB- IRIS in children starting ART are between 5-20%.

in HIV infected people and increases the risk of HIV progression to AIDS. TB is the leading cause of death among people living with HIV/AIDS. Overall, an increase in TB among HIV-infected persons increases the risk of TB transmission in the general population.

Diagnostic Challenges of TB/HIV in Children

Because of the high rates of co-infection with HIV and TB, children diagnosed with TB need to be tested for HIV, and children diagnosed with HIV need to be screened for TB. To diagnose HIV in children with TB, perform HIV testing on all children suspected of having or diagnosed with TB. An HIV test is still the only point-of-care test for TB management. Exclusion of HIV makes management more straightforward, and confirmation of HIV requires additional care and assessment of family. If test results are positive, refer the patient to HIV care.

To diagnose TB in HIV-infected children, screen all HIV-infected children for TB disease at time of HIV diagnosis and at every HIV care visit afterwards. Be aware that HIV-infected children with TB disease will have fewer TB bacteria than children who are not HIV-infected. Because they have fewer TB bacteria (paucibacillary disease), the yield of sputum smear microscopy is even lower. Use the normal procedure for diagnosing TB, found in the Unit on Diagnosis of TB in Children. Extrapulmonary TB and disseminated disease will be more common in HIV-infected children.

Clinical Presentations

The natural history of TB in HIV-infected children depends on the stage of HIV disease. Before HIV infection advances, the child will still have good immunity, and TB will present with signs and symptoms as in a child who does not have HIV. However, infants have immature immune systems so their immune status is already somewhat compromised. As HIV disease progresses, immunity declines and dissemination (manifest as TB meningitis and/or miliary TB) and extrapulmonary TB (such as widespread TB lymphadenopathy) are more common.

Treatment of TB/HIV

HIV-infected children with TB have worse outcomes and higher rates of mortality than children without HIV infection. This is due to severe immunosuppression, co-existing malnutrition, HIV-related co-infections, immune reconstitution, and greater adherence problems. Most deaths of HIV-infected children receiving TB treatment occur within the first two months of starting TB treatment.

TB treatment should be started immediately in all HIV-infected children with TB disease. The same dosages of anti-TB medicines are prescribed to children whether or not they are infected with HIV. Treatment in Care and Treatment Centres (CTCs) and TB clinics should be monitored as per national guidelines. Provide Cotrimoxazole preventive therapy to all children with TB/HIV.

Simultaneous Treatment of TB/HIV

ART will reduce mortality and risk of TB recurrence in HIV-infected children with TB disease, as well as decrease the risk of progressing from latent TB infection to TB disease. Start ART in all children with TB/HIV regardless of CD4 levels once TB treatment is tolerated. Earlier treatment is associated with better outcomes so, ideally, begin ART 2 weeks after the start of anti-TB, and definitely by 8 weeks.

Special considerations for TB/HIV co-treatment include pill burden, adherence concerns, increased likelihood of drug toxicity, and drug interactions with rifampicin and ARVs.

The coughing patient is more infectious than the specimen sample to the staff. Instruct the patient to cover his/her mouth and nose when coughing. Never collect sputum in the laboratory or clinic room. Do not stand in front of the patient during specimen collection.

Induced Sputum

Induced sputum has a yield higher than expectorated sputum and comparable to or better than gastric aspiration. The procedure is safe, effective and can be done in children as young as 1 month. Sputum induction is recommended for young children unable to expectorate and should be performed by trained personnel at facilities with appropriate equipment. For more details, see Annex 1 in the Guidelines.

Gastric Aspiration

This procedure uses nasogastric feeding tube to collect sputum swallowed overnight from children who are unable to expectorate (or undergo induction). Gastric aspiration requires hospitalization. Two early morning specimens are collected on consecutive days before the child eats, drinks or ambulates by trained personnel at a district, regional or zonal hospital.

Transportation of sputum samples: Transport specimens to the nearest diagnostic center if not microscopy is available your facility. Transportation of sputum samples should occur within 72 hours of collection and samples should be carefully packed and protected from direct sunlight. Label the container with infectious hazard marks. Samples should be accompanied by a completed laboratory record.

AFB Sputum Smear Microscopy

Sputum smear microscopy using a Ziehl-Nelsen stained smear or Light Emitting Diode (LED) fluorescence microscopy is the main diagnostic test most widely available in Tanzania.

AFB sputum smear results are reported as follows:

- 3+ AFB = > 10 AFB per field
- 2+ AFB = 1-10 AFB per field
- 1+ AFB = 1-10 AFB per 10 fields
- 1 - 9 AFB = Exact number of AFB found in 100 fields
- No AFB = No AFB found in 100 fields

One or more positive test results = sputum smear positive, this means that the person has PTB, is infectious and needs treatment.

Note that negative sputum smear DOES NOT rule out TB disease in children.

Other Diagnostic Tests

Other tests include a mycobacterial culture, which has a higher yield than smear microscopy but requires 2-8 weeks for growth. It is only performed at referral laboratories.

GeneXpert MTB/RIF is another diagnostic technique, which is a cartridge-based PCR test using sputum. Results are available in 2 hours. This method detects rifampicin resistance and is available in a few sites in Tanzania.

Blood tests such as ESR (erythrocyte sedimentation rate) and FBP (full blood picture) are not specific to TB and therefore are not recommended.

Tuberculin Skin Test (TST)

A TST, called a Mantoux or PPD, indicates mycobacterial infection ONLY and NOT necessarily the presence of TB disease. Although it cannot distinguish TB disease from latent TB infection, a positive TST result can be used as an adjunct tool for diagnosing TB disease in children. A positive TST result alone is NEVER diagnostic of TB disease. Trained personnel should perform the TST. The needle should be placed in the subcutaneous tissue and 0.1ml of fluid should be placed. Follow-up in 48-72 hours. Results are read 48 - 72 hours after TST placement by measuring the size of induration.

How to interpret TST results is shown in Table 3.2.

Table 3.2: Interpretation of TST Results

Patient Characteristic	Positive TST Result
HIV-infected	≥ 5 mm diameter induration
Severely malnourished (marasmus or kwashiorkor)	≥ 5 mm diameter induration
Contact to a case of infectious TB (smear positive)	≥ 5 mm diameter induration
All other children (regardless of whether they have received a BCG vaccination or not)	≥ 10 mm diameter induration

NOTE: A negative TST does not rule out TB.

False Positive and Negative Results TST

False positives (i.e. when the test is positive but there is no TB) may result from: BCG (Bacille Calmette-Guérin) vaccination, infection with non-tuberculosis mycobacterium and improper administration or interpretation.

False negatives (i.e. when the test is negative but there is TB) may result from: incorrect administration or interpretation of the TST, age of less than 6 months, severe malnutrition, advanced HIV disease, immune suppression by disease or medication, viral illness or recent live virus immunizations or overwhelming TB disease.

Chest X-Ray

Chest x-rays can be used to support a diagnosis of TB. Obtain anteroposterior and lateral views on all children suspected of having pulmonary TB. Abnormal chest x-ray findings are suggestive of TB but in general chest x-rays are not specific and there is no typical x-ray appearance for pulmonary TB.

Indications for obtaining a chest x-ray:

- Cough not improving and present for >2 weeks (or any cough in HIV positive children)
- Fever for >2 weeks without other source
- Concerns for extrapulmonary TB
- TB suspect with negative smears

The most common chest x-ray findings in a child with TB disease are 1) persistent opacification with hilar or subcarinal lymphadenopathy and 2) advanced adenopathy causing bronchial compression leading to infection or lung collapse. Children with miliary TB usually have the classic miliary pattern of diffuse “millet seed” opacities. Another findings consistent with TB is an opacification of any lobe that does not improve after a course of antibiotics. In general, adolescents with TB present with typical adult disease findings including upper lobe infiltrates, pleural effusions, and cavitations.

6

PAEDIATRIC TB IN SPECIAL SITUATIONS: TB/HIV IN CHILDREN

Introduction

The goal of this unit is to provide participants with knowledge and skills to diagnose TB in HIV-infected children, to provide effective treatment for children co-infected with TB and HIV, and to manage drug-drug interactions.

By the end of this unit you should be able to:

- Explain how to approach the diagnosis of TB in HIV-infected children
- Explain how to manage HIV-infected children with TB disease, including potential drug-drug interactions and recommended regimens
- Demonstrate skills in managing TB/HIV co-infection in children through case studies

Brief Overview of HIV/AIDS

HIV (Human Immunodeficiency Virus) is a retrovirus that leads to AIDS. It causes immune suppression by infecting and depleting the CD4 cells of the immune system. HIV infection means that this virus is present in the human body. AIDS (Acquired Immune Deficiency Syndrome) occurs when chronic HIV infection progresses to severe disease as a consequence of immune suppression. Signs and symptoms of AIDS are indicative of immune deterioration.

HIV can be transmitted through mother-to-child transmission (MTCT) during pregnancy, during labor and delivery, or through breast milk. The HIV virus can also be transmitted through unprotected sexual contact with an infected partner and contact with HIV-infected blood or blood products. Examples include blood transfusions, needle sharing during injection drug use, needle stick accidents, and use of unsterilized needles.

TB and HIV Interaction

HIV is fueling the TB epidemic in many parts of the world, including in Tanzania. The MOHSW estimates that 38% of TB patients are co-infected with HIV, and that 5-10% of HIV patients have TB disease. Due to the overlap between TB and HIV, the global community and Tanzania specifically has adopted the “Two Diseases, One Person” policy and an integrated care approach for serving these patients.

The limited data on children with TB/HIV indicate that TB is the major cause of morbidity and mortality in HIV-infected children. In Zambia, children with TB and HIV had a 6-fold increase in mortality compared to children with HIV alone. In South Africa, HIV-infected children had a 24-fold increase in pulmonary TB and a 15-21-fold increase in other forms of TB disease. MTCT is the most common source of HIV infection in children, making the peak age prevalence for HIV less than 5-years-old. Mothers with HIV are also at higher risk for TB, which increases their children’s risk too.

HIV infection promotes progression to active TB in people with recently acquired or latent M. tuberculosis, and increases the risk of recurrent TB. TB is the most common opportunistic infection

TB Infection Prevention and Control

Clinical presentation of TB in children is variable and often overlaps with the presentation of pneumonia, HIV, and malnutrition. Every health care facility needs a TB Infection Control Plan for rapid investigation, appropriate management, and rapid treatment of suspected TB cases. Children with TB may also transmit TB, therefore infection control measures are important even in facilities that only treat children, in both outpatient and inpatient areas.

Educating patients, family, and the community about signs of TB can help achieve an early diagnosis. Information about respiratory hygiene can reduce the likelihood of transmission in the community. When a child is diagnosed with TB, promptly screen contacts to identify the source case and start treatment for confirmed TB as soon as possible. Isolate infection source cases from vulnerable contacts, if possible. Schedule suspected TB cases early in the day to minimize transmission to others, and place them in a well-ventilated waiting room with open air and sunlight. In inpatient pediatric wards, children with suspected or confirmed TB should be cared for in a separate, well-ventilated room, away from HIV-infected children.

Key Points

- BCG vaccine is effective in preventing serious forms of TB in very young children
- BCG vaccine should be administered to HIV negative/unexposed infants and asymptomatic HIV-exposed infants
- Contact tracing should be done for every smear positive TB patient
- When active TB is ruled out, give IPT to:
 - Child TB contacts under age 5 and
 - HIV-infected children >1 year of age
- Treat LTBI in children with 6 months of isoniazid (IPT)
- IPT protects against TB for about 2 years
- Every health care facility needs a TB Infection Control Plan
- While most children are smear negative, some children will transmit TB
 - Children with suspected or confirmed TB should be cared for in a separate, well-ventilated room, away from HIV-infected children

Scoring Chart for the Diagnosis of TB in Children

A clinical diagnosis of TB in children is aided by use of a scoring chart. Use this chart in child TB suspects without bacteriologic confirmation. A score of 7 or higher is highly suggestive of TB. The Tanzania Score Chart is shown in Table 3.3.

Table 3.3 Score Chart for Diagnosis of TB in Children*

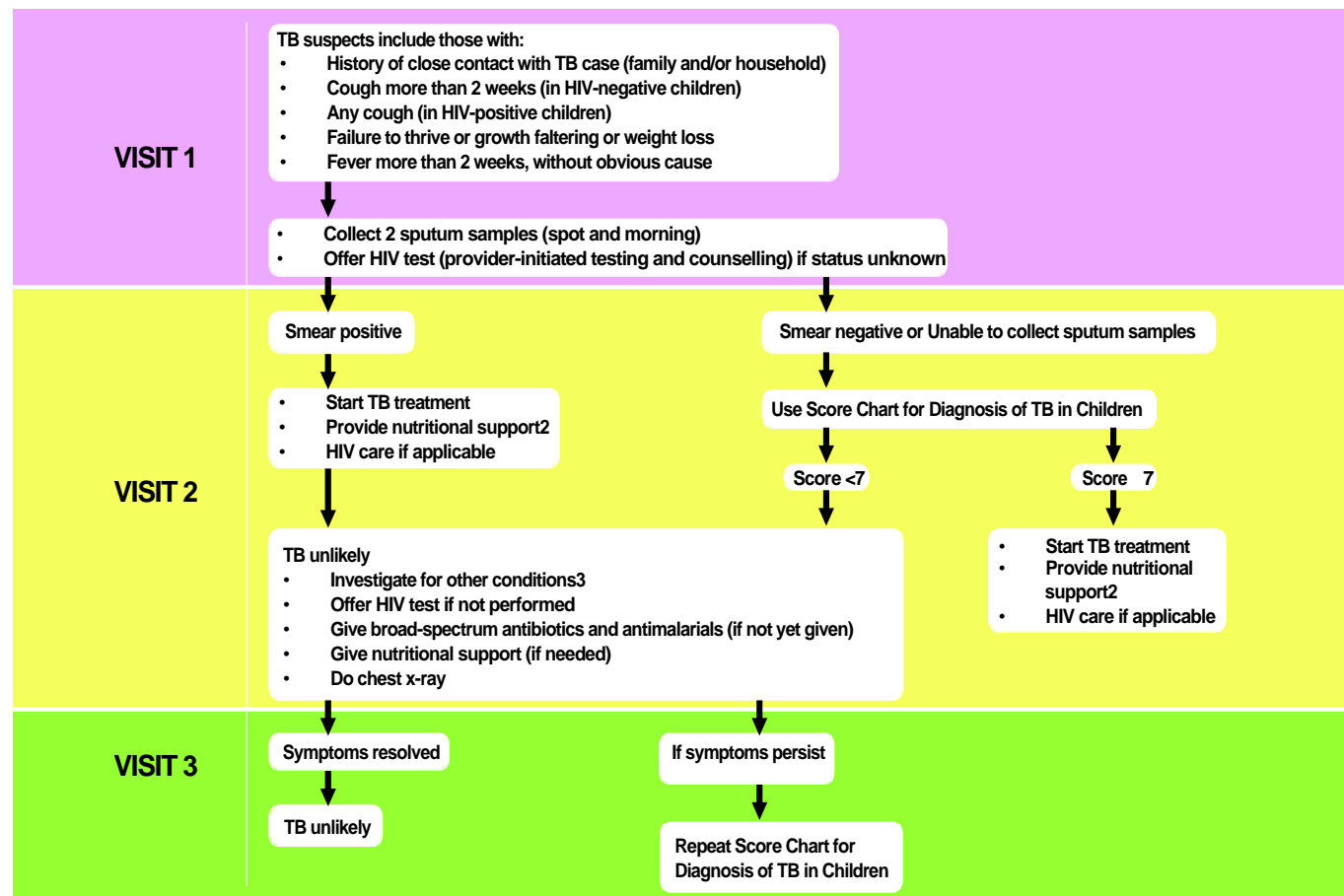
SCORE IF SIGN OR SYMPTOM PRESENT						
	0	1	2	3	4	Score
GENERAL FEATURES						
Duration of illness	Less than 2 weeks	2-4 weeks		More than 4 weeks		
Failure to thrive or weight loss	Weight gain	No weight gain or weight faltering		Weight loss		
TB contact	None	Reported (but no documentation), reported smear negative or extrapulmonary TB		Smear positive (with documentation)		
TST	Negative, not done			Positive		
Malnutrition not improved after 4 weeks of therapy				Present		
Unexplained fever not responding to appropriate therapy**			Positive			
LOCAL FEATURES						
Painless, enlarged lymph nodes*		Any non-cervical lymph nodes		Positive cervical lymph nodes		
Swelling of bones or joints*				Positive		
Unexplained ascites or abdominal mass*				Positive		
LOCAL FEATURES						
Central nervous system findings: meningitis***, lethargy, irritability and other behaviour changes				Positive		
Angle deformity of the spine					Positive	
*Score of 7 or more indicates a high likelihood of TB. Refer to the text for further details.						

*HIV infection, sickle cell disease, rheumatologic disease alone (in the absence of TB disease) can cause scores of >7. Therefore, best clinical judgment must be used when using this scoring system (see section 5.1, "TB/HIV in Children" for further guidelines)

**Do not use aminoglycosides and fluoroquinolones, as they are active against *M. tuberculosis* complex and, thus, may cause transient improvement in persons with TB.

***Meningitis not responding to conventional antibiotics. Other causes of meningitis (e.g. bacterial) must be excluded

Figure 3.4 Algorithm for Diagnosing Pulmonary TB in Children below 6 years old



Diagnosis of Extrapulmonary TB in Children

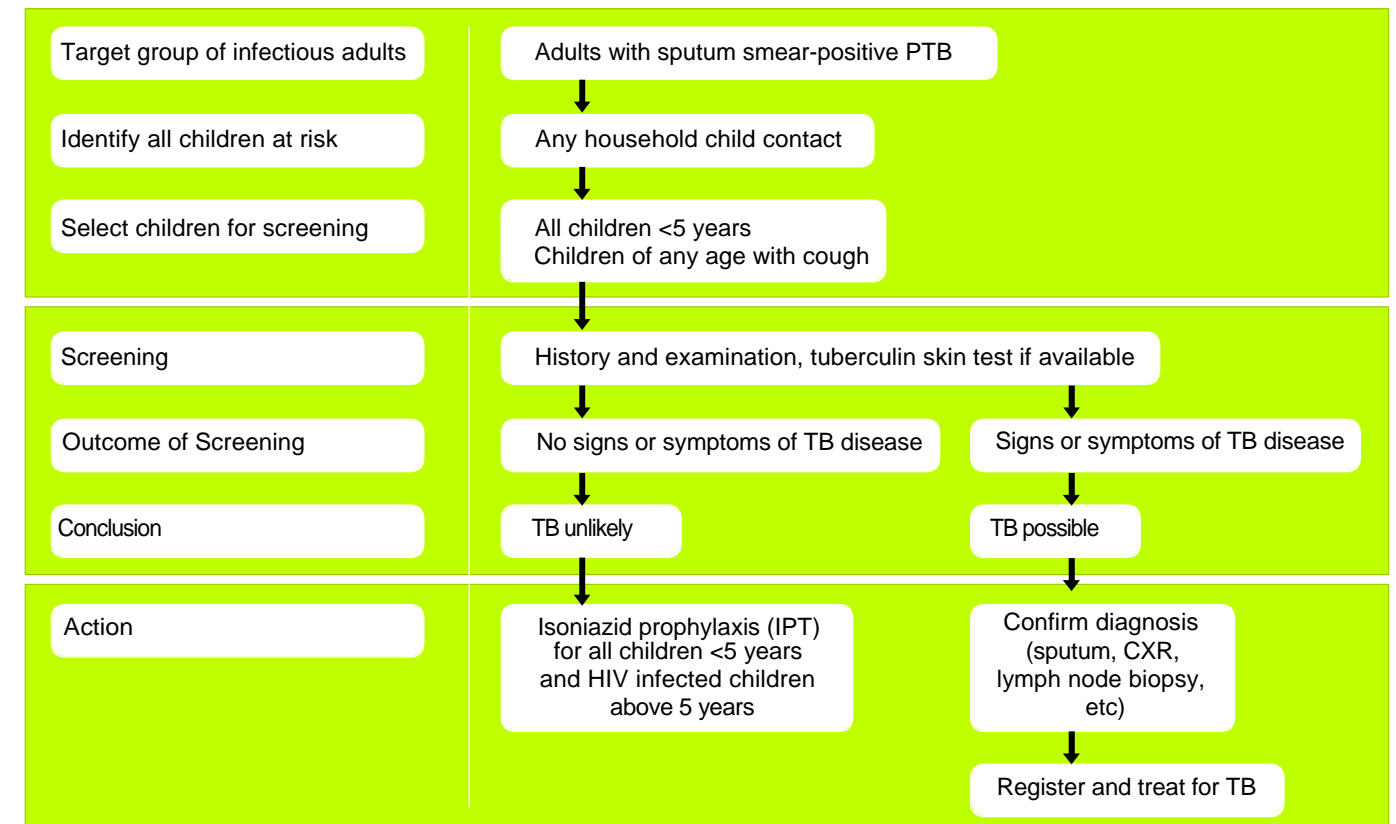
The clinical presentation of extrapulmonary TB will depend on site of disease. TB can affect many tissues of the body but the most common sites in children are the superficial lymph nodes and central nervous system. Neonates have the highest risk for developing miliary TB and TB meningitis.

Collect specimens for smear and/or culture from any site where disease is suspected including lymph nodes, cerebrospinal fluid, urine and pleural fluid. If the child is also coughing, evaluate for pulmonary TB.

TB Lymphadenitis

TB lymphadenitis presents with painless, fixed, enlarged lymph nodes usually in the cervical region that persist for weeks. Fistulas can develop. TB lymphadenitis is not associated with upper respiratory illness. To diagnose, perform fine needle aspiration or excisional biopsy and send tissue for AFB smear microscopy, culture, and histopathology. The presence of caseating granulomas on histopathology is very suggestive of TB.

ALGORITHM FOR ASSESSING CHILD HOUSEHOLD CONTACTS



PTB: pulmonary tuberculosis, CXR: chest x-ray, IPT: Isoniazid prophylactic therapy

Definitions

- Source case: a case of pulmonary TB that is a possible source of infection
- Contacts for screening: all children <5 years and children ≥5 years with signs and symptoms of TB who are in close contact with a source case
- Household contact: persons living in the same household with a source case

Monitoring Treatment of LTBI

A health care worker should monitor children on LTBI treatment every 4 weeks to

- Reinforce adherence
- Assess for drug toxicity
- Evaluate for progression to TB disease

IPT protects against TB for about 2 years. Patients with a positive TST should not have a repeat TST.

LTBI treatment consists of daily INH for 6 months. If treatment interruption is < 3 months, the remaining doses should be given and treatment duration extended up to 9 months. If the interruption is > 3 months, restart IPT for 6 months.

Counseling for Children on Isoniazid Preventive Therapy (IPT):

Describe potential side effects and duration of therapy. Emphasize that the child must adhere to and complete treatment, even when not feeling ill, because this therapy prevents progression from latent TB to active TB disease. Children should return to the clinic if ill while on IPT or if they develop TB symptoms, but there is no need to limit their activities.

using the first-line TB regimen, with the exception of pyrazinamide, to which *Mycobacterium bovis* is resistant.

Latent Tuberculosis Infection (LTBI) in Children

LTBI is usually established with the tuberculin skin test (TST) in children with recent TB contact and HIV-infected. All family members of a child with a positive TST should be screened for active TB. Where available, a TST result of 5 mm or more induration is positive and means TB disease. Children and adolescents have a high risk of progressing from LTBI to TB disease and also have a high risk for developing disseminated disease.

Isoniazid preventive therapy (IPT) prevents progression of LTBI to TB disease, and it should be initiated only after TB disease has been ruled out. Children eligible for IPT include:

- All newborns with no symptoms of active TB disease who are born to mothers with active TB disease
- All HIV infected children less than 12 months with no symptoms of active TB disease and have a known TB contact
- All HIV infected children who are 12 months or older with no symptoms of active TB disease.
- All children younger than 5 years with no symptoms of active TB disease and have a known TB contact

Isoniazid should be used to treat LTBI in a child if the source case is known to have INH-susceptible TB, or if the source case is unknown. Isoniazid dosing for LTBI is the same as for treatment of TB disease. Pyridoxine (B6) supplementation is given to patients with conditions that can predispose to neuropathy, such as HIV infection, malnutrition and diabetes.

LTBI Treatment: Contact screening

Contact screening is used to identify new TB cases. Contacts to active TB cases are asked if they have signs and symptoms of active TB, and undergo a physical examination. Household contacts of all smear positive TB cases should be screened for signs and symptoms of TB. Children diagnosed with TB disease through contact screening should immediately be registered for anti-TB treatment under DOT, and children without TB disease should be given IPT.

TB Meningitis

TB meningitis is a medical emergency. It often presents with a subacute onset, cranial nerve involvement (such as visual or hearing loss or facial paralysis), hydrocephalus, stroke and increased intracranial pressure as well as a poor response to antibiotics.

Clinical presentation of the first stage of TB meningitis is characterized by personality/behavior change, irritability, anorexia, listlessness (lethargy) and fever. Progression to the second stage occurs 1-2 weeks later and is characterized by classic meningitic symptoms and signs such as headache, neck pain, neck stiffness, fever and convulsions from increased intracranial pressure. Clinical presentation of the third stage includes loss of consciousness, irregular pulse and respirations, and fever, with death often ensuing.

If there are no signs of increased intracranial pressure, perform a lumbar puncture and send cerebrospinal fluid (CSF) for white blood count, protein, glucose, AFB smear and culture. The table below shows the typical CSF results seen at early vs. late stages of disease.

Table 3.6 CSF Results in TB Meningitis by Stage of Disease

CSF component	Early Stage of TB meningitis	Late Stage of TB meningitis
WBC	High amount of neutrophils	Greater proportion of lymphocytes
Glucose	Lower limits of normal	Lower limits of normal
Protein	Normal	High

TB Meningitis Treatment

If TB meningitis is suspected, **START TREATMENT IMMEDIATELY**, even before CSF smear and culture results return positive. If unable to obtain a smear and culture, start treatment if the CSF shows a low glucose, elevated protein, and increased lymphocytes. In lower level facilities, stabilize and refer to a nearest hospital for further management.

Disseminated/Miliary TB

Compared to older children, miliary TB is more common in children less than 2 years old. Children often present very ill-appearing with failure to thrive, lethargy, anorexia, coma, and meningitis. They may develop multi-organ failure and coma. These children will have failed to improve on standard antibiotics. Patients are usually too ill to provide sputum, therefore, diagnosis is made by lumbar puncture and chest x-ray which may show a miliary appearance. As with TB meningitis, children with suspected or confirmed miliary TB should be started on treatment **IMMEDIATELY**.

Figure xx: Newborn with miliary TB (mother had active TB)

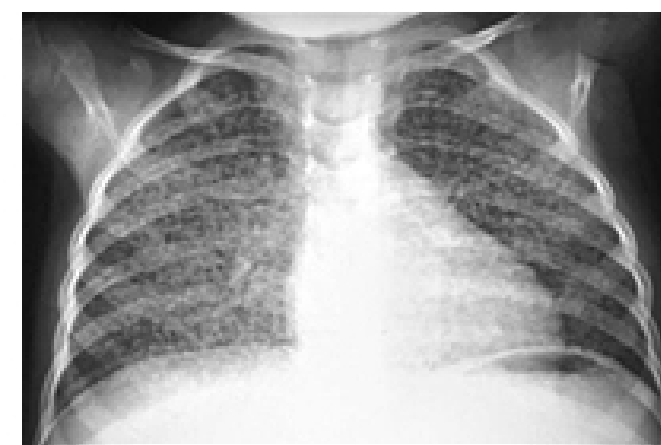


Table 3.6 Extrapulmonary TB - Summary Presentations and Investigations

Anatomical Site	Signs and symptoms	Recommended investigations
Pleural TB (pleural effusion)	Cough, fast breathing, decreased breath sounds, decreased tactile and vocal fremitus, displaced trachea and cardiac apex, homogeneous opacification of whole hemithorax or obliteration of costophrenic angle	CXR, pleural tap for: protein, glucose, cell count, AFB smear, mycobacterium culture, sputum (smear AFB+ in <10%)
Pericardial TB	Shortness of breath, cough, chest pain, fainting/dizziness, increased heart rate	CXR, chest ultrasound, pericardial tap for WBC, protein, glucose, AFB smear, mycobacterium culture, sputum
Abdominal TB	Increase of abdomen size, abdominal discomfort, shortness of breath	Abdominal ultrasound, tap ascites looking for WBC, protein, glucose, AFB smear, mycobacterium culture, CXR, sputum if coughing
TB of spine, bones, joints	Acute angulation of spine, weakness in limbs, joint effusions, joint destruction, retropharyngeal mass, psoas abscess	X-ray, joint tap for WBC, protein, glucose, AFB smear, mycobacterium culture, synovial biopsy
TB adenitis	Painless, fixed, enlarged lymph nodes,	Lymph node biopsy or fine needle aspiration; sputum if coughing.
Miliary TB	Very ill with failure to thrive, lethargy, anorexia, coma, meningitis and sepsis-like.	Sputum and CXR. Perform additional diagnostic tests as appropriate for associated symptoms and signs (e.g., lumbar puncture to test for meningitis
TB meningitis	Subacute onset, cranial nerve involvement, hydrocephalus, stroke, increased intracranial pressure and signs of meningism	Lumbar puncture (CSF for white blood cell count with differential); biochemical analysis for protein and glucose concentration, AFB smear, and mycobacterial culture; CXR; and sputum.

CXR = chest x-ray

Neonatal Tuberculosis

Congenital TB results from hematogenous spread of TB from the mother to the infant during pregnancy or from exposure to maternal fluids during delivery. Neonatal TB is TB disease that occurs after being exposed to someone with infectious TB after birth (usually their mother or another household member). It is often difficult to distinguish between congenital and neonatal TB, and management is the same for both. Thus, both forms will be referred to here as neonatal TB.

The typical signs and symptoms of neonatal TB are lethargy, poor feeding, low birth weight, respiratory distress, non-resolving pneumonia, hepatosplenomegaly, lymphadenopathy and ascites.

To diagnose, ask about a history of maternal TB and perform a TST, CXR, lumbar puncture and send cultures of blood, CSF and gastric aspirate specimens. When possible, send the placenta for

5

PREVENTION OF TUBERCULOSIS IN CHILDREN

Introduction

The goal of this unit is to provide participants with knowledge and skills regarding the appropriate use of BCG vaccine, how to diagnosis and treat latent tuberculosis infection (LTBI) in children, and infection prevention and control practices for health settings.

By the end of this unit you should be able to:

- Explain the benefits and risks associated with BCG vaccination
- Explain the diagnostic approach used for Latent TB Infection (LTBI) in children
- Explain the treatment and monitoring of children with LTBI
- Explain contact screening and the management of child contacts
- Explain infection control issues in pediatric TB

Bacille Calmette-Guerin (BCG) Immunization

The BCG vaccine is a live attenuated vaccine and is administered according to the Expanded Programme of Immunizations (EPI) and NTLP guidelines. The vaccine is effective in protecting against TB meningitis and other severe forms of TB. However, it is not 100% effective and so TB must still be considered in BCG vaccinated children with TB symptoms.

All infants should be given BCG vaccine at birth regardless of HIV status. However BCG should not be given to HIV exposed infants who presents with clear signs and symptoms of HIV disease or full blown AIDS.

Infants born to mothers with tuberculosis disease

If the infant is born to a mother with TB disease, DO NOT give BCG vaccine. The infant first must be evaluated for TB disease (see neonatal TB section). If the neonate has TB disease, treat. If TB disease is ruled out, give IPT for six months. If the infant remains asymptomatic and is HIV negative at the end of six months of treatment, give BCG vaccine two weeks after completing IPT. During the course of IPT, the infant should be monitored on a monthly basis.

Adverse Reactions to the BCG Vaccine

Common adverse reactions to BCG vaccination include redness, swelling, and pain at the site of injection that may last several weeks. Local skin infection may spread to the regional lymph nodes, causing a suppurative lymphadenitis. However, this occurs in only 1-2% of infants.

More severe adverse reactions include BCG immune reconstitution and disseminated BCG. In BCG immune reconstitution, the vaccine site will develop an abscess and/or ipsilateral lymphadenitis with or without systemic illness. Symptoms may occur within weeks or months after initiation of ART (see section on IRIS in TB/HIV unit). Disseminated BCG is a life threatening condition. Symptoms include prolonged fever or other systemic symptoms. Infants who develop prolonged fever or other systemic symptoms after BCG immunization should be investigated for HIV status if unknown. Treat as for TB

- Encourage the parents/care givers to continue discussing with the child about the disease and his/her condition.

Key Points

- The aim of TB treatment is to cure patients and to prevent: relapse, death, drug resistant organisms, and further transmission
- TB treatment needs to be tailored based on the type of TB disease
- Most children tolerate anti-TB medications well
- TB treatment must be monitored in order to assess adherence, identify side effects, and prevent drug resistance
- Since most children are smear negative, monitoring and treatment outcome is based on response to therapy (clinical improvement) and treatment completion
- Major and minor adverse drug reactions must be properly managed
- Counseling is important to ensure adherence
- Counselling should include HIV testing and psychosocial support and referrals and nutritional counselling
- TB management should include nutritional assessment and its treatment

histological examination (to identify granulomata), AFB smear, and mycobacterial culture. Include neonatal TB in the differential diagnosis of a neonate with a chronic infection and a poor response to antibiotics, a congenital infection and atypical pneumonia. The most important clue is maternal history of TB.

TB in Pregnant Women

All pregnant women should be screened for TB. Pregnant women who are HIV-infected and have TB disease should be treated according to national guidelines.

Refer to the adult NTLN guidelines for information on the diagnosis and treatment of TB during pregnancy.

Key Points

- Bacteriologic confirmation should be attempted in all children suspected of having TB.
- Sputum can be collected by expectoration (coughing into a cup), sputum induction, or gastric aspiration.
- Check for the classic tetrad of TB contact history, signs and symptoms, positive TST , and suggestive laboratory and radiographic findings.
- In the absence of bacteriologic confirmation, use the TB Score Chart to make a clinical diagnosis of TB
- Younger children are at greater risk for disseminated or miliary TB.

- Note: BCG can only be administered after TB disease has been excluded and isoniazid treatment for latent TB has been completed). Exposed neonate should be monitored for 1 year.

Nutrition

A balanced diet throughout childhood is important for healthy development, but good nutrition is especially important during TB treatment to maximize immune response and treatment outcomes. Balanced diet includes a diet with at least one item from each of the 5 groups of food carbohydrates (cereals, tubers and bananas); protein (animals or plants); vegetables; fruits and oils and sugar)

Weight loss and failure to thrive are important clinical features in TB diagnosis in children. Malnutrition is seen frequently in children with TB and contributes to poor outcomes, including death. Malnourished children with latent TB infection (LTBI) are at higher risk of progressing to TB disease, which will worsen malnutrition and cause wasting. In HIV-infected children, wasting is associated with poor survival, so proper nutrition is even more important. Once anti-TB treatment is started, adequate nutrition can counteract the child's prolonged catabolic state.

Breastfeeding is recommended for all infants irrespective of the mother's TB status, with the exception of infectious MDR TB as discussed in the MDR TB section.

Children should undergo a complete nutritional status assessment including:

- Detailed dietary history to identify feeding problem and family support networks
- General exam to identify features of malnutrition including anthropometric measurements and growth pattern

Develop an individualized nutrition support plan and provided therapeutic feeding as indicated. Follow national guidelines for management of malnutrition in children.

Counseling

Counseling helps children and families to cope with the stress of TB diagnosis and should be an ongoing process. Encourage parents/caregivers to talk with their child to allow them to verbalize any fears and concerns they may have. Encourage proper rest and balanced diet, link families to social assistance and instruct family not to segregate the child from other family members, as this stigmatizes and affects child psychologically.

Often TB is stigmatized, so children and the parent/caregivers may fear social rejection, increasing the likelihood of non-adherence to treatment. At every visit, encourage continued treatment and remind them TB is curable. During each visit, review the following general key points with the patient and parent/caregiver:

- TB disease and symptoms
- TB treatment regimen and duration, DOT options
- Importance of adherence, what to do if child misses a dose
- Possible medication side-effects
- Importance of screening other household children

Counseling to children - key messages

At every visit, review with parent/caregiver and/or child:

- Perception of the child on the disease
- Any other psychosocial problem related to the child's condition
- Problems related to treatment adherence
- Possible medication side-effects
- Any suggestion to improve the child's treatment

Drug Challenge for Hepatitis:

1. Start with isoniazid at small doses (one-fourth to one-third of the total dose), and gradually increase the dose over 3 days to the recommended daily dose.
2. If no symptoms, next add rifampicin using a rifampicin/isoniazid FDC tablet.
3. If the child can tolerate rifampin and isoniazid (and received less than 2 months PZA), he/she can be treated for 9 months total duration
4. If the child cannot tolerate rifampin or isoniazid, he/she will require an alternate regimen for 9-12 months
 - Reintroduction of one drug at a time is the optimal approach
 - If unable to do a drug challenge because single drugs are not available from DTLC/RTLTC, management depends on the onset of the hepatitis.
 - If onset is during intensive phase, once resolved, restart RH and individual ethambutol. Send samples for DST and modify treatment based on results.
 - If onset is during continuation phase, once resolved, restart RH to complete.

Treatment Interruptions

- Contact within 1 day any patient who misses DOT or a medical appointment during the intensive phase.
 - Contact within 1 week any patient who misses DOT or a medical appointment during the continuation phase.
 - If a child has missed less than 2 weeks of treatment, the duration of his/her treatment must be extended until all 168 doses are taken.
 - If a child misses 2 - 4 weeks of treatment collect a sputum sample (if able to produce one) for smear microscopy and send for culture and DST if any of the following apply:
 - Patient is sputum smear positive after return to treatment
 - The interruption is during the intensive phase
 - Patient was responding poorly to treatment before the interruption
 - Drug-resistant TB is suspected
- Continue treatment while waiting for sputum results and extend therapy by adding missed doses.
- If a child misses more than 4 weeks of treatment the patient must restart treatment from the beginning. Send sputum for culture and DST. Restart standard TB treatment while awaiting culture and DST results. Refer to MDR TB treatment centre if MDR TB is confirmed

Ancillary and Supportive Care

All severely ill, debilitated children should be admitted to the hospital for stabilization, nutritional support, and initial drug therapy. Examples include a comatose child with TB meningitis, an infant with military/disseminated TB, or children with severe respiratory distress. Young children are usually hospitalized to obtain diagnostic specimen through nasogastric aspiration.

Neonate Exposed to Maternal TB

- Young infants are at higher risk for developing TB, therefore, any neonate exposed to maternal TB should be screened for TB disease. If the evaluation rules out TB disease, treat the exposed neonate with daily isoniazid (10mg/kg for 6 months).
- Separate the neonate if the mother is not on treatment
- Once the mother has been on TB treatment for two weeks, no limitations in contact with the neonate are necessary. The mother may continue breastfeeding throughout.
- If TB disease develops in the neonate, start TB treatment.
- If the neonate is asymptomatic after completing 6 months of isoniazid, perform aTST if available and test for HIV if indicated. If the TST is negative or not done and HIV serostatus is negative, administer BCG two weeks after IPT is completed.

4

MANAGEMENT OF TB IN CHILDREN

Introduction

The goal of this unit is to provide participants with knowledge and skills to provide effective TB treatment for children at different ages, to manage of treatment interruptions and adverse reactions, and to provide effective counseling and treatment monitoring.

By the end of this unit, you will be able to:

- Explain the treatment regimens and dosing approach used in children with TB disease
- Explain the management of adverse reactions and treatment interruptions in children with TB disease
- Explain the ancillary and supportive care, nutritional support, and counseling for children with TB disease
- Demonstrate skills in managing TB disease in children through case studies

Principles and aims of TB Treatment

The aims of anti-TB treatment are to cure TB patients, prevent death, avoid relapse, prevent drug-resistant organisms, and prevent transmission of TB to the community. In order to achieve effective treatment, adequate chemotherapy should be prescribed in appropriate combination, with the right dosage, in an appropriate formulation, and for the right duration of treatment. In general, treatment regimens for children are similar to those used for adults.

The cornerstone of TB treatment is DOT, directly observed treatment. DOT means that an observer (a parent, caregiver or other trained supervisor) watches the child swallow his/her tablets every day for the full duration of treatment. If children do not take their drugs as directed or stop before completing full treatment, they will not be cured. They may even die of TB, or simply prolong the disease and make it more difficult to treat in the future. DOT ensures that children do not miss doses and continue their medicines even when they start to feel better.

The role of the healthcare worker in this process is to:

- Diagnose TB and other concomitant diseases (HIV and malnutrition) in a child
- Prescribe an appropriate regimen and formulation
- Counsel the child and parent/caregiver's ability to ensure the child adheres to the regimen
- Address poor adherence when it occurs
- Ensure treatment is completed
- Assess and treat adverse drug reactions
- Provide referrals as per need

TB Treatment Regimens and Drugs

TB treatment regimens require two phases, an intensive phase and a continuation phase. During the intensive phase, TB bacilli are killed rapidly and most patients with smear-positive disease become non-infectious after about 2 weeks. During the continuation phase, drugs kill the remaining bacteria

and prevent relapse after treatment completion. The four essential first-line drugs are Rifampicin (R), Isoniazid (H), Pyrazinamide (Z), and Ethambutol (E). Combined, they produce a greater effect than the sum of the individual drugs. The drugs R, H, Z, E are combined in modern short-course multidrug TB chemotherapy.

WHO recommends 4-drug therapy during the intensive phase for all children with TB. All retreatment cases should be tested for multidrug-resistant TB (MDR TB).

Recommended treatment regimens for paediatric patients in Tanzania

Disease category	Recommended regimen	
	Intensive phase	Continuation phase
All forms of new pulmonary and extrapulmonary TB* <i>except TB meningitis and TB of the spine/bones/joints</i>	2 months of daily RHZE	4 months of daily RH
TB meningitis; miliary TB; TB of the spine/ bones/ joints	2 months of daily RHZE	10 months of daily RH
Previously treated smear-positive pulmonary TB (relapse, return after default, treatment failure)**	3 months of daily RHZE***	5 months of daily RHE
MDR TB	See Section 5.2, "Drug-resistant tuberculosis in children"	

E: ethambutol; H: isoniazid; R: rifampicin; Z: pyrazinamide.

You may use streptomycin in special considerations e.g drug re-challenging or when susceptibility is confirmed.

Anti-TB medicine dosages should be calculated based on weight. Children should be weighed using a reliable and appropriate scale at every visit. Table 4.1 shows the recommended milligrams per kilogram doses and the acceptable range, along with the maximum dose.

Cutaneous Reactions:

- Itching without a rash and no other obvious cause can be treated with symptomatic treatment. Continue TB therapy while observing the patient closely.
- If a skin rash develops, stop all anti-TB drugs and refer to the nearest hospital. Once rash has resolved, perform drug challenge.

Example of re-introduction of TB drugs following drug reaction in a 15 kg child*

Anti TB drug	Day 1 (challenge dose)	Day 2	Day 3	Day 4
Isoniazid	25 mg (¼ tablet)	50 mg (½ tablet)	100 mg (1 tablet)	125 mg (1 ¼ tablet)
Rifampicin (using pediRH)	60 mg (1 tablet)	120 mg (2 tablets)	180 mg (3 tablets)	Full dose (4 tablets)
Pyrazinamide (using pediRHZ)	150 mg (1 tablet)	300 mg (2 tablets)	450 mg (3 tablets)	Full dose (of pediRHZ)
Ethambutol	50 mg (½ tablet)	100 mg (1 tablet)	200 mg (2 tablets)	Full dose (3 tablets)

H: isoniazid; R: rifampicin; Z: pyrazinamide.

*Always dose anti-TB drugs in children based on weight.

Drug Challenge for Cutaneous Reaction:

1. Start with small doses (1/3 of total dose) of the drug least likely to be the cause (i.e. ethambutol)
2. Gradually increase the dose over 3 days
3. Repeat process, adding one drug at a time (next giving pyrazinamide, then isoniazid and finally rifampicin).
4. If rash recurs, it is likely the last drug added is responsible
5. Stop that drug and do not give again
 - Note a reaction from a small challenge dose likely to be less severe
 - If possible, give 2 anti-TB drugs the patient has not had before

Drug-induced Hepatitis:

- Isoniazid, pyrazinamide, and rifampin can cause liver damage.
- Liver enzymes do not need to be routinely monitored because asymptomatic elevations often occur and are not an indication to stop treatment. However, you should evaluate for the signs and symptoms of hepatitis at each visit (nausea, vomiting, loss of appetite, poor weight gain, dark urine, hepatomegaly, jaundice, abdominal pain).
- If a child has liver tenderness, jaundice, or hepatomegaly stop all hepatotoxic drugs and obtain liver enzymes. Refer the patient to a hospital promptly for treatment and to assess for other causes of hepatitis.
- Recheck liver enzymes after 1-2 weeks and do not restart anti-TB drugs until liver enzymes are in a normal range and symptoms have resolved. If you are unable to check liver enzymes, wait until 2 weeks after symptoms have resolved.
- If symptoms do not resolve, or patient is too ill to stop treatment, start streptomycin and ethambutol (non-hepatotoxic), and send samples for DST. Adjust remaining treatment based on results of DST.
- If hepatitis resolves, experienced health care worker/DTLC/RTLTC can perform a drug challenge.

Table 4.3 Symptoms-based management approach to Major and Minor Reactions to anti-TB medications

Adverse reaction(s)	Drug(s) probably responsible	Management
Stop anti-TB drug(s) and refer to a hospital immediately		
Skin rash with or without itching	Streptomycin, isoniazid, rifampicin, pyrazinamide	Stop anti-TB drugs.
Decreased hearing or deafness (no wax in ear canal)	Streptomycin	Stop streptomycin.
Dizziness (vertigo and nystagmus)	Streptomycin	Stop streptomycin.
Jaundice (other causes excluded), hepatitis, confusion	Isoniazid, pyrazinamide, rifampicin	Stop anti-TB drugs.
Visual impairment (other causes excluded)	Ethambutol	Stop ethambutol.
Shock, purpura, acute renal failure	Rifampicin	Stop anti-TB drugs.
Decreased urine output	Streptomycin	Stop streptomycin.
Continue anti-TB drugs; check drug dosages		
Anorexia, nausea, abdominal pain	Pyrazinamide, rifampicin, isoniazid	Give drugs with small meals or just before bedtime, and advise patient to swallow pills slowly with small sips of water. If symptoms persist or worsen, or there is protracted vomiting or any sign of bleeding, consider the side effect to be major and refer to a clinician immediately.
Joint pain	Pyrazinamide	Give non-steroidal anti-inflammatory drug or paracetamol.
Burning, numbness, or tingling sensation in the hands or feet (consult paediatrician)	Isoniazid	Give pyridoxine (1-2 mg/kg/day), especially if on high-dose isoniazid and/or malnourished.
Drowsiness	Isoniazid	Provide reassurance. Give drugs before bedtime.
Orange/Red urine	Rifampicin	Provide reassurance. Patients should be told when starting treatment that this may happen and is normal.

Adapted from: World Health Organization, Stop TB Department. Treatment of Tuberculosis Guidelines: Fourth Edition. WHO/HTM/TB/2009.420.

Figure 4.1 Drug Dosing for the Treatment of Tuberculosis in Children

Drug	Drug formulation	Daily dose (mg/kg)	Maximum dose	Adverse reactions
Isoniazid	Scored tablets: 100 mg, 300 mg Syrup: 10 mg/ml	10 (10-15)	Daily: 300 mg	Mild hepatic enzyme elevation, hepatitis, peripheral neuritis, hypersensitivity
Rifampicin	Capsules: 150 mg, 300 mg	15 (10-20)	600 mg	Orange discoloration of secretions or urine, vomiting, hepatitis, influenza-like reaction, thrombocytopenia, pruritus
Pyrazinamide	Scored tablet: 500 mg	35 (30-40)	2 g	Hepatotoxic effects, hyperuricemia, arthralgias, gastrointestinal tract upset
Ethambutol*	Tablets: 100 mg, 400 mg (scored)	20 (15-25)	1200 mg	Optic neuritis (usually reversible), decreased red-green color discrimination, gastrointestinal tract disturbances, hypersensitivity
Streptomycin	Vials: 1 g	15 (12-18)	1500 mg	Irreversible auditory nerve damage

*Ethambutol was previously omitted from treatment regimens for children due to concerns about optic toxicity, but a review of the literature indicates it is safe and should be used to treat TB in children of all ages at recommended dosages.

Adapted from: World Health Organization, Stop TB Department. Rapid Advice: Treatment of Tuberculosis in Children. WHO/HTM/TB/2010.13.

When available, give pyridoxine supplementation to children receiving TB treatment at a prophylactic dosage of 1-2 mg/kg per day.

Fixed-Dose Combination Tablets

Fixed-dose combination (FDC) tablets are used in Tanzania for the treatment of TB to facilitate adherence and simplify regimens. The MOHSW endorses the use of FDCs in both the intensive and continuation phases of TB treatment. Three different FDCs are available for use in children:

- R/H : 60/30 mg or 150/75 mg
- R/H/Z: 60/30/150 mg
- R/H/Z/E: 150/75/400/275 mg

Figure 4.2 Weight-based Dosing of Anti-TB Medicines Using Pediatric Formulations (2-20kg)

Weight (kg)	Intensive phase* (2 months)		Continuation phase (4 months)
	RHZ (paediatric) 60/30/150 mg	Ethambutol 100 mg	RH (paediatric) 60/30 mg
2-2.9 kg	½ tablet	½ tablet	½ tablet
3-3.9 kg	1 tablet	½ tablet	1 tablet
4-5.9 kg	1 tablet	1 tablet	1 tablet
6-7.9 kg	1.5 tablets	1.5 tablets	1.5 tablets
8-10.9 kg	2 tablets	2 tablets	2 tablets
11-13.9 kg	3 tablets	2 tablets	3 tablets
14-19.9 kg	4 tablets	3 tablets	4 tablets

*WHO recommends four-drug therapy during the intensive phase for all children.

Figure 4.3 Weight-based Dosing of Anti-TB Medicines Using Adult FDC Formulations (≥5kg)

Weight (kg)	Intensive phase* (2 months)	Continuation phase (4 months)
	RHZE (adult) 600/75/400/275 mg	RH (adult) 150/75 mg
5-9.9 kg	½ tablet	Use paediatric formulation; if not available, ½ tablet adult
10-14.9 kg	1 tablet	Use paediatric formulation; if not available, 1 tablet adult
15-19.9 kg	1.5 tablets	Use paediatric formulation; if not available, 1.5 tablets adult
20-24.9 kg	2 tablets	2 tablets
25-29.9 kg	2.5 tablets	2.5 tablets
30-40 kg	3 tablets	3 tablets
>40 kg	4 tablets	4 tablets

*WHO recommends four-drug therapy during the intensive phase for all children.

Note that: one can use a quarter adult tablet FDC for children below 5kg

Practical Guidance for Administering Medicines to Children

Since no syrups are available for anti-TB treatment, parents/caregivers will need to crush tablets to administer correct doses to young children. Instruct parents/caregivers to ensure that the entire pill portion is retained. Remind them to always use clean water when administering medicines. Advise parents/caregivers to repeat the dose as soon as possible if their child spits up or vomits their medicine within 30 minutes of receiving it.

Steroid Use in TB

Children with serious forms of TB may benefit from having steroids added to their treatment. Steroids are generally indicated when treating TB meningitis, severe miliary/disseminated TB, pleural TB with massive effusions, and pulmonary TB with mediastinal lymph nodes obstructing airways.

Dose of Prednisolone: 1-2mg/kg/day up to 4mg/kg (max dose 60mg/day) for 4-6 weeks, followed by 2 weeks of tapering.

Monitoring Treatment Progress

Monitoring during treatment is vital to ensure the patient adheres to and completes treatment, and is cured. Bacteriologic monitoring (sputum smear microscopy) is needed in sputum smear positive cases. Clinical evaluations should take place at 1-week intervals during the intensive phase and at 2-week intervals during the continuation phase. Remember to adjust doses as needed as children gain weight. Evaluations should include:

- Weight measurement and assess growth and development
- Assessment of response to treatment (checking for signs and symptoms which the child had before starting TB therapy)
- Adherence
- Any adverse drug reactions or events
- Screen for new cases in the home (or close contacts)

Children who have smear negative or extrapulmonary TB can only be evaluated clinically. If a child is not improving, these patients may have drug-resistant TB, poor treatment adherence, or another condition. These children should be referred to secondary/tertiary centers for further investigations of MDR TB or other diagnoses. If these centers are unable to obtain bacteriological confirmation of MDR TB, the child should be referred to the MDR TB Treatment Centre in Kibong'oto for further evaluation.

Routine monitoring of chest x-rays in children with pulmonary TB is unnecessary since radiographic changes occur very slowly.

In sputum smear positive cases, assess for clinical improvement and obtain sputum at the end of the 2nd month of treatment for new cases and at the end of the 3rd month for retreatment cases. If the smear result is negative, start the continuation phase. If the smear result is positive, confirm adherence and extend the intensive phase for one more month and recheck sputum at that time. If a repeat sputum smear is positive and adherence is confirmed, send a sputum sample for culture and Drug Susceptibility Testing (DST) and refer the patient for MDR TB evaluation.

When to Start the Continuation Phase of Treatment

For sputum smear negative and EPTB cases (most children), start the continuation phase after the child has taken all of the required 56 doses (2 months) of the intensive phase of treatment. For sputum smear positive cases, start the continuation phase if the follow-up sputum result at the end of the 2nd month (3rd month for retreatment cases) is negative.

End of Treatment

Children should be monitored for clinical improvement throughout their treatment. If they are not improving, confirm adherence and refer for MDR TB evaluation. For smear negative and EPTB cases, complete the full course of treatment (6 or 12 months depending on site of disease). For smear positive cases, obtain sputum during the 5th month of treatment; if the result is negative, complete the remaining therapy, if the result is positive, refer for MDR TB evaluation.

Management of Adverse Reactions to Anti-TB Medications

Adverse reactions can impact adherence, and therefore clinical outcome. Inform parents/caregivers and children about potential adverse reactions and instruct them to report them immediately.